Adherence to Antiepileptic Drug Therapy

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What is adherence?
Adherence is defined as the extent to which a person's behavior coincides with medical or health advice.[1,2]

What is the prevalence of non-adherence to AEDs in epilepsy?
AED non-adherence ranges from 25-50%[3-6] in adults and 43-58%[7,8] in children with epilepsy.

Why does adherence matter?
The consequences of non-adherence can be severe for patients with epilepsy. Non-adherence can lead to any of the following:

- Continued seizures[9-11]
- Poor quality of life[12,13]
- Unnecessary antiepileptic drug (AED) changes[14]
- Higher healthcare costs[15]
- Higher healthcare utilization[15-17]
- Pharmacoresistence[18]
- Death[5,19]/sudden unexpected death in persons with epilepsy[20]

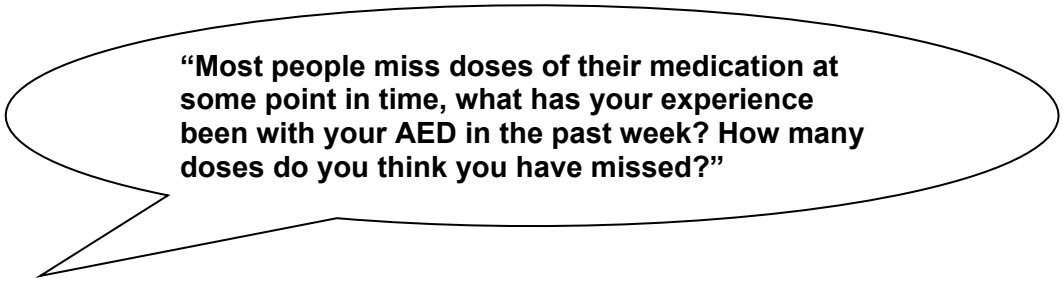
How do you measure adherence?
There are a variety of methods to measure adherence, both clinically and in research. In the table below, strengths and weaknesses of the various approaches are listed.

Table 1: Strengths and Weaknesses of Different Adherence Measurement Methods

TYPE	STRENGTHS	LIMITATIONS
Self-report	▪ Easy to obtain ▪ Assesses patient perception ▪ Inexpensive ▪ Comprehensive ▪ Can obtain multiple perspectives	▪ Social desirability ▪ Recall biases ▪ Cannot be obtained from young children
Provider Estimate	▪ Inexpensive ▪ Easy to obtain	▪ Generally an overestimate ▪ Poor accuracy

	▪ Simple	
Pill Counts	▪ Inexpensive ▪ Objective	▪ Variable prescription sources or unknown source ▪ Does not account for samples ▪ Presumptive dosing ▪ Potential for medication discarding ▪ Requires patients bring prescriptions back to clinic
Prescription Refills/ Medication Possession Ratio	▪ Easy to collect in managed care setting ▪ Inexpensive	▪ Presumptive dosing ▪ Potential for medication discarding
Electronic monitors	▪ Continuous measurement of adherence ▪ Provides precise data ▪ Provides objective data	▪ Expensive ▪ Technical problems ▪ Lost monitors ▪ Presumptive dosing
Blood serum levels	▪ Objective ▪ Quantifiable ▪ Sensitive to dosing regimens	▪ Affected by pharmacokinetic variation ▪ Short-term-only reflects past 48-72 hours ▪ Invasive
Hair serum levels	▪ Objective ▪ Quantifiable ▪ Sensitivity ▪ Less invasive than blood serum testing	▪ Debatable effectiveness ▪ Affected by pharmacokinetic variation
Saliva concentration	▪ Objective ▪ Quantifiable ▪ Painless (no venous access needed)	▪ Debatable efficacy ▪ May be affected by pharmacokinetic variation ▪ Needs calibration to individual saliva production

The most frequently used adherence measures in clinical practice are self-report, provider estimate, and blood serum levels. Blood serum levels are the most objective but only reflect adherence in the 48-72 hours prior to the blood draw. While self-report and provider estimates are easy to obtain and inexpensive, they are notoriously inflated and inaccurate unless a validated and reliable questionnaire is used. For example, the Morisky Medication Adherence scale[21] is a commonly used 4-item self-report measure. Epilepsy-specific self-management and adherence measures are also valuable, including the Pediatric Epilepsy Medication Self-Management Questionnaire[22] and the Adult Epilepsy Self-Management Measurement Instrument.[23] If clinicians cannot use validated instruments, open-ended and non-judgmental questions can be asked, such as:

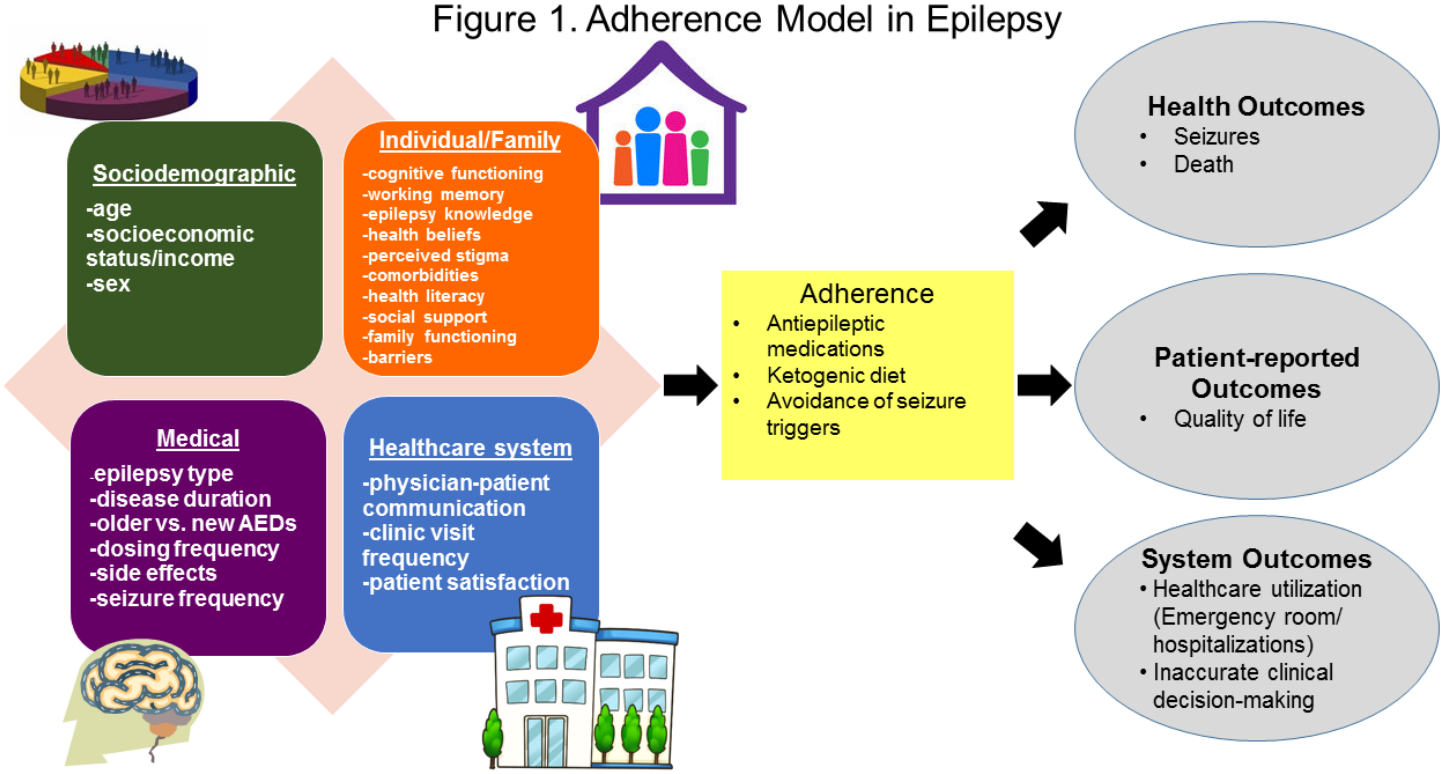


In the research context, we highly recommend using either the Medication Possession Ratio (MPR) or electronic monitors, depending on the type of research being conducted. For example, electronic monitoring data can provide specific and individualized information for intervention, while MPRs can provide population estimates of adherence.

What puts a patient with epilepsy at risk for non-adherence?

A model of risk factors and outcomes for non-adherence is presented in Figure 1. The model is not exhaustive, but represents major drivers of adherence in patients with epilepsy. Predictors or factors that influence adherence fall into four major categories: sociodemographic, medical, individual/family, and healthcare system.

Figure 1. Adherence Model in Epilepsy



Sociodemographic Factors:

- ***Age.*** Adherence is worse for adolescents and young adults[24,25] compared to other age groups.
- ***Socioeconomic status/Income.*** Low income or socioeconomic status is associated with non-adherence.[8,26]
- ***Sex.*** No major sex differences have been found consistently; however, adherence needs to be carefully examined in pregnant women who may worry about the effects of AEDs on the fetus[27].

Medical Predictors:

- ***Epilepsy Type.*** Some studies find lower adherence for individuals with localized seizures[17] whereas others find lower adherence for generalized seizures.[25,28]

- ***Disease Duration.*** Adherence typically declines over time,[29,30] with the best adherence exhibited in the first 6 months.

- ***Older versus newer generation AEDs.*** Higher adherence is associated with the use of newer versus older AEDs[3,17]

- ***Dosing Frequency.*** Less frequent dosing is ideal to improve adherence[6], with non-adherence being worse for dosing that is greater than 2 times a day.[3]

- ***AED Side Effects.*** Real or perceived side effects of AEDs is related to non-adherence.[30-33]

- ***Seizure frequency.*** Although seizures are usually considered an outcome of poor adherence, they may also negatively influence adherence behaviors.[34-36]

Individual and Family Predictors of Adherence:

- ***Cognitive Functioning.*** The patient's and family's ability to think clearly and problem-solve barriers that impact adherence[37] (e.g., change in schedule, titration or switch in medicines) results in better adherence compared to individuals or families with cognitive difficulties (e.g., low IQ[38]).

- ***Executive Functioning.*** Better memory is associated with better adherence.[39]

- ***Lack of Knowledge.*** Knowledge about epilepsy and its treatments is associated with better adherence.[37,40,41]

- ***Health Beliefs.*** Patient beliefs and perceptions about their health and their illness impact adherence behaviors.[34,42-45]

- ***Perceived Stigma.*** Perceived stigma is associated with worse adherence.[30,46]

- ***Psychological Comorbidities.*** Depression,[39,45,47,48] anxiety[48], and behavior problems[38] negatively impact adherence. Parental fears and stress are also predictive of AED non-adherence.[49,50]

- ***Health Literacy.*** Lower health literacy (e.g., the degree to which individuals have the capacity to obtain, process, and understand basic health information and the services need to make appropriate health decisions[51]) is associated with poorer adherence.[52]

- ***Social support.*** Increased social support is a predictor of better adherence.[30,45,53]

- ***Family functioning.*** Better family problem-solving and communication are significant predictors of adherence in children.[37]

- ***Barriers.*** Individual and family-identified barriers can impede adherence and include forgetting[22,31,32,34,54-56], difficulty obtaining medication[32,57], difficulty swallowing pills, poor AED taste, embarrassment in taking AEDs in front of others, and competing activities/inconvenience.

Healthcare System Predictors of Adherence:

- ***Physician-Patient Communication.*** Poor communication between providers and patients results in worse adherence (e.g., misunderstanding dosing).[33]

- ***Clinic Visit Frequency.*** More frequent clinic visits typically results in better adherence,[58,59] which may be due to more frequent monitoring or white coat adherence (e.g., adherence increases prior to and after clinic visits).

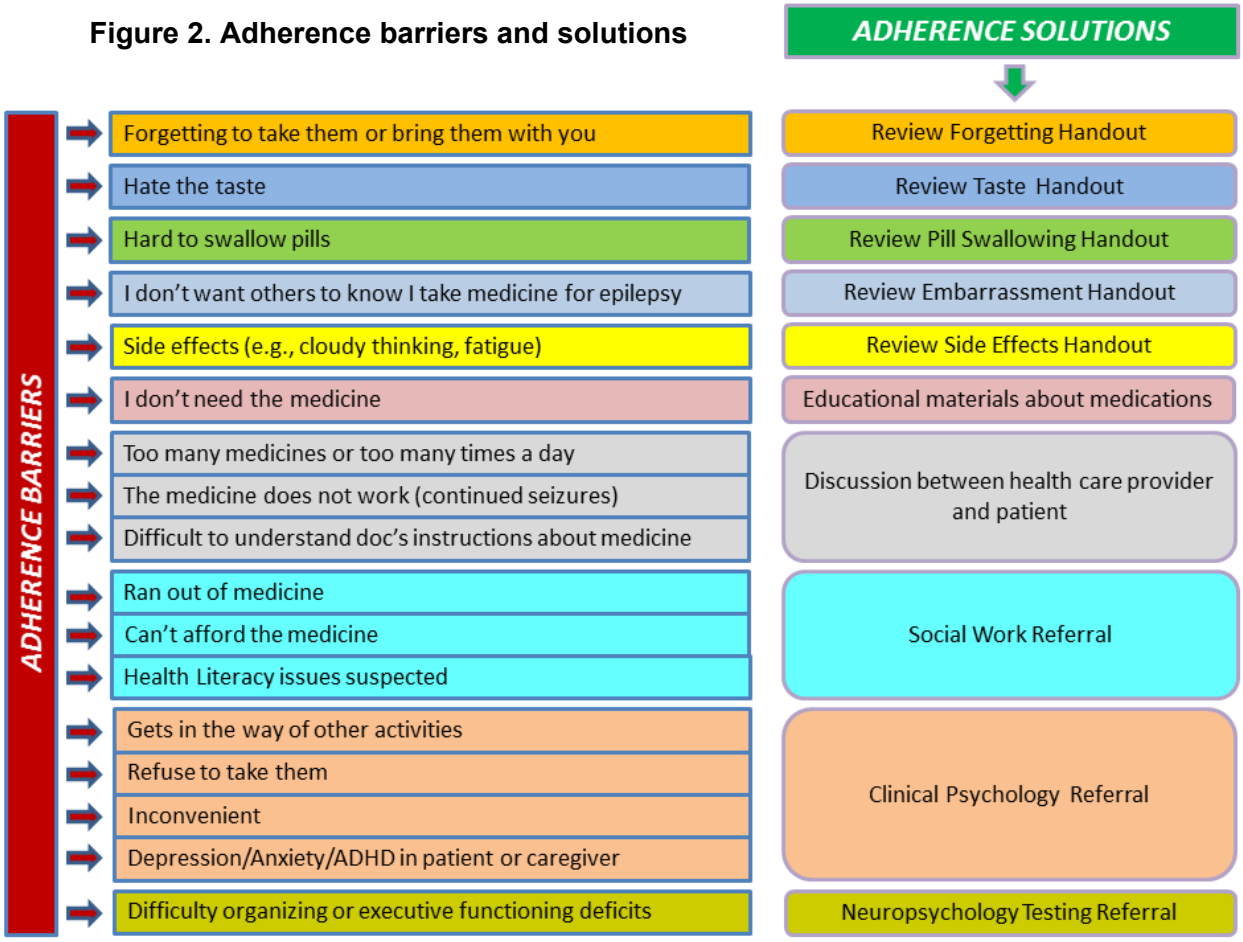
- ***Patient Satisfaction.*** A positive relationship between patient and physician results in better adherence.[32,45] Additionally, patient satisfaction with the healthcare they receive more broadly (e.g., shared decision making) can improve adherence.[50]

How can we improve adherence?

A 2017 Cochrane review of adherence interventions in epilepsy identified 12 studies, with 8 focused on adults, three focused on children and/or caregivers and 1 focused on all ages.[60] The review indicated that intensive reminders and multi-component interventions (e.g., education, problem-solving) demonstrate positive results. However, higher evidence-based interventions to improve adherence are still needed.

Notably, strategies to improve adherence should be tailored to individual patients and their relevant risk factors. Figure 1 identifies the most common adherence barriers and highlights ways for healthcare providers to address these barriers in the clinical setting. A handout regarding how to help patients who forget to take their AEDs is at the end of this document and can be used in clinical settings. A multidisciplinary approach, involving social workers and psychologists, may be necessary for some barriers.

Figure 2. Adherence barriers and solutions



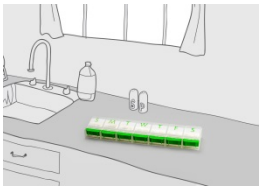
Remembering to Take Medication

Having a child who needs medication every day can be a challenge. Many families *intend* to give their child's medication as prescribed, but sometimes simply forget. Your child may need to take medicines several times a day and it is hard to remember if you gave each dose. Here are some tips that may help you.

Use signs or symbols

- Post notes in places you see often, like the refrigerator, bathroom mirror or front door. Change the location of the notes every once in a while.
- Wear a bracelet or some other object that reminds you to give the medicine.
- Make yourself a calendar or schedule that you can put on the refrigerator or someplace else that you will see.

Keep the medicine where you can see it



- You want to keep the medicine where children cannot reach but where you can see them
    - Use a pillbox and place it at the back of the kitchen counter
    - Keep it in a place that you walk by every day

Link giving the medicine with a routine

- At mealtime
- When your child brushes their teeth
- At the same time each day, like at 8 am and 8 pm
- Give your child their medicine at the same time you take your medicine
- Come up with a time that has meaning for your family

Use technology as a reminder

- Set an alarm – on your cell phone, stove, TV, FitBit, or other electronic device
- If your child is taking medicine at school, send them a text message as a reminder
- Put a free smartphone app on your phone – ask us for more information about this!

General Tips for Parents:

Plan ahead if you are going on vacation or changing your routine in some way

- Try to get extra medicine from the pharmacy if you are leaving the area
- Print out a medication schedule that you can take with you
- Keep extra doses of medicine in your purse, backpack or sleepover bag in case you forget to bring their medicine with you.

Plan for "Remembering to Take your Medicine"

Plan to help give every dose of medication:

Which plan did you pick?

☐ Visual reminder ☒ Pair with Routine ☐ Person reminder ☐ Alarm ☐ Smartphone App

Who will be involved?

Where will this happen?

When will this happen?

How will you know it's working?

If this plan does not work, we will try:

☐ Visual reminder ☐ Person reminder ☐ Smartphone App

☐ Pair with routine ☐ Alarm

If we need help, we can call:

☐ Nurse: _____

☐ Social Worker: _____

☐ Other: _____

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