# How to Improve Clinical Outcome of Epileptic Seizure Control Based on Medication Adherence? A Literature Review

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## Abstract

Anti-Epileptic Drugs (AEDs) are the main therapy for epilepsy to prevent seizures. Non-adherence situation plays an important factor in the failure of seizure control. Such a condition may generate several impacts on clinical, social, and economic aspect. Several methods are used to measure adherence in epilepsy patients, including direct and indirect measurement. The direct measure involves measurement of drug levels in hair or body fluids such as blood and saliva. Whereas, indirect measure involves the non-biological tools, for example, a self-report measure, pill counts, appointment attendance, medication refills, and seizure frequency. Numerous factors may affect adherence in epilepsy patients, such as age, sex, and seizure aetiology, seizure sites, which are categorised as irreversible factors and hardly to be improved. However, there are factors that can be influenced to improve adherence such as patient knowledge, medication, cultural, health care professionals, and national health policies, which are related to treatment and education factor which is associated with behaviour to be likely adherence.

## Introduction

Epilepsy is an unprovoked seizure condition, while epileptic status is a seizure activity that does not improve spontaneously or seizures repeatedly without any improvement between seizures [1] [2]. Based on the duration, seizure, when the duration is less than 5 minutes, if the duration between 5 to 30 minutes is categorised as prolonged seizure, while status epilepticus is defined as seizure, occurs with duration greater than 30 minutes, or repeated seizure activity (2 x or more) with or without any improvement in awareness among repeated seizures [3]. Epilepsy is a chronic brain disease characterised by recurrent seizures (2 or more times), involving partial body, involuntary movements, and often accompanied by loss of consciousness and control of gastrointestinal or urinary tract function. Approximately, 4 to 10 in 1000 people are predicted suffering from active epilepsy and persistent seizures. Additionally, a study of epilepsy in developing countries population indicated that the prevalence of epilepsy is higher, with a ratio of 7 to 14 in 1000 people [4].

Anti-epileptic drugs (AEDs) are the main therapy for epilepsy to prevent seizures thoroughly and an easy to follow a treatment schedule. Approximately 67% of patients with epilepsy could reduce or even combat their seizure frequency effectively using AEDs [5]. As a result, it is indicated that the substance could control epilepsy symptom, which is shown as seizure free at least for 18 months [6]. On the other hand, uncontrolled epilepsy is illustrated with considerably uncontrolled seizures with a high frequency of its symptoms. A study implied that this condition might cause disruption and even degradation of the quality of life of the patients [7].

Non-adherence is considered as one of the most important factors for controlling epileptic

seizures. It is acknowledged as a worldwide health problem and has impacts on clinical, social, and economic outcomes [8]. Non-adherence includes prescription or delay inappropriate failure dose, and missed dose of treatment [9]. Many retrospective studies have demonstrated the most crucial impact of non-adherence in AEDs. It was identified that non-adherence would increase costs due to hospitalisation as well as a decrease in productivity [10] [11] [12]. Therefore, identifying obstacles to AEDs adherence is important to allow practitioners are developing appropriate strategies to improve adherence [10]. Patients need support and specific information to achieve adherence.

This literature review is developed to address the importance of AEDs adherence factors for improving clinical outcomes for patients with epilepsy.

## Discussion

Adherence is the extent to which a person's behaviour-taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider [13]. Adherence implies that health professionals have a responsibility to form a therapeutic relationship with patients, to encourage them to agree to a recommended treatment regimen. This means that patients should be better informed about their medicines, and in theory, have greater power to decline treatment [14].

Adherence in AEDs, defined as the extent to which patients follow the agreed instructions given by the prescribers and persistence in a regimen of treatment epilepsy such as the duration of initiation for discontinuation of therapy [15]. The World Health Organization (WHO) has concluded that increasing the effectiveness of adherence may have a greater impact on the health of the population than any improvement in specific medical treatments [16].

Drug adherence can be used to predict the remission condition in epilepsy. Non-adherence term may cause breakthrough attacks at several months or years after the previous episode of seizure [17]. It is indicated that patients who adhere a routine use AEDs, have 6, 12 and 24 months continuous remissions compared to those non-adherence patients. An adherence to epilepsy is a milestone of the success and the effectiveness of pharmacological therapies. It has impacts in helping to prevent seizure events and reducing the cumulative negative impact of seizures in daily life [18].

Non-adherence of AEDs in epilepsy patients may cause an increased risk of convulsive status epilepticus [19]. And the most serious consequence of non-adherence would be the increased risk of sudden

unexplained death in epilepsy patients. Due to those consequences, identifying the barriers to adherence of AEDs is observed as imperative to allow practitioners are developing some appropriate strategies to improve adherence rates [20].

**Table: 1 Method to Measure Adherence in Epilepsy Patients [21]**

| Measures adherence | Method | Disadvantages | Advantages |
|---|---|---|---|
| **Direct Measures** | | | |
| Plasma or serum Antiepileptic drug levels | Plasma or serum levels of medication are measured | Patient factors (albumin, hepatic & kidney condition) and drug types can Cause measurement variability | Commonly used, well understood by Clinicians, effective in extreme low adherence situations, to determine the range of therapy and the possibility of overdose-related side effects |
| Detection in human hair | Hair medication levels analysed using gas or liquid chromatography | Researchers disagree on the effectiveness | Less invasive than blood testing |
| Saliva antiepileptic drug concentration | Levels of aeds excreted in saliva are measured | Measurement must be calibrated to individual saliva production and serum/saliva medication ratios | Painless, does not require venous access (good for pediatric and geriatric patients); as accurate as blood plasma or serum monitoring |
| **Indirect Measures** | | | |
| Self-report measures | Patient reports medication adherence through methods such as survey or interviews | No standardised and validated Measures exist for epilepsy treatment adherence; can be inaccurate due to patient misperceptions or tendency to give a desirable response | Low cost; not physically invasive; adaptable to the target population |
| Pill counts | Doses monitored through counts of remaining pills or use of an event recorder | Does not guarantee that medication is taken outside of a controlled environment | Not physically invasive; event recorders measure regularity of dosing |
| Appointment attendance | The regularity of attendance at appointments is documented | Tends to be the limited term, while epilepsy is lifelong; not proof of proper medication use | Easy to collect information can be related to others adherence behaviours |
| Medication refills | Medical/pharmacy records reviewed to see if medication is refilled at appropriate intervals | Not proof of proper medication use | Can be correlated to blood serum levels |
| Seizure Frequency | The frequency of seizures is logged over time | Non-adherence patients may not have frequent seizures | An essential indication of the degree to which epilepsy is managed |

From the literature, there are two types of poor adherence, which are primary non-adherence and secondary non-adherence. Primary non-adherence is implied in a condition where the patient does not have a prescription for medicine dispensed. Meanwhile, the secondary non-adherence is defined as the patient has medicine dispensed but does not take medicine according to the prescribed regimen [14]. Another study implied there are three types of non-adherence: (i) in medication; (ii) in dietary/exercise; and (iii) in an appointment. First, non-adherence in medication defined as a non-adherence which includes failure to have the prescription dispensed or renewed, the omission of doses, errors of dosage, incorrect administration, errors in the time or frequency of administration, and premature discontinuation of the drug regimen. Second, a non-adherence in dietary/exercise occurs if the patient fails to follow the diet and exercise recommendations. Last, a non-adherence in an appointment occurs if the patient fails to come at clinics for the scheduled check-up [15].

Two different methods to measure adherence are direct and indirect measurements. Direct measurement includes a measurement of drug levels in hair or body fluids such as blood or saliva. Indirect measurement involves non-biological tools, such as self-report measures, pill counts, appointment attendance, medication refills, and seizure frequency

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(Table 1) [21].

A study on adherence of epilepsy patients with an indirect measure to treatment includes adherence to outpatient epilepsy treatment in Saudi Arabia. There were 38.3% of patients who did not adhere to the prescribed drug based on self-reported measurement of Morisky Medication Adherence Scale (MMAS) score [9]. Another study on adherence in some hospitals in Ethiopia for treating epilepsy indicated that prevalence of AEDs non-adherence is about 37.8% [22].

WHO has identified five dimensions of influencing factors on patient adherence, which are: (i) social/economic factors; (ii) health system/healthcare team factors; (iii) condition-related factors; (iv) therapy-related factors; and (v) patient-related factors [13]. A systematic review regarding adherence in epilepsy therapy implied that the factors that influence patient adherence are including factors in patients, confidence in treatment, depression and anxiety, treatment management, disease factors, factors related to medication, health care factors, and socio-economic factors (Table 2) [20].

Patient age is associated with different levels of adherence. For example, adolescents tend to deny that a medication regimen can impose on their lives. On the other hand, a patient with older ages might be not adhered to medication due to the complexity of medication regimens and presence of multiple comorbidities [14].

The seizures that characterise primary epilepsy have been considered to be signs of demonic possession. It also can be affected by depression and anxiety patients, thus influencing the adherence. A study from Shallcross et al., [23] about non-adherence to a regimen with AEDs reported that there is a significant correlation between being depressed and non-adherence with a score of -0.379 on Pearson correlation coefficient and rates of probability values being $P < 0.05$. Another study conducted in Southern Ethiopia indicated that the most common of non-adherence were forgetfulness (75.4%) and ran out of pills (10.8%). Furthermore, the study illustrated that duration of epilepsy treatment, marriage status, level of education, and the absence of comorbidity may affect adherence to medication.

Medication factor is another important factor that might affect adherence. For example, complex dose regimens are associated with poor adherence due to the difficulties of drug administration. Medication regimens can be complex because they contain multiple different medicines (polypharmacy), or because they need to be taken frequent times a day. A study indicated that adherence is much lower with regimens that require medication to be taken three or four times daily, by 65% and 51% respectively compared to once daily dose [24]. Moreover, two types of research about adherence in patients with epilepsy to take AEDs observed that

forgetting the dose and administration time were given contributions for non-adherence [25] [26].

Another patient's related factor that influence of adherence is patient's belief in medication and health professionals. The types of patient's beliefs about medicines are perceived efficacy of medicine, the danger of becoming immune over time, unnaturalness of manufactured medicines, the danger of addiction and dependence, anti-drug attitude and balancing risks and benefits that all types of patient's belief can influence of adherence [14]. To overcome the problem, a good relationship and communication between patients and health professionals are likely in helping patients to adhere to their medication. Maintaining contact between patients and health professionals is required to achieve patient adherence [27]. Conversely, healthcare systems with poorly trained or overworked health professionals, short consultation times, inadequate patient education and follow-up, and lack of help for patients to pay for treatment can contribute to poor adherence [14]. Hovinga et al., [28] investigated that adherence percentage in patients who trust their doctor is higher by 34% compared to 17% in patients who have lower trust. This indicates that the impact of the patient and physician relationship can affect adherence. Furthermore, adherence participants reported being comfortable discussing missed medications with their doctor can be decreased non-adherence medication.

Other potential factors that may cause non-adherence in patients with epilepsy from an area with the low-quality health care system are level of healthcare development, cultural belief, economy, distance from health care facilities, supply antiepileptic drug, lack priority in national health policies, and belief in traditional medicine [29]. In some area, there were various misunderstandings and stigma about epilepsy that can affect adherence to epilepsy. A study in Vientiane, the capital city of Lao Peoples' Democratic Republic (Lao PDR), observed that epilepsy was acknowledged as a disease caused by supernatural powers or ancestral factors [30]. This negative stigma may diminish appropriate treatment for patients with epilepsy [31]. Moreover, the stigma may affect the level of knowledge about the proper treatment of patients, their family, and the society. The low level of knowledge about the treatment would trigger the trust in traditional medicine utilisation [29].

**Table 2: Factors Affecting Medication Adherence in Epilepsy Patients**

| Aspect | Factors affecting medication adherence in epilepsy patients, ethnic origin (the cultural belief that epilepsy is a disease that has supernatural manifestations (associated with ancestors or evil spirits) |
|---|---|
| Patients factors | Age, sex, confidence in treatment, depression & anxiety |
| Disease factors | The onset of epileptic, aetiology of the seizures, the location of the epileptogenic zone |
| Medication factors | Treatment management (monotherapy or polytherapy), adverse effect of AED, beliefs in medication |
| Health care factors | Belief in health care providers (clinician, pharmacist) |
| Socioeconomic factors | Cost of treatment and income patients |
| Distance from healthcare facilities | The measure of distance from the health service can affect the level of adherence and the type of treatment the epilepsy patient receives |
| National health policies | The lack of prioritisation in national health policies can affect the treatment of epilepsy |

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Essential strategies to improve medication adherence with long-term therapy involve multiple interventions are: more convenient care, comprehensive information, a reminder to take medication, self-monitoring of treatment effectiveness, psychological therapy, and telephone follow-up [14]. Pharmacological intervention in people with epilepsy is only one aspect of their management in medication. Patients with epilepsy also require support from the society as having epilepsy has a widespread effect and impact psychologically on the social life [18].

Another approach to improve adherence is the involvement of other health workers such as pharmacist in the provision of education and changes in the behaviour patterns of epilepsy patients to treatment. A study in China described that providing educational interventions through counselling could alter the patient behaviour to be more concern about the administration schedules. This may provide a better effect on the level of medication adherence with a reduction in the percentage of the forgetful taking of drugs from more than 70% to 45% [32].

According to Cochrane database of systematic reviews, the strategies for improving adherence to AEDs consist of three interventions, which are educational, behavioural, and mixed interventions [33]. Additionally, several supporting approaches, such as reminder systems, cognitive educational, behavioural counselling, social support (family member support), and multifaceted interventions (reminder systems combined with cognitive, educational interventions) were observed as efficient methods to improve adherence [34] [35] [36].

Communication and information about pharmacological treatment and diseases are important. Providing comprehensive information as an education intervention must be focused not only on patients but also on others like family. To achieve better adherence, it is required to provide information to the patient about their disease, how to manage missing dose, the importance of adherence, in need of adopting patient-centered care, and sharing decision. Decreasing number of patients who missed the AEDs along with an increased percentage of patients taking the AEDs were the results of a positive effect of the educational intervention. Education has become the most common strategy used by many researchers to improve adherence [32].

Health education is a powerful tool, which can give a positive impact on both drug adherence and self-management ability in patients with epilepsy. From a study from Dash et al. [18], it is observed that the epilepsy health education group, can affect different MMAS score from 6.58 to 7.53 (P = 0.001), and indicated that health education is significant to improve adherence.

Another research about the impact of pharmacist educational interview on medication of Saudi Arabia showed a significantly different result in post-intervention for epilepsy patients with education intervention (P = 0.024) [37]. Medication education provided by the pharmacist helped to improve adherence, seizure control, and the knowledge of AEDs.

Provision of an educational intervention on epilepsy treatment, especially in a region that has a belief that epilepsy is a disease with ancestral cultural-influence should be conducted together with cultural approaches to the family and carried out continuously with long-term education [29]. Family support is a major strategy in the treatment of epilepsy, but it is challenging when families feel ashamed of having a family with epilepsy [38] [39]. Hence, communication and information about the disease and therapy for patients with epilepsy must be provided as an educational intervention to the family as well. In other words, an intervention with a single component or intervention (information or education) seems to be ineffective to improve adherence or other clinical outcomes, but there is some evidence that education intervention may improve knowledge.

Behavioural interventions are characterised by the cognitive behavioural techniques and therapies focused on dysfunctional emotions, behaviours and cognitions with the aim to promote healthy lifestyles and positive changes toward symptoms or treatment [40]. Additionally, behavioural interventions are aimed to change individual behaviour in those aspects related to their daily life, which can modify patient's behaviour toward treatment. Intensive treatment reminders provide favourable effects on adherence (moderate-quality evidence) and can be conducted by suggesting the patient consume the drug with the place and other routine activities, thus minimising the forgetting to take the drug. This tool for improving adherence in patients who are forgetting to take their medications, much less research has shown that forgetfulness is found to be the main reason for non-adherence in patients with epilepsy [41].

Mixed intervention is a combination of one or more interventions, both educational and behavioural, which can be performed by health professionals. The mixed intervention was intended to help patients incorporate drug administration into their daily lives. The European Declaration on Epilepsy recommends interdisciplinary action to help people with epilepsy understand their condition and do the search for a proper treatment possible in order to improve their quality of life such as pharmaceutical care and give significantly improves quality of life (QOLIE-31 score for the intervention group was 12.45 points (P-value < 0.001) compared to the control group it was 2.61 (P-value = 0.072) [17]. All interventions to improve the quality of treatment of epilepsy patients should be based on local perceptions, social conditions and cultural backgrounds as well as the spirits possession of epilepsy patients [31]. And understanding why patients do not take their medicines can help to avoid some of this frustration and, in some cases, enable

health professionals to improve patient adherence.

In conclusion, adherence to AEDs for patients with epilepsy is an important factor and affects the outcome of seizure control. Several irreversible factors may affect treatment adherence in epilepsy patients, including such as age, sex, seizure aetiology, seizure sites. However, there are reversible factors that can be altered by conducting the approaches to improve patient adherence including patient knowledge and treatment regimens, cultural factor, health care factors, and national health policies. Various interventions to improve clinical outcome of epileptic seizure control are behaviour interventions, educational or combination of some of this intervention.

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