Health Innovation East

Medication Adherence in Paediatric Epilepsy (MAPE) Rapid Evidence Review

EVIDENCE REVIEW COMMISSIONED BY NHS EAST OF ENGLAND.

COMPLETED ON BEHALF OF HEALTH INNOVATION EAST:

ELLICE PARKINSON, NATASHA ELMORE, HOLLY CLEGG & AVIVA STAFFORD.

JUNE 2024

Contents

Background and context
Rationale 3
Review aim
Outcomes
Methods 3
Eligibility criteria
Exclusion criteria
Search strategy
Selection of sources and evidence
Data extraction
Synthesis of results
Results
Selection of sources and evidence7
Synthesis of results
Characteristics of courses of ovidence
Characteristics of sources of evidence
Factors influencing adherence (including variation)
Factors influencing adherence (including variation). 10 What leads to better medication adherence? 11 What leads to poorer medication adherence? 12 Best practice for supporting paediatric patients' medication adherence. 13 Discussion 15 Recommendations 15 Strengths and limitations 16
Factors influencing adherence (including variation)
Factors influencing adherence (including variation). 10 What leads to better medication adherence? 11 What leads to poorer medication adherence? 12 Best practice for supporting paediatric patients' medication adherence. 13 Discussion 15 Recommendations 15 Strengths and limitations 16 Limitations 16
Factors influencing adherence (including variation)
Factors influencing adherence (including variation) 10 What leads to better medication adherence? 11 What leads to poorer medication adherence? 12 Best practice for supporting paediatric patients' medication adherence 13 Discussion 15 Recommendations 15 Strengths and limitations 16 Limitations 16 References 17

Background and context

Rationale

The NHS East of England Children and Young People (CYP) Transformation Programme team was interested in understanding children and young people's adherence to epilepsy medication, including factors that influence adherence, variation, and best practice in supporting patients, parents and carers. The NHS East of England CYP Programme team therefore commissioned Health Innovation East to conduct a rapid evidence review of the literature, pertaining to factors influencing medication adherence and best practice. The rationale is that this review will enable the region to implement evidence-based approaches to improve medication adherence for this population and inform qualitative interview topic guides to be used with young people affected by paediatric epilepsy.

Review aim

This review aimed to identify which factors influence medication adherence for paediatric epilepsy, for children and young people aged 16 years and younger.

Outcomes

The primary outcomes of the review were to:

- 1. Describe the factors which influence medication adherence for young people with paediatric epilepsy.
- 2. Describe any factors influencing variation relating to young people's adherence to epilepsy medication.
- 3. Report on best practice in supporting patients, parents and carers with young people's adherence to epilepsy medication.

Methods

We conducted this review using scoping review methodology (1). Scoping reviews are useful to identify and inform further areas for research, and provide insights to decision-makers about a concept, when the literature is complex or heterogeneous (1). Given that much of the epilepsy medication adherence literature is focussed on adults, it was appropriate to use scoping review methodology. The review is reported in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) checklist (2).

We developed a protocol in line with the specification provided by NHS East of England, and in collaboration with the MAPE Operations group, and MAPE Steering group. We ensured that all parties were satisfied with the protocol

throughout the review process. The specification set out the scope for the review using JBI's PICo (Population, Phenomenon of Interest, Context) framework (1).

Eligibility criteria

Included studies were written in English, and reported factors influencing epilepsy medication adherence in children and young people aged 16 years or younger with paediatric epilepsy, variation to their medication adherence, and/or made recommendations for best practice in supporting patients, parents and carers with regards to medication adherence. Studies published in any country of origin and study design were included. We included systematic reviews for the purpose of citation searching the reference lists.

At the MAPE steering group meeting on 13th May 2024, it was decided that we needed to revise the eligibility criteria, to ensure that we captured the breadth of literature on this topic. The eligibility criteria was therefore revised to include all study designs, and restricted inclusion of studies to the past 10 years. In acknowledging the shift away from more paternalistic approaches and a move towards shared decision-making around medication adherence in clinical care, it was decided that studies prior to 1st January 2014 may be less relevant for inclusion within this review. The inclusion criteria can be found below in Table 1.

TABLE I: INCLUSION	CRITERIA FOR THE MAPE REVIEW
Population (P)	Children aged ≤16 years
Phenomenon of	Factors influencing epilepsy medication adherence
Interest (I)	Variation in young people's medication adherence
	Best practice in supporting patients, parents and carers for
	medication adherence
Context (Co)	Paediatric epilepsy

TABLE 1: INCLUSION CRITERIA FOR THE MAPE REVIEW

Exclusion criteria

Study protocols, conference abstracts and registrations of drug trials were excluded from the review. Studies were also excluded if adherence outcome data could not be separated by age (e.g. outcomes from paediatric and adult populations), if adherence factors had been attributed to the impact of Covid-19, or in instances whereby adherence outcome data could not be related to factors influencing the outcomes.

Search strategy

We searched three online databases for peer-reviewed literature: Cochrane Library of Systematic Reviews, Embase (Ovid) and MEDLINE (PubMed). We searched for grey literature in the form of published reports from NICE, Epilepsy Society and AAP.org relating to medication adherence and best practice in supporting a young person's adherence. We citation searched reference lists from relevant systematic reviews for potentially eligible included studies.

The search was developed based on the following PICo framework: [Medication Adherence OR Medication Compliance] AND [Epilepsy OR Seizures] AND [Child OR Infant OR Adolescent]. We used the PRESS Checklist (3) to comprehensively develop the search strategy, ensuring precision and specificity.

We searched online databases from 1st January 2014 to 10th April 2024. The search was adapted for use in each database. Table 2 shows the search strategy and results from Embase (Ovid).

TABLE 2. SEARCH STRATEGY FOR EMBASE (OVID)

		Results
#	Query	from 10
		Apr 2024
1	exp medication compliance/	49,466
2	"adher*".ab,ti.	370,045
3	"non-adher*".ab,ti.	23,287
4	"nonadher*".ab,ti.	16,425
5	"complian*".ab,ti.	263,768
6	"non-complian*".ab,ti.	17,134
7	"non-complian*".ab,ti.	17,134
8	"medication adherence".ab,ti.	24,262
9	"epilep*".ab,ti.	235,915
10	"seizure*".ab,ti.	223,884
11	childhood epilepsy/ or epilepsy/	156,847
12	"pediatric*".ab,ti.	602,173
13	"neonate*".ab,ti.	148,076
14	"newborn*".ab,ti.	223,997
15	child/	2,174,621
16	adolescent/	1,828,917
17	infant/	716,315
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	630,109
19	9 or 10 or 11	368,547
20	12 or 13 or 14 or 15 or 16 or 17	3,910,193
21	18 and 19 and 20	1,792

Selection of sources and evidence

We exported citations from each online database into EndNote reference management software (4), and then exported the XML files of the records into Covidence (5), a web-based collaboration software platform that streamlines the production of evidence reviews. All stages of the review, including screening and data extraction were completed within Covidence.

Two reviewers screened the titles and abstracts of all records using the eligibility criteria to assess inclusion. The lead reviewer independently duplicated the screening of 20% included and excluded studies to ensure consistency and accuracy. We tagged all studies which required a full text PDF uploading for review, and where available, sourced and uploaded PDFs for these eligible records. We then conducted full text screening, assessing each of these records for inclusion within the review. The lead reviewer independently duplicated the screening of 20% of these records.

As a result of the eligibility criteria refinement detailed in the 'eligibility criteria' section of this report, we completed the process of title, abstract and full text review again, with any study that had previously been excluded for study design reasons, e.g. RCTs which were previously ineligible for this review.

Data extraction

The lead reviewer developed the data extraction template in Covidence, enabling the team to extract details relating to the PICo framework: document details, participant information, study design, setting and data items relating to the review outcomes (factors influencing medication adherence and best practice). Reviewers extracted details from each included study independently, and the lead reviewer checked each data extraction for accuracy and completeness. For quantitative studies, we extracted factors that had a statistically significant association with medication adherence. For qualitative studies, we extracted factors reported to influence medication adherence or best practice relating to a young person's medication adherence.

Synthesis of results

We tabulated data items into the 'brief characteristics of included studies table' (See Table 4) which can be found in Appendix 1 at the end of this document. We have provided the full data extraction table in Supplementary File 1. We have provided the table of excluded studies in Supplementary File 2. We narratively synthesised determinants of medication adherence, and best practice for supporting parents, carers and young people in improving medication adherence for young people with paediatric epilepsy.

Results

Selection of sources and evidence

A total of 2569 studies were identified from the searches of the Embase (n=1803), PubMed (n=764) and Cochrane library of systematic reviews (n=2) databases. Citation searching identified a further 70 references from other sources. We found no additional documents from searching organisational websites. Automatic de-duplication in Covidence removed 601 duplicate citations. We screened the title and abstracts of 2038 studies. At this stage, we excluded 1716 studies as they did not meet the inclusion criteria. This resulted in 322 studies screened for full text review. We were unable to source full texts for 64 studies. We full-text reviewed 258 studies, of which 20 were included in the final review. See Figure 1 for the PRISMA flow diagram.



FIGURE 1. PRISMA DIAGRAM OF INCLUDED STUDIES

Synthesis of results

We present a narrative synthesis of review findings, categorised by review outcomes. The most common outcome reported within the included studies was of factors influencing medication adherence. We retrieved fewer studies describing best practice. It is important to note that not all included studies aimed to meet all outcomes explored in this review.

Characteristics of sources of evidence

Twenty studies were eligible for inclusion within this review. Sample sizes ranged from 24 (6) to 3,316 (7) with a total sample size of 6,927 participants. Further study characteristics are outlined in Table 4 at the end of this document.

All but one study (6) were quantitative. Studies were cross-sectional (n=9) (7-15), randomised controlled trials (n=4) (16-19), non-randomised controlled trial (n=1) (20), longitudinal cohort studies (n=4) (21-24) or retrospective chart reviews (n=1) (25), by design.

Outcome data all pertained to infants, children, or adolescents, whose ages ranged from <1yr to 16yrs. There was limited data relating to ethnicity, which was only reported in seven studies (13, 17-19, 21-23). Of the seven studies that did report on ethnicity, participants were predominantly white. In 13 of the 17 studies which reported on gender, males comprised a higher proportion of the participant samples, compared to females (10-12, 15-17, 19-25).

Studies were conducted across 10 countries, including Iran (n=1) (11), Saudi Arabia (n=1) (14), Ethiopia (n=1) (10), USA (n=8) (13, 21) Turkey (n=1) (26), China (n=3) (15, 20, 25), Germany (n=1) (7), Thailand (n=1) (16), Uganda (n=1) (12) and the UK (n=2) (6, 24).

All studies reported on factors which influenced adherence, and 11 studies reported on best practice (9, 10, 12, 13, 15, 17, 18, 20-22, 25).

Factors influencing adherence (including variation)

Table two below presents and briefly summarises the factors reported in the included studies as being associated with, or influencing children and young people's adherence to medication, broken down into modifiable and non-modifiable factors. It should be noted that there is mixed evidence for some determinants, such as age of child. We then present a narrative synthesis providing more context and detail about the determinants, below Table 2.

	Positive influences	Negative influences		
Non- Modifiable	Younger child age	Ethnicity (Black, Asian, or multiracial ethnicity)		
	Older child age	Older child age		
	Higher familial SES	Longer duration of illness		
	Seizure type (focal impaired awareness seizure)	Younger child age		
	Better parental education	Time since epilepsy diagnosis		
	Duration of epilepsy <1 year	History of prenatal morbidities		
	Absence of seizure attack in the last three months	Co-morbid ADHD		
	Having another primary caregiver other than the CYP's mother	Younger age of caregiver		
		Lower familial SES		
		Seizure type (Atonic seizure)		
Modifiable	Patient Education (Improving knowledge around Epilepsy diagnosis, treatment and medication)	Family size ≥5		
	Better carer QOL	Lower family income		
	Family members involved in child(s)' care	One or more seizures in the last 3 months prior to clinic appointment		
	Child perceives medication as a 'status symbol'	Lower parental health literacy knowledge		
	Number of drugs taken ≤ 2	Cost of drugs		
	Having health insurance	Fear of side effects		
	Absence of seizures in last 3 months prior to clinic appointment	Caregiver having an occupation		

TABLE 2: FACTORS INFLUENCING MEDICATION ADHERENCE OR VARIATION

Implementation of a hospital- community-family ternary linkage continuous nursing model	Lack of availability of drugs
Good family problem-solving	Negative beliefs and perceptions about antiepileptic drugs
Good family communication	Running out of medication (individual level)
Higher caregiver health literacy knowledge	Medication shortage (system level)
Fewer parental fears and concerns	Difficulty obtaining prescription
Reduced parental distress /stress	Parent forgetting to give medication
Observing that child's heath improves on medication	Child forgetting to take medication
Higher family income	Swallowing difficulties
Good family functioning	Child refusing medication
	Child embarrassment around taking medication
	Taste of medication
	Child independently responsible for taking medication
	Number of drugs taken ≥ 3
	Greater parental fears and concerns
	Increased parental distress / stress
	Not having health insurance

What leads to better medication adherence?

Non-modifiable factors which were identified as having a positive influence or association with adherence in children with epilepsy were the age of the child, with better adherence reported in younger children (7, 8, 15, 24). A higher familial socioeconomic status was associated with improved adherence (13, 19, 22, 23).

Having a parent educated to a higher education level (11, 13) and better health literacy was associated with improved adherence (8, 12, 13, 16, 17). Good family functioning (19), children from families with a higher income (15) and those that had health insurance (13) were more likely to adhere to their medication regime. One study reported influence on medication adherence was whether children perceived taking their medication as a 'status symbol' (6).

Caregiver self-reported quality of life score was associated with better medication adherence in the child (14), with higher levels of caregiver quality of life linked to higher rates of adherence. Adherence was better for young

people who had family members involved in their care, and where the caregiver attributed improvements in the child's health as resulting from the medication (12). Having another primary caregiver other than the young person's mother, was also found to improve adherence (12).

Some determinants directly related to the diagnosis of epilepsy. Medication adherence was more optimal for young people diagnosed with focal impaired awareness seizures (11). Children and young people were more likely to adhere to their medication regime if they had been diagnosed with epilepsy for less than one year (10), and if they had not experienced a seizure in the last three months (10).

What leads to poorer medication adherence?

There were more factors identified in the literature as being negatively associated with medication adherence in children with epilepsy.

Lower adherence was reported in older children (8, 24) and those from Black, Asian, or multiracial ethnic backgrounds (19). Children diagnosed with comorbid ADHD (7) and those with a history of prenatal disorders (11) were less likely to adhere to their medication regimes.

Children with caregivers aged younger than 35 years old, and caregivers with an occupation, had higher rates of non-adherence (12). Having a larger family size (\geq 5) (10), a lower familial socioeconomic status (13, 15, 19, 22) and having a lower family income (defined as monthly family income of <1000 Ethiopian Birr) (10) was associated with poorer adherence. Greater parental distress was identified as being associated with lower levels of medication adherence (19, 22). The child experiencing one or more seizures in the three months prior to attending the paediatric neurology follow up clinic (noting that having more seizures may also be caused by poorer adherence to medication) (10), and atonic seizures (11) were associated with lower levels of medication adherence. Young people diagnosed with epilepsy for longer than four years were less likely to be adherent (15). A lower level of parental education (15), poorer health literacy and knowledge of epilepsy, or negative beliefs towards medication (12, 13) were associated with poorer adherence.

Factors that were linked to the medication itself, reported to be associated with poorer adherence in children, were the cost of drugs, fear of side effects, lack of availability of drugs (12) and medication shortages either at an individual level or at a system level (12, 21) which led to difficulties obtaining prescriptions.

Behavioural factors that were reported as being associated with poorer adherence in children included, the parent forgetting to give medication (21), the child forgetting to take medication (21), difficulty swallowing medication (6, 21), the taste of medication (6), the child refusing medication (6), and the child experiencing embarrassment around taking medication (6). Parental fears and concerns around epilepsy medication (22) and the child being solely responsible for taking their medication (6), was related to less optimal medication adherence.

Best practice for supporting paediatric patients' medication adherence

Table 3 presents findings of best practice reported in the included studies, along with recommendations from authors for improving medication adherence in children and young people. We reported best practice involving the patient themselves, parents, and healthcare professionals, for improving the young person's medication adherence. No data was available for carers. Although it was not requested as part of the initial scope of this review, we thought it was useful to report on best practice involving health care professionals, as this may be useful context for developing an intervention.

Many of the recommendations for best practice to support medication adherence for young people relate to improved health literacy and knowledge of epilepsy and treatment plans for parents and patients (9, 12, 13, 15). Creative suggestions were made for medication reminders, such as implementing medication regimens within daily routines (21), or creating visual or auditory reminders (9). There is a need to specifically address some of the behavioural and psychosocial barriers to young people's adherence involving family-focussed interventions, such as parental fears and concerns, problem-solving and communication skills, and forgetfulness (9, 18, 22). Healthcare professionals should aim to involve patients within their treatment plans, minimising the complexity wherever possible (10). Healthcare professionals should understand that young people's adherence may change over the course of their disease (21, 27), and so interventions should be personalised and responsive, recognising the benefit of early intervention (15).

	Recommendation
Patients	• Provision of adequate information on epilepsy and the drugs (12).
	 Electronic monitoring of adherence behaviours (e.g. blood glucose monitors) (17).
	 Evidence-based adherence interventions that target problem-solving and communication, such as Behavioural Family Systems Therapy (22).
	• Emphasis on management of timely medication (15).
	• Incorporate medication administration into daily routines (21).
	• Education to increase epilepsy knowledge (13).
Parents	 Formal behavioural plan including follow up telephone contacts and subsequent sessions (17).

TABLE 32: BEST PRACTICE RELATING TO MEDICATION ADHERENCE

	 Identify adherence factors which can change over time; teaching families problem-solving strategies (18).
	 Parent focused interventions to address fears, concerns, and life stress (22).
	 Detailed assessment of the contributing factors to parent forgetfulness (e.g. logistical burden, psychosocial stressors, cognitive functioning) to inform the types of supports and interventions that caregivers need (9).
	• Clarification of treatment plans to improve health literacy (9).
	 Problem-solving skills and communication interventions for parents (22).
	 Provide psychological support, including praise and rewards, to child (15).
	• Incorporate medication administration into daily routines (21).
	• Improved knowledge of epilepsy and health literacy (13, 15).
	 Visual or auditory reminders for caregivers who forget to give medication (9).
	• Involvement in child's treatment plan (15).
Healthcare	• Early prevention and nursing intervention measures (15).
(HCPs)	 Drug treatment based on the type of seizures and other individual factors (15).
	• Regular telephone follow-up reminders for patient (15).
	 Assess and provide interventions for difficulties swallowing medication at diagnosis and throughout treatment (21).
	 Understand and assess barriers over time that may impact adherence differentially over the disease course (21).
	• Offer access to drugs from the hospital pharmacy (12).
	• Education delivered by a pharmacist to patients (20).
	• To proactively screen children with epilepsy throughout their disease course (22).
	 Targeted interventions at critical time points (e.g. one-month after diagnosis, one-year after diagnosis) incorporated into clinical care (22).
	• Improve knowledge of the strongest modifiable predictors of adherence over the course of epilepsy treatment (22).
	 Brief evidence-based interventions by members of the psychosocial service (social workers, pharmacists, and Psychologists) to address key parent and family behavioural predictors of adherence (22).

- Hospital-community-family linkage continuous nursing model (25).
- Prescribe less complex treatment regimens (10).
- Supply free antiepileptic drugs to children living in poverty (10).

Discussion

This scoping review found many modifiable and non-modifiable determinants of medication adherence for children and young people affected by paediatric epilepsy. We tabulated both positive and negative influences on medication adherence, which may be useful for understanding why some young people may find adherence more problematic, and these findings may also prove useful in informing an evidence-based intervention to improve medication adherence. We also reported on the best practice for improving medication adherence, involving patients, parents, and healthcare professionals, to acknowledge and understand shared roles and responsibilities in young peoples' medication adherence.

In this next section, we summarise some themes from the recommendations reported in the included studies and discuss the strengths and limitations of this review.

Recommendations

The eleven studies which provided recommendations for best practice could be broadly classified into the following themes for future interventions to address. These are summarised in Box 1 below.

BOX 1. KEY RECOMMENDATIONS FOR FUTURE INTERVENTIONS

Key recommendations for future interventions

Patient level: Improve patient knowledge and empowerment about the condition, importance of adherence, and ways they can help to self-manage (maybe supported by remote monitoring).

Familial level: Increase early and ongoing family centred/tailored care and support from HCPs for families and carers, improve parent/caregiver knowledge and empowerment, family-focussed support on family functioning, problem-solving and communication, and encourage parents/carers to remind patients to take medication.

Clinical level: Improve knowledge of, and early identification of factors of adherence, patient-centred prevention, and intervention by HCPs, assessments of children throughout disease course, patient-centred care, telephone reminders for appointments, less complex treatment regimens where possible, psychosocial input for young people.

System level: Improve accessibility/equity of medications for patients and their carers, integrate hospital and community services with a linkage system.

Strengths and limitations

Strengths

We conducted a comprehensive review applying scoping review methodology (1). This included systematic methods and quality control throughout the review process. We conducted a thorough review of both qualitative and quantitative factors influencing medication adherence for children and young people aged less than 16 years, living with paediatric epilepsy. We only included quantitative factors which were statistically significant and thus their influence on medication adherence can be inferred as not just being due to chance. We tabulated findings in an accessible format, as well as reporting a narrative synthesis, to ensure that the knowledge can be mobilised more readily from this review. We have generated useful findings which may underpin an evidence-informed intervention to improve adherence in young people.

Limitations

There is a chance that we have not included all potentially eligible studies, due to the scope of the search strategy and/or human error. We were unable to source some full texts for studies, which may have been eligible for inclusion. We did not conduct critical appraisal of included studies and therefore cannot provide information about the risk of bias or robustness of each included study. Many studies included outcome data combining data from those aged over 16 years and so we excluded these, as they were ineligible, but may have provided useful insights. However, these studies may have provided less appropriate or specific findings to the population of interest for this review. Many of the studies included in this review did not originate from the UK and therefore recommendations about potential future areas for intervention may not be applicable to the UK health system or population. Few studies reported on ethnicity, limiting generalisability and insight into the possible effect of ethnicity in medication adherence.

Conclusions

We conducted a comprehensive scoping review of factors influencing medication adherence, and best practice, for supporting medication adherence in young people affected by paediatric epilepsy. We included 20 studies, all of which reported factors influencing medication adherence, and 11 of which reported on best practice. We identified positive and negative influences on modifiable and non-modifiable determinants of medication adherence, along with a list of recommendations for improving medication adherence in young people. Insights from this review may be useful for informing topic guides of qualitative interviews to further explore young people's medication adherence. The review findings may also be useful for informing an evidence-based intervention to improve medication adherence in young people, living with paediatric epilepsy.

References

1. Peters MDJ, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, et al. Updated methodological guidance for the conduct of scoping reviews. JBI Evidence Synthesis. 2020;18(10).

2. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Annals of Internal Medicine. 2018;169(7):467-73.

3. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. Journal of Clinical Epidemiology. 2016;75:40-6.

4. The EndNote Team. EndNote. EndNote 21 ed. Philadelphia, PA: Clarivate; 2013.

5. Covidence systematic review software. Melbourne, Australia: Veritas Health Innovation.

6. Webster M. Similarities and differences in the meanings children and their parents attach to epilepsy medications. Social Science and Medicine. 2017;177:190-7.

7. Jacob L, Hamer HM, Kostev K. Adherence to antiepileptic drugs in children and adolescents: A retrospective study in primary care settings in Germany. Epilepsy and Behavior. 2017;75:36-41.

8. Korkmaz MF, Erdem-Uzun M, Korkmaz M, Ekici A. Adherence to Antiepileptic Drugs and the Health Literacy of Caregivers in Childhood Epilepsy. Puerto Rico health sciences journal. 2020;39(1):45-50.

9. Gutierrez-Colina AM, Smith AW, Mara CA, Modi AC. Adherence barriers in pediatric epilepsy: From toddlers to young adults. Epilepsy and Behavior. 2018;80:229-34.

10. Dima SA, Shibeshi MS. Antiepileptic drug adherence in children in southern Ethiopia: A cross sectional study. PLoS ONE. 2022;17(2 February):e0263821.

11. Afsharkhas L, Zamani S, Tavasoli A, Zamani B, Talebi A. The prevalence and major determinants of non-compliance with anti-seizure medication among children. Current Journal of Neurology. 2022;21(1):23-8.

12. Nazziwa R, Kakooza Mwesige A, Obua C, Ssenkusu JM, Mworozi E. Adherence to antiepileptic drugs among children attending a tertiary health unit in a low resource setting. Pan African Medical Journal. 2014;17.

 Paschal AM, Mitchell QP, Wilroy JD, Hawley SR, Mitchell JB. Parent health literacy and adherence-related outcomes in children with epilepsy. Epilepsy and Behavior. 2016;56:73-82.
 Asiri A, Mohammad A, Otaif M, Amer KA, Aldosari AA, Al-Maalwi RS, et al. Quality of life

among caregivers of epileptic children with degree of controlling seizures in Aseer region. J Family Med Prim Care. 2022;11(9):5340-4.

15. Wang S, Zhang X, Wang Y, Zhou J. Medication compliance of children with epilepsy: a cross-sectional survey. Italian Journal of Pediatrics. 2023;49(1):153.

16. Saengow VE, Chancharoenchai P, Saartying W, Pimpa W, Chotichanon N, Lewsirirat T, et al. Epilepsy video animation: Impact on knowledge and drug adherence in pediatric epilepsy patients and caregivers. Clinical Neurology and Neurosurgery. 2018;172:59-61.

17. Modi AC, Guilfoyle SM, Mann KA, Rausch JR. A pilot randomized controlled clinical trial to improve antiepileptic drug adherence in young children with epilepsy. Epilepsia. 2016;57(3):e69-e75.

18. Modi AC, Guilfoyle SM, Glauser TA, Mara CA. Supporting treatment adherence regimens in children with epilepsy: A randomized clinical trial. Epilepsia. 2021;62(7):1643-55.

 Bakula DM, Junger KW, Guilfoyle SM, Mara CA, Modi AC. Key predictors of the need for a family-focused pediatric epilepsy adherence intervention. Epilepsia. 2022;63(8):2120-9.
 Ma M, Peng Q, Gu X, Hu Y, Sun S, Sheng Y, et al. Pharmacist impact on adherence of

valproic acid therapy in pediatric patients with epilepsy using active education techniques. Epilepsy and Behavior. 2019;98:14-8.

21. Ramsey RR, Zhang N, Modi AC. The Stability and Influence of Barriers to Medication Adherence on Seizure Outcomes and Adherence in Children With Epilepsy Over 2Years. Journal of pediatric psychology. 2018;43(2):122-32.

22. Loiselle K, Rausch JR, Modi AC. Behavioral predictors of medication adherence trajectories among youth with newly diagnosed epilepsy. Epilepsy and Behavior. 2015;50:103-7.

23. Aylward BS, Rausch JR, Modi AC. An examination of 1-year adherence and persistence rates to antiepileptic medication in children with newly diagnosed epilepsy. Journal of pediatric psychology. 2015;40(1):66-74.

24. Shetty J, Greene SA, Mesalles-Naranjo O, Kirkpatrick M. Adherence to antiepileptic drugs in children with epilepsy in a Scottish population cohort. Developmental Medicine and Child Neurology. 2016;58(5):469-74.

25. Gao Y, Tang X, Wen Y, Qian D, Pan X, Zhang L. Effects of the hospital-communityfamily ternary linkage continuous nursing model on compliance, cognitive function, resilience, and quality of life for children with epilepsy: a retrospective study. Translational Pediatrics. 2022;11(2):239-48.

26. Korkmaz MF, Erdem-Uzun M, Korkmaz M, Ekici A. Adherence to Antiepileptic Drugs and the Health Literacy of Caregivers in Childhood Epilepsy. P R Health Sci J. 2020;39(1):45-50.
27. Loiselle KA, Ramsey RR, Rausch JR, Modi AC. Trajectories of Health-Related Quality of Life Among Children With Newly Diagnosed Epilepsy. Journal of pediatric psychology. 2016;41(9):1011-21.

Appendix 1: Characteristics of included studies table

TABLE 4. CHARACTERISTICS OF INCLUDED STUDIES

StudyID (ref)	Study design	n	Count ry	Age range; M (SD)	Adherence measure	Factors associated with higher adherence	Factors associated with lower adherence	Best practice to support adherence
Afsharkh as (2022) (11)	Cross- sectional	120	Iran	1–15yrs; 7.58 (3.6)	MMAS	 Higher parental education (p<0.05) Seizure type (p=.022) – focal impaired awareness seizure (57.1% adherence) 	 History of prenatal morbidities (p=.001) Seizure type (p=.022) – atonic seizures (11.1%) 	NR
Asiri (2022) (14)	Cross- sectional	133	Saudi Arabia	>1yr- 15yrs; NR	MARS	NR	1. Caregiver quality of life (p<.001)	NR
Aylward (2015) (23)	Longitudinal cohort study	117	USA	2–12yrs; 7.2 (2.9)	MEMS TrackCap	1. Higher familial SES (p=.003)	NR	NR
Bakula (2022) (19)	Randomised controlled trial	117	USA	NR; 7.5 (2.9)	MEMS TrackCap; SimpleMed+ Pillbox	 Higher familial SES (OR=.98, p<.001) Good family functioning (OR=.08, p=.032) 	1. Lower familial SES (OR=.98, p <.001) 2. Black, Asian, or multiracial ethnicity (OR=3.26, p =.009) 3. Black ethnicity (OR=2.90, p =.002) 3. Parent distress (OR=1.05, p =.027)	NR
Dima (2022) (10)	Cross- sectional	192	Ethiopi a	3m- 14yrs; 6.85 (4.25)	MMAS-8	1.Children with a family size of \leq 5 (AOR= 2.34, p =.03) 2. Average monthly family income of \leq 3000ETB (AOR=0.18, p=.005)	 Parent forgets to give medication (77.6%) Children with ≥5 family members (AOR=2.34, p=.03) Children with an average monthly family income of 	 Less complex treatment regimens should be prescribed for caregivers with low levels of literacy Free supply of AEDs to children living in poverty

StudyID (ref)	Study design	n	Count ry	Age range; M (SD)	Adherence measure	Factors associated with higher adherence	Factors associated with lower adherence	Best practice to support adherence
						 Duration of epilepsy 1year (AOR=5.83, p=.012) and 1-2yrs (AOR 4.58, p=.035) Absence of seizure attack in the last three months (AOR=.23, p=.001) 	<1000ETB (AOR=.18, p=.005) 4. Duration of epilepsy \leq 3yrs (AOR=4.58, p =.03) 5. Presence of seizure attack in last three months (AOR=0.23, p =0.001)	3. Regular provision of information about expected treatment response to children with epilepsy and caregivers
Furkan- Korkmaz (2020) (8)	Cross- sectional	154	Turkey	0-11yrs; NR	MMAS-8	 Younger child age (0– 5yrs) (OR=2.9, p=.007). Good caregiver health literacy knowledge (OR=0.8; p=.008) 	1. Younger child age (12– 18yrs) (OR=2.9, p=.007) 2. Poorer caregiver health literacy knowledge (OR=.8; p=.008)	NR
Gao (2022) (25)	Retrospective chart review	136	China	4-14yrs; 6.11 (NR)	MMCS-4	1. Hospital-community- family ternary linkage continuous nursing model ¹ (p < .05)	1. Routine nursing model (<i>p</i> <.05)	1. Adoption of a hospital- community-family linkage continuous nursing model can improve the compliance, resilience, and QoL of CYP with EP
Gutierrez -Colina (2018) (9)	Cross- sectional	194	USA	2–12yrs; NR	Barriers sub-scale of PEMSQ; MEMS TrackCap	NR	 Dislike taste (p<.05) Parent forgetfulness (p<.001) Child refusal (p<.001) 	1. Detailed assessment regarding parent forgetfulness is essential to inform types of support and interventions that caregivers need (e.g., providing clarification of treatment plans or using visual/auditory reminders)
Jacob (2017) (7)	Cross- sectional	3,316	Germa ny	>5- 13yrs; NR	MPR	1. Younger child age (≤5yrs) (OR=1.22, p=.004)	1. Comorbid Attention- Deficit Hyperactivity Disorder (OR=.81, p=.003)	NR

StudyID (ref)	Study design	n	Count ry	Age range; M (SD)	Adherence measure	Factors associated with higher adherence	Factors associated with lower adherence	Best practice to support adherence
						2. Living in Western Germany (OR=1.71, p<.001) 3. Comorbid asthma (OR=1.59, p <.001)		
Loiselle (2015) (22)	Longitudinal cohort study	91	USA	2–12yrs; 7.3 (2.8)	MEMS TrackCap	Predictors at diagnosis: 1. Higher familial SES (OR=1.058, p =<.001) 2. Good parent epilepsy knowledge (OR=1.095, p=.04) 3. Good family problem solving (OR=0.621, p=.001) 4. Good family communication (OR=1.611, p =.002) Predictors at 1yr post- diagnosis: 1. Higher familial SES (OR=1.065, p =.002) 2. Fewer parent fears/ concerns (OR=0.762, p=.01) 3. Lower parent life stress (OR=.980, p =.04)	Predictors at diagnosis: 1. Lower familial SES ($OR=1.058$, $p=<.001$) 2. Poorer parent epilepsy knowledge ($OR=1.095$, p=.04) 3. Poorer family problem solving ($OR=0.621$, p=.001) 4. Poorer family communication ($OR=1.611$, $p=.002$) Predictors at 1yr post- diagnosis: 1. Lower familial SES ($OR=1.065$, $p=.002$) 2. More parent fears/ concerns ($OR=.762$, $p=.01$) 3. More parent life stress ($OR=.980$, $p=.04$)	 Behavioural interventions to improve adherence-related factors should continue to be modified and used with paediatric epilepsy, particularly at critical time points (e.g., one- month after diagnosis, one-year after diagnosis) MDT care may be beneficial throughout the treatment process to address key parent and family behavioural predictors of adherence
Ma (2019) (20)	Non- randomised controlled trial	1031	China	>1- 13.9; 4.5 (NR)	SMAQ; Therapeutic Drug Monitoring (TDM)	1. Repeated intervention sessions delivered by pharmacists (p<.01)	NR	1. Active education by a pharmacist can improve adherence to valproic acid therapy in paediatric epilepsy
Modi (2016) (17)	Randomised controlled trial	50	USA	2–12yrs; 7.6 (3.0)	MEMS TrackCap	STAR ² intervention improved adherence via: 1. epilepsy knowledge (<i>p</i> <.05) 2. self-management (<i>p</i> <.01) 3. epilepsy management (<i>p</i> <.01)	NR	1. Continued monitoring and engagement around adherence behaviours is critical to maintaining improvement

StudyID (ref)	Study design	n	Count ry	Age range; M (SD)	Adherence measure	Factors associated with higher adherence	Factors associated with lower adherence	Best practice to support adherence
Modi (2021) (18)	Randomised controlled trial	56	USA	2-12yrs; 7.64 (NR)	MEMS TrackCap or SimpleMed+ Pillbox	1. STAR intervention (<i>d</i> =.83, <i>p</i> =.04)	NR	1. Identifying adherence barriers, which can change over time, and teaching families problem-solving strategies may allow for a more proactive approach to addressing adherence in the clinic setting
Nazziwa (2014) (12)	Cross- sectional	122	Ugand a	6m– 16yrs; NR	Self-report questionnair e; Assay of serum drug levels of the AEDs	 Having another primary caregiver other than the CYP's mother (AOR=0.25, p=.015) Focus groups (qualitative): Availability of drugs Involvement of family members in care Observing improvements in child's health, as a motivation for adherence 	 Caregiver having an occupation (AOR=5.83, p=.03) Focus groups (qualitative): Difficulty obtaining prescription Inadequate counselling and awareness about duration of taking antiepileptic drugs Negative beliefs and perceptions regarding AEDs Forgetfulness 	1. Clinicians should ensure regular weighing and review of drug doses to promote adequate dosages for children with epilepsy
Paschal (2015) (13)	Cross- sectional	146	USA	1-12yrs; 5.8 (2.1)	Self- reported: missed medication doses, missed medical appointment s, seizure frequency	1. Higher familial SES $(r_{pb}=729, p=.029)$ 2. Good caregiver health literacy knowledge $(r_s=828, p=.001)$ 3. Having health insurance $(r_{pb}=.582, p=.032)$ 4. Higher parental education $(r_s=-682, p=.041)$ 5. Older child age $(r_{pb}=.349, p=.003)$	1. Lower familial SES $(r_{pb}=729, p=.029)$ 2. Poor caregiver health literacy knowledge $(r_s=828, p=.001)$ 3. Not having health insurance $(r_{pb}=.582, p=.032)$ 4. Lower parental education $(r_s=-682, p=.041)$ 5. Younger child age $(r_{pb}=.349, p=.003)$	 Strategies for addressing adherence should include input from the families and individuals affected by the disorder Health education efforts can be instrumental in providing parents the skills required to obtain the support they need to work with their children in becoming co-managers of their epilepsy care.

StudyID (ref)	Study design	n	Count ry	Age range;	Adherence measure	Factors associated with higher adherence	Factors associated with lower adherence	Best practice to support adherence
	5			M (SD)		5		
								Interventions that consider parent health literacy might help.
Ramsey (2017) (21)	Longitudinal cohort study	118	USA	1–12yrs; 7.24 (2.93)	PEMSQ; MEMS TrackCap	NR	One month post-diagnosis: 1. Parent forgets to give medication (p=.03) Twenty-five months post- diagnosis: 2. Swallowing difficulties (p=.01) 3. Child refusing medication (p=.04)	 Organisation-focused strategies, including reminders via technology (e.g., cell phone reminders and text messaging services) or incorporating AEDs into daily routines (e.g., pairing with brushing teeth and use of pillbox) can help address barriers like forgetfulness Providers should assess and provide interventions for swallowing difficulties at diagnosis and throughout treatment It is important that providers continue to assess barriers over time and understand that barriers may impact adherence differentially over the disease course
Saengow (2018) (16)	Randomised controlled trial	214	Thaila nd	1m– 15yrs; 7.6 (NR)	MMAS-8	1. Patient education video about epilepsy ³ (p < .001)	NR	NR
Shetty (2016) (24)	Retrospective chart review	320	UK	7-14yrs; NR	Adherence Index (% ratio of the encashed AED over recommend ed AED)	1. Younger child age (p=.019)	1. Older age child $(p=.019)$ (the odds of adherence decreases by a factor of .81 with every three years of age)	NR

StudyID	Study	n	Count	Age	Adherence	Factors associated with	Factors associated with	Best practice to
(ref)	design		ry	range;	measure	higher adherence	lower adherence	support adherence
				M (SD)				
wang (2023) (15)	Cross- sectional	156	China	2–15yrs; 7.68 (2.55)	MMAS-8	1. Age \leq 6yrs (OR=2.104, p<.05) 2. Length of epilepsy diagnosis/course \leq 3yrs (OR=2.661, $p<.05$) 3. Monthly household income $>$ 5000 RMB (OR=2.812, $p<.05$) 4. Higher parental education (OR=1.977, p<.05) 5. Number of drugs taken \leq 2 (OR=3.02, $p<.05$)	1. Age \geq /yrs (OR=2.104, p<.05) 2. Length of epilepsy diagnosis/course \geq 4yrs (OR=2.661, p <.05) 3. Monthly household income \leq 5000 RMB (OR=2.812, p <.05) 4. Lower parental education (OR=1.977, p<.05) 5. Number of drugs taken \geq 3 (OR=3.02, p <.05)	 In follow-up medication education for patients, the importance of timely, dose-based and frequency-based medication should be emphasised, especially the management of timely medication and self-adjustment of medication The guardian should provide more psychological support, such as praise and reward for the children after medication to help them establish a positive attitude and improve AED adherence Parents of children should improve their cognitive ability and knowledge about epilepsy Early prevention and nursing intervention measures should be taken for children affected by (factors outlined above) to improve the medication compliance of children. Drug treatment should be based on the type of seizures and other individual factors. If necessary, parents should be invited to participate in the

StudyID (ref)	Study design	n	Count ry	Age range; M (SD)	Adherence measure	Factors associated with higher adherence	Factors associated with lower adherence	Best practice to support adherence
								development of treatment plans. 7. Regular telephone follow-up can remind children of the importance of taking medicine according to the doctor's advice
Webster (2017) (6)	Qualitative	24	UK	3–13yrs; NR	Semi- structured interviews	1. Child perceives taking medication as a status symbol	 Dislike taste of medication Child embarrassed to take medication Swallowing difficulties Child views medication as unpleasant necessity Child initially saw treatment as a cure Child being independently responsible for taking medication 	NR

¹Hospital-community-family ternary linkage continuous nursing model consisted of 1) establishing a networked platform, a ternary linkage group, hospital responsibilities, community responsibilities and family responsibilities.

²Supporting Treatment Adherence Regimens' (STAR) is an education and problem-solving intervention for young children with epilepsy and their families.

³An 8.52-minute video animation for educating patients and caregivers, including six basic tenets (diagnosis of epilepsy, aetiology of epilepsy, treatment of epilepsy, first aid seizure care, prognosis of epilepsy, and safe activity for epilepsy), supervised by paediatric neurologists.

MARS, Medication Adherence Rating Scale; MCR, medication possession ratio; MEMS, Medication Event Monitoring System; MMAS, Modified Morisky Medication Adherence Scale; MMAS-8, 8-item Morisky Medication Adherence Scale; MMCS-4, Morisky Medical Compliance Scale 4-item Version; Self-Management Questionnaire (PEMSQ); SMAQ, Simplified Medication Adherence Questionnaire