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COLLEGE OF HEALTH SCIENCE

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DEPARTMENT OF PHARMACOLOGY AND CLINICAL PHARMACY

Assessment of Health-Related Quality of Life, Treatment Outcome, Medication Adherence, and Associated Factors among Epileptic Patients at Meklle City Hospitals: A Multicentre Observational Study.

July, 2024 G.C

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Assessment of Health-Related Quality of Life, Treatment Outcome, Medication Adherence, and Associated Factors among Epileptic Patients at Meklle City Hospitals: A Multicentre Observational Study.

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This is to certify that thesis prepared by G/micheal G/hannes entitled "**Assessment of Health-Related Quality of Life, Treatment Outcome, Medication Adherence, and Associated Factors among Epileptic Patients at Meklle City Hospitals: A Multicentre Observational Study"** and submitted in partial fulfillment of the requirements of Master of Science Degree in Pharmacy Practice complies with the regulations of the University and meets the accepted standards to originality and quality.

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ABSTRACT

Background: Epilepsy is a chronic brain disorder with unpredictable treatment responses and a substantial impact on the patient's health-related quality of life (HRQoL). Understanding the treatment response and its determinants, patient's HRQoL, and medication adherence is crucial for designing an optimal treatment strategy for individuals living with epilepsy. However, there is no/limited data about HRQoL, treatment outcomes, and medication adherence in people living with epilepsy in the study settings.

Objective: This study aimed to assess the HRQoL, treatment outcome, medication adherence, and associated factors among epileptic patients; at three selected hospitals in Mekelle City, Tigray, Ethiopia.

Methodology: A multicenter observational study was conducted from May 10 to September 27 2023 G.C. Study participants were selected through stratified systematic random sampling. The HRQoL and medication adherence were evaluated using the Euro Quality of Life (Euro-QoL) questionnaire and the 8-item Morisk medication adherence scale (MMAS-8). Data analysis was done through STATA version 14. Mann-Whitney U test, Kruskal Wallis H test, tobit regression model, and logistic regression were used to analyze the data. Statistical significance was declared at a 95% Confidence Interval (CI) and p-value of <0.05.

Results: A total of 351 study participants with a mean (±SD) age of 37.98 ±14.27 years were involved. More than half (179,51%) of the study participants had poor HRQoL, and the median (IQR) values for EQ-5D-5L utility and EQ-VAS of the study participants were 0.774 (0.56-0.85) and 65 (50-80), respectively. Age over 60 years (β = -0.21, 95% CI = -0.402, -0.017), and frequent seizure episodes before treatment (β =-0.0054, 95% CI: -0.0102- 0.006) were negatively associated with HRQoL. On the other hand, the absence of co-morbidities (β = 0.095, 95% CI: 0.012 -0.178) and not experiencing seizure remitting-relapsing (β = 0.062, 95% CI: -0.0007- 0.125) were positively associated with HRQoL. More than one-third (39%) of the study participants had poorly controlled seizures with one out of five epileptic patients having seizure relapse. Living in urban areas (AOR=3.36, 95% CI; 1.1-10.4, p=0.037), being government-employed (AOR= 4.0, 95% CI; 1.1-14.5, p=0.035), and a student (AOR=4.0, 95% CI; 1.1-14.5, p=0.035) were factors significantly associated with good seizure control. In addition, half (50.6%) of the study participants were non-adherent to their medications, and being a farmer (AOR=4.2, 95% CI: 1.5-11.3, p=0.005), housewife (AOR=4.9, 95% CI: 1.4-

17.2, p=0.012), absence of co-morbidities (AOR=1.8, 95% CI: 1.11-11.28, p=0.008), and good seizure control (AOR=2.38, 95% CI: 1.55-3.71, p<0.001) were factors significantly associated with AED treatment adherence.

Conclusion: More than half of the study participants had poor HRQoL, with anxiety/depression being the most frequently reported health problem. More than one-third of the study participants had poorly controlled seizures, and one out of five epileptic patients experienced seizure remission-relapse. In addition, half of the study participants were non-adherent to their medications.

Keywords*: Antiepileptic drugs, Morisk Medication Adherence Scale, Health-related Quality of Life, seizure control, Euro-Qol, utility.*

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List of Acronyms and Abbreviations

AAU	Addis Ababa University
ACSH	Ayder Comprehensive Specialized Hospital
ADEs	Adverse Drug Events
ADRs	Adverse Drug Reactions
AED	Antiepileptic Drugs
AOR	Adjusted Odd Ratio
CI	Confidence Interval
CT	Computer Tomography
COR	Crude Odds Ratio
EEG	Electroencephalo Graphy
EQ-5D-5L	Euro-Qol Five Dimensions Five Level
EQ-VAS	Euro-QoL Visual Analogue Scale
HRQoL	Health-Related Quality of Life
ILAE	International League Against Epilepsy
GTCS	Generalized Tonic-Clonic Seizure
MGH	Mekelle General Hospital
MMAS	Morisky Medication Adherence Scale
MRI	Magnetic Resonance Imaging
MU	Mekelle University
QGH	Quiha General Hospital
QALYS	Quality Adjusted Life Years
TASH	Tikur Anbessa Specialized Hospital
WHO	World Health Organization

1. Introduction

1.1. Background

Epilepsy is a chronic non-communicable neurological disorder characterized by recurrent seizure attacks resulting from paroxysmal hyper-synchronization and hyper-excitability of neurons within the central nervous system (1, 2). The international league against epilepsy (ILAE) defines epilepsy as having at least two unprovoked (reflex) seizures occurring in more than 24 hours or one unprovoked seizure with more than a 60% chance of more seizures like the general recurrence risk after two unprovoked seizures occurring in the next 10 years or diagnosis of the epilepsy syndrome (3-5).

Epilepsy affects population of all ages, races, social classes, and geographical areas (6, 7). Globally more than 4.6 million new cases of epilepsy are annually reported with a prevalence of 51.7 million active epilepsy cases, and 82.3 million people diagnosed in their lifetime (8, 9). More than 80% of epileptic patients live in low and middle-income countries, and there is a substantial treatment gap (10-15). In Ethiopia, it is difficult to find the exact epidemiological distribution of the disease condition. However, individual studies are reporting that the prevalence of epilepsy is 64 per 100,000 populations, with active epilepsy cases ranging from 5.2 to 29.5 per 1000 people (16, 17).

Globally, neurological disorders including epilepsy are associated with significant death and disability-adjusted life-years (DALYs) (18). It is habitually portrayed as incurable, contagious, or an illness of evil spirits, which makes people with the condition socially isolated and reluctant to seek healthcare facilities and treatment (19).

Medical treatment with AEDs is the primary treatment modality in the majority of epileptic seizures (20-22). The ultimate goal of treatment in epilepsy is to optimize seizure control with minimum AED side effects and maintain the patient's quality of life (23, 24). Seizure control can be achieved in about 70% of epileptics with optimum treatment of AEDs, while the remaining 30% are the most challenging to treat (25). To optimize both the seizure control status and AED adherence, the selection of AEDs should consider the type of epileptic seizures, patient-specific factors such as age, co-morbidity, organ function test, childbearing potential, and drug-related factors such as cost (insurance coverage), pharmacokinetic and pharmacodynamic profile, safety, and dosage regimen (26-28).

Treatment adherence, the extent to which patients can follow the agreed recommendations for prescribed treatments with healthcare providers, is a key component of chronic disease management (29). However, the overall AED non-adherences in epileptic patients range from 26 to 79% (30-33). In people living with epilepsy, the cultural and spiritual perspectives, preference for traditional and complementary treatment modalities, stigma and discrimination, poor access to healthcare facilities, repeated seizure attacks, complex treatment regimens, cost of medications, unemployment, and substance use/abuse are some of the factors which influence medication adherence (34, 35). The main impact of AED non-adherence is mainly poor seizure control which results in a significant incidence of physical and psychological injuries, frequent hospital visits, higher healthcare costs, frequent absenteeism from routine activities, poor HRQoL, and increased morbidity and mortality (36-39).

Measuring the health-related quality of life (HRQoL) is crucial in determining the impact of medical treatment on the patient's survival, and minimizing the morbidity and mortality of chronic medical conditions (40). The term quality of life is a broad concept that is defined as an individual's perception of the position of their life concerning their culture and its value system (41, 42). It encompasses the physical, social, psychological, and behavioral comfort of an individual's welfare (43-45). HRQoL is a patient-reported measure of the overall health status and comfort of patients used to assess the impact of treatment on patients' survival, the number of years added, and the cost that will be invested (46-48). It is a crucial means to assess health-related economic evaluation and determine the cost-effective of an intervention that helps for equitable use of limited resources especially in developing nations (49, 50)

1.2. Statement of the problem

Successful medical treatment for people living with epilepsy should not be solely measured by the rate of seizure control; it should also include the impact of the condition on the well-being of the patients. Determining the effect of epilepsy and its treatments on memory, learning, physical harm, and cost is crucial and is getting more attention in current times (51, 52). It is a crucial means to assess health-related economic evaluation and determine the cost-effectiveness of an intervention that helps for equitable use of limited resources especially in developing nations (49, 50).

Epilepsy is a major health problem in the world, especially in low and middle-income countries which negatively affects the physical, mental, and social welfare of persons (53, 54). It is also associated with significant mortality and disability as compared to the general population (55, 56). The Global Burden of

Diseases, Injuries, and Risk Factors Study 2010 ranked epilepsy as the second burden of disease based on disability-adjusted life years (57, 58).

In low- and middle-income countries like Ethiopia, the high prevalence of infections (malaria and meningitis), frequent accidents, and trauma are responsible for the high prevalence of epilepsy. Despite the high prevalence of epilepsy in resource-limited countries, there is a high treatment gap; more than three-fourths of people living with epilepsy in those countries did not get appropriate treatment, and the availability of AEDs is less than 50% (59-63). Lack of experienced healthcare professionals to diagnose and treat epileptic patients, unavailability of AEDs, cost of treatment, and limited and long distance from healthcare facilities are among the factors that contribute to the high treatment gap in low and middle-income countries (64, 65).

The impact of epilepsy is not only on the patients living with the condition but has a tremendous influence on the well-being of the caregivers. In a survey conducted in five European countries more than one-third of epileptic patients had poorer HRQoL than the general population and other disease conditions. A significant proportion of the patients had limitations in conducting their routine activities (66).

Societies living in developing countries including Ethiopia have false perceptions about epileptic seizure and its treatment and prefer to attend traditional herbal medicines and holly water (religious leaders) (67-69). This all leads to poorly controlled repeated active epileptic seizures including status epileptics, which are responsible for physical and psychological harm, substantial stigma and discrimination, and sometimes sudden unexpected death from epilepsy which adversely affects the treatment outcome and quality of life of epileptic patients (16, 67, 70).

A study done in Southwest Ethiopia, on the knowledge and attitudes toward epilepsy showed that 40.6%, 49%, and 49.4% of the study participants believed that epilepsy was hereditary, contagious, and God's curse respectively. In addition, more than one-third of the participants think epileptic patients should be isolated from the community, and 46.1% and 40% of the respondents from the community did not want to shake hands with epileptic patients and keep their children away from epileptic patients respectively (70).

Another community-based study conducted in Ethiopia also revealed that 94.2% of participants will not employ a person with epilepsy. Only 6.7% of the participants will allow a family member to marry a person with epilepsy, and more than half of the participants believe the cause of epilepsy is spiritual (71).

These studies showed that there is a high misconception about epilepsy and its treatment which is responsible for the poor HRQoL in individuals living with epilepsy.

Currently, many AEDs with diverse mechanisms of action, pharmacokinetic and pharmacodynamic profiles, and varying costs are available in the market (43, 72). While AEDs are effective in controlling seizures, more than two-thirds of epilepsy patients are challenging to treat and experience adverse effects and drug interactions that have a significant impact on their HRQoL (19, 73). Studies have shown that patients receiving polypharmacy with multiple AEDs tend to have poorer HRQoL and lower medication adherence compared to those on monotherapy (74, 75). Epileptic patients taking a combination of two or more AEDs often have inadequately controlled seizures, a higher rate of adverse drug events, and a compromised quality of life compared to those on single-drug regimens (76).

Adherence to medical treatment of epilepsy has a critical role in reducing the frequency of seizure attacks and improving the HRQoL. Unfortunately, treatment adherence in people living with epilepsy is poor and associated with recurrent seizure attacks (77). In Ethiopia, the level of AED adherence ranges from 34.1%-40.27% (78-80). Patients who are non-adherence to their medication can have a three-fold increase in mortality, repeated emergency department visits and hospitalization, and frequent absenteeism from the workplace (39, 81, 82). The long-term treatment duration, acute and chronic side effects of AEDs, co-morbid psychiatric disorders, and poor awareness about the disease condition are some of the factors responsible for treatment discontinuation and poor medication adherence thereby significantly affecting the treatment outcome (77, 83, 84).

Despite the tremendous impact of epilepsy and its treatment on the HRQoL, treatment outcome, and medication adherence, only limited studies have been conducted in Ethiopia (85-88). In addition, the majority of the studies have been limited to specific geographic areas, predominantly conducted within teaching hospitals. Thus, this study aimed to assess the HRQoL, treatment outcomes, and medication adherence at three selected hospitals.

1.3. Significance of the study

The findings of this study are expected to contribute to the understanding of epilepsy as a major public health challenge, marked by substantial disability, mortality, stigma, and discrimination. The study will expand the existing knowledge on HRQoL, treatment outcomes, medication adherence, and associated factors among epilepsy patients in the study context. These insights can serve as a valuable reminder for

healthcare professionals to critically evaluate the services provided to epileptic patients and make necessary improvements or collaborative efforts to enhance the quality of care. Furthermore, the study's findings may offer guidance to neurologists and clinical pharmacists on AED prescribing patterns, medication adherence, seizure control, and their determinants. The study's outcomes will also provide valuable input for regional and national health institutions, and administrative bodies, enabling them to assess current practices and inform the development of further services and health promotion policies aimed at optimizing the quality of care for individuals living with epilepsy.

2. Literature review

2.1. Health-related quality of life and associated factors

A multicenter cross-sectional study conducted in Germany showed that epileptic patients had poor HRQoL as compared to the general population. The mean HRQoL score of the study participants was 61.7%, with a mean (±SD) Visual Analog Scale (VAS) of 66.6±18.3. According to the study anxiety and depression (β=-0.27, p<0.001), AEDs side effects (β=-0.28, p < 0.001), seizure-related worry (β=0.18, p < 0.001), and frequent seizure attacks (β=0.14, p <0.001) were predictors of HRQoL in epileptic patients (89).

A survey was conducted in five European countries on 500 epileptic patients taking more than one AED and 500 controlled groups. The study reported that most of the epileptic patients defined their overall health status as poor or fair and were restricted from carrying out their routine daily activities. Patients who were receiving more than 3 AEDs were more restricted in their daily activities as compared to those on two AEDs. Besides, epileptic patients were more concerned about their capability to drive, mood, and self-esteem (66).

Another study conducted in Malaysia reported that the mean (SD) HRQoL was 68.9 ± 15.9, with seizure worry 47.5 (SD 25.0) as the lowest dimension. Study participants who had one or more seizure attacks in one month had lower HRQoL (63.4, 95% CI: 59.2, 67.5) than those without a seizure (73.5, 95% CI: 69.3, 77.9) (90).

In a hospital-based study done in Uganda, the mean HRQoL of the epileptic patients was 58 (SD = 13) on the 0-100 scale, and frequency of seizure (P=0.00) and polytherapy (0.01) were two factors negatively associated with HRQoL. Besides drug side effects, socio-demographic factors like gender, marital status, and educational background were significantly associated with overall HRQoL (91).

A cross-sectional comparative study was conducted among 300 people living with epilepsy. The study found that the mean quality of life in the epilepsy group (49.90%) was significantly lower compared to the normal control group (77.60%. HRQoL was determined by socio-demographic factors; where low level of education, higher seizure burden, low annual income, unemployment, unskilled employment, and living in a rural residence were factors significantly ($p < 0.05$) associated with poor HRQoL epileptic patients (73).

Another hospital-based study revealed that mean QoL of 75.36%, with a minimum of 10 to a maximum of 40. While the majority (73.7%) of participants reported having enough energy most of the time, a sizable proportion (50.85%) felt downhearted or blue for at least some of the time. Notably, for more than half (54%) of the patients, their epilepsy and/or AED did not significantly disrupt their daily lives. These mixed findings suggest a complex picture, with many patients maintaining good energy levels and daily functioning, but also experiencing emotional distress related to their condition (92).

An institutional-based cross-sectional study on 385 epileptic patients conducted in Ethiopia, revealed that nearly 95% of the study participants had generalized seizures, and 64.3% of them were taking two-drug combinations. Anxiety and depression were reported in 37% and 12.2% of the epileptic patients respectively. The overall mean HRQoL of the respondents was 51.98 ±10.08; 95% CI. Good HRQoL was significantly determined by age, education level, marital status, occupation, residence, current comorbidity, family support, and recreational activities ($p \leqslant 0.05$ (93).

The studies have revealed that a substantial proportion of individuals living with epilepsy experience poor HRQoL. The poor HRQoL is the result of a complex interplay of various factors that can significantly impact the overall well-being and functioning of epileptic patients. Seizure-related worry, and fear of unpredictable seizures, can lead to anxiety and uncertainty, undermining the patient's sense of control and security. Additionally, the social stigma and discrimination often faced by those with epilepsy can result in feelings of isolation, low self-esteem, and social withdrawal, further exacerbating the challenges they encounter. Comorbid mental health conditions, such as anxiety and depression, also have an impact on determining the emotional and cognitive burdens experienced by these individuals. Finally, the degree of seizure control is a crucial factor, as effective management of seizures can significantly improve the patient's ability to engage in daily activities and maintain a satisfactory quality of life

2.2. Treatment outcome and associated factors

Medical treatment with AEDs is the primary treatment modality in epileptic patients. Currently, more than 20 AEDs are available in the market and are important in reducing the number of seizure attacks. However, those medications did not have a disease-modifying effect and seizure recurrence is common in about 30% of epileptic patients (94). Globally studies have been conducted on treatment outcomes and AED adherence including in low-income countries (95, 96).

A longitudinal observational cohort study was conducted in Scotland in 1440 epileptic patients. The findings of the study showed that 63.7% of study participants had achieved seizure control. Furthermore, most of the patients (86.8%) were on a single AED and 89.9% of them had good control of seizure with the first AED. Patients who did not achieve seizure control with the first AED regimen were 1.73 times more likely not to respond with subsequent AED regimens, and patients with generalized tonic-clonic seizure (GTCS) had good outcomes as compared to those with focal onset seizures (95).

In a prospective observational study conducted in India, a one-year seizure-free period was achieved in 60% of the study participants. Also, the study showed that participants with age at disease onset less than 5 years (P = 0.0016, OR = 2.02 (95% CI = 1.31-3.13), cryptogenic type of epilepsy (48% vs. 32%, P = 0.0049, OR = 1.61 [95% CI = 1.16-2.24), and frequent seizure attacks before treatment P < 0.0001, OR = 2.21 [95% CI = 1.61-3.05) had poor seizure control (97).

Seizure remission was achieved in 61.3% of epileptic patients in a retrospective cohort study conducted in China. Out of the epileptic patients who achieved a one-year seizure-free period 36.6% of them experienced relapse. Idiopathic type of epilepsy (P< 0.001), normal electroencephalograph (EEG) (P< 0.05), number of AEDs (P< 0.05), and seizure frequency of < 0.001) at the first arrival were independent predictors of seizure remission (98).

In a two-year follow-up study conducted in Nigeria, 62.8% of newly diagnosed epileptic patients had achieved seizure control. Female sex, age greater than 20 years, being educated, employed, having family support, regular follow-up, AED adherence, and with a generalized type of epilepsy were predictors of seizure control (99).

A retrospective cohort study was conducted at Jimma University Medical Center with a median follow-up period of 44 months. The study reported that 64.4% of the respondents had been seizure-free for at least one year. Frequent seizure episodes before treatment (AHR= 0.716, 95% CI: 0.558–0.919), poor early response to AED treatment (AHR= 0.339, 95% CI: 0.256–0.449), poor medication adherence (AHR= 0.719, 95% CI 0.546–0.942), and receiving polytherapy (AHR= 0.563, 95% CI: 0.420–0.756) were significant predictors of poor seizure remission (100).

Another multicenter hospital-based cross-sectional study was conducted in Ethiopia on a total of 422 epileptic patients. More than three-fourths (78%) of the study participants had controlled seizures (were seizure-free for one year), poor medication adherence, and duration of disease less than 5 years were

negative predictors of treatment outcomes. In addition, the study revealed that most of the study participants had GTCS (83.4%), and the majority (87.9%) of the participants were on monotherapy with phenobarbitone as the commonly utilized AED followed by phenytoin and valproic acid (101).

2.3. Antiepileptic drug adherence and associated factors

Medication adherence is a key factor in achieving optimal treatment outcomes in patients with chronic disease conditions. However, this remains a challenge in epileptic patients because of the disease's nature, longer medical treatment, and drug-related side effects (102, 103). This results in poor treatment outcomes and compromised HRQoL. Having a depressed or anxious mood, specific belief about medications, poor medication self-administration practice, poorly controlled current seizure, multiple dosing of medication, and weak interaction between physician and patient are some of the factors associated with low AED adherence found in different studies (102, 104, 105).

A hospital-based cross-sectional study conducted in Malaysia reported that 49.3% of the epileptic patients were non-adherent to their medications. The study also attempted to identify predictors of medication adherence, seizure frequency (p= 0.048), patient satisfaction (p= 0.043), and knowledge of the patients about their disease (p=0.001) were factors significantly associated with medication adherence (106).

The medication adherence in newly diagnosed epileptic patients of India was good. The study revealed that 72.3% of the epileptic patients were taking their AEDs as prescribed. Besides, socioeconomic class (p=0.043) and types of epilepsy (p=0.033) were significantly associated with medication adherence, while forgetfulness was the primary reason for medication non-adherence (107).

In a study done in the United Arab Emirates (UAE) in patients taking AED for a minimum of six months, 70.8% of the study participants were adherent to their medications. AED adherence was significantly associated with a low level of educational background (OR=2.6; 95% CI, 1.2-5.8) and seizures within the previous 6 months (OR=2.5; 95% CI, 1.3-5.2). Additionally, the study reported that patients who were on levetiracetam had a low risk of non-adherence (OR=0.5; 9% CI, 0.2-0.9) (108).

A study conducted in four tertiary hospitals in Nigeria demonstrated that 22 (17.2%), 49 (38.3%), and 57 (44.5%) of the study participants had high, medium, and low adherence, respectively. The use of herbal/complementary medicines and the long duration of AED use were factors that were significantly

associated with medication adherence. Fatigue (30.4%), headache (22.5%), and difficulty in concentrating (19.6%) were frequently reported ADRs (109)

An institutional-based Cross-sectional study was conducted on 450 epileptic patients at two referral hospitals in Ethiopia. The study showed that the majority of the respondents were on single AED, and more than two-thirds of them were treated for at least two years. The AED adherence of the study participants was evaluated through the MMAS-8. According to the study, AED adherence was reported in 62.2% of the study participants, and treatment duration of 6 years and above, receiving AEDs with charge, lack of health education, perceived stigma, and AEDs side effects were significantly associated with AED non-adherence (110).

Similar study conducted in the country also reported more than one-third of the study participants were non-adherent to their medication, and patients unable to read and write (AOR=22.30; 95% CI, 5.84-85.21), having primary education level (AOR=5.63; 95% CI, 1.90-16.69), male sex (AOR=2.37; 95% CI, 1.33-4.20), had AED side effects (AOR=13.68; 95% CI, 3.27-56.97) and receiving medications through charges (AOR=2.06; 95%CI, 1.04-4.11) were all factors significantly associated with medication non-adherence (111).

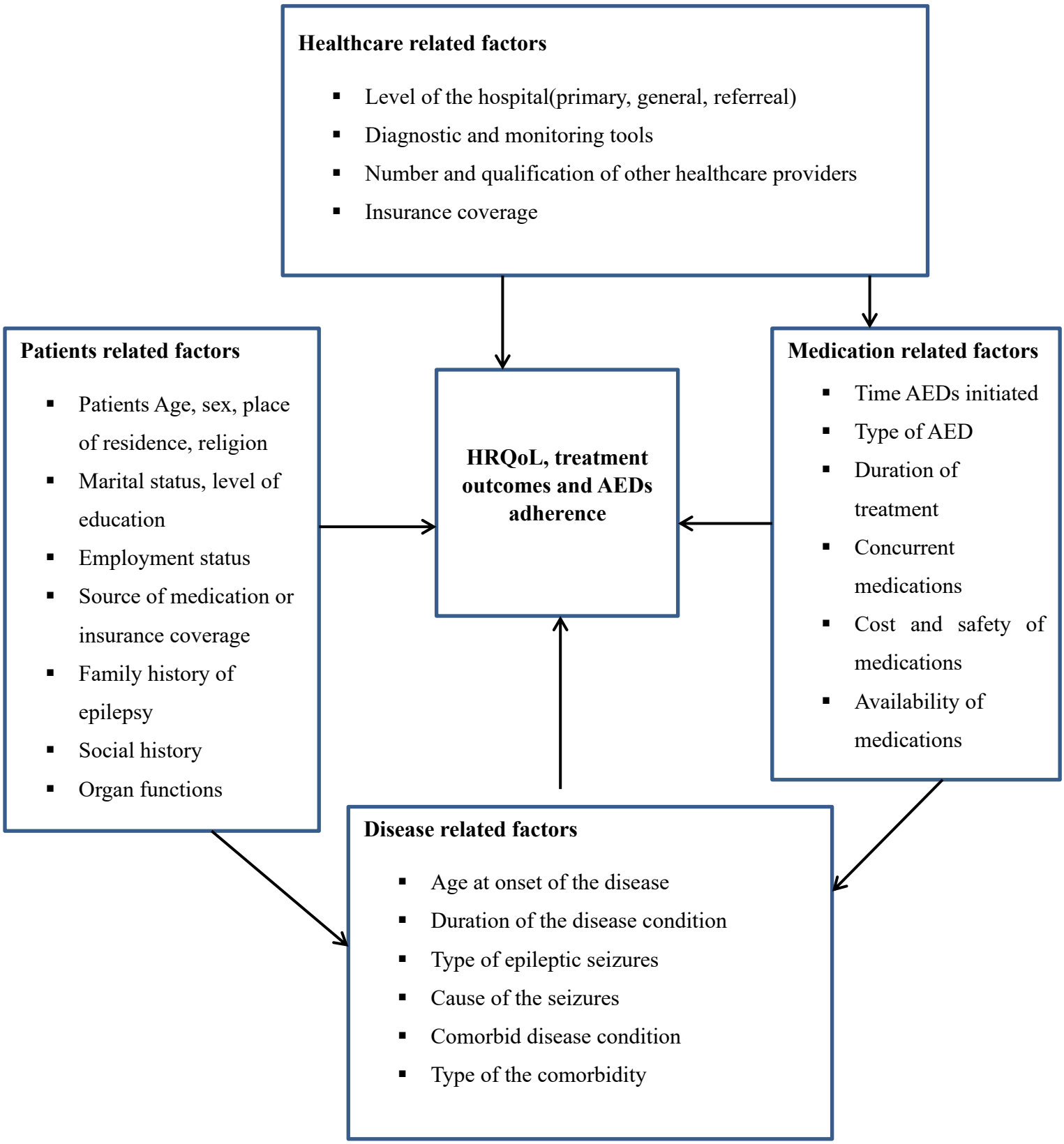

Figure1. Conceptual framework of factors that determine health-related quality of life, treatment outcomes, and antiepileptic drug adherence in epileptic patients **(19, 45, 65, 70, 80, 95, 100)**.

3. Objectives

3.1. General objective

To assess HRQoL, treatment outcome, AED adherence, and associated factors among epileptic patients on AED visiting neurology clinics of the three selected hospitals, Mekelle City, Tigray, Ethiopia.

3.2. Specific objectives

To determine the HRQoL among epileptic patients on AEDs of the three selected hospitals.

To identify factors associated with HRQoL among epileptic patients on AEDs of the three selected hospitals.

To assess treatment outcomes of epileptic patients on AEDs of the three selected hospitals.

To identify factors associated with treatment outcomes among epileptic patients on AEDs of the three selected hospitals.

To assess the level of AED adherence among epileptic patients on AEDs of the three selected hospitals.

To identify determinants of AED level of adherence among epileptic patients of the three selected hospitals.

4. Method and materials

4.1. Study Setting

The study was conducted at three selected hospitals, Ayder Comprehensive Specialized Hospital (ACSH), Mekelle General Hospital (MGH), and Quiha General Hospital (QGH) located in Northern Ethiopia, Tigray region, Mekelle City located 783 Kilometer from the capital city, with a total estimated population of 310, 436, including 140,067 (45.1%) men and 170,369 (54.9%) women (112). The city is 109 square kilometers in size and has one comprehensive specialized hospital, three general hospitals, nine health centers, and more than 20 private hospitals. Only three of the hospitals (ACSH, MGH, and QGH) provide outpatient neurological services. ACSH and MGH each offer a neurologic service in a separate clinic, while QGH provides integrated neurological and mental health services. ACSH renders both referral and non-referral services to more than 8 million populations in its catchment areas of the Tigray, Afar, and Southeastern parts of the Amhara Regional States. The hospital has 500 inpatient beds, with four major departments and specialty units. MGH delivers almost a comparable service to ACSH. The hospital contains more than 100 beds for inpatients and is serving for referral to nearby primary hospitals and health centers. QHG hospital is located 8 Kilometer to the southeast of Mekelle City and has more than 8 departments including an ophthalmology specialty clinic, with more than 70 inpatient beds.

4.2. Study design and period

A hospital-based observational multicenter study was conducted among epileptic patients who had regular follow-ups at the three selected hospitals of adult outpatient neurology clinics from June 10 to September 27, 2023, G.C.

4.3. Source and study population

4.3.1. Source population

The source population was all adult epileptic patients who had follow-ups in the three selected hospitals (ACSH, MGH, and QGH).

4.3.2. Study population

All adult epileptic patients at the three selected hospitals who fulfilled the inclusion and had follow-ups during the study period were included.

4.4. Eligibility criteria

4.4.1. Inclusion criteria

Adult patients (age ≥18 years old) with a diagnosis of epilepsy who had been on regular follow-up for at least one year before the study period and were taking at least one AED.

4.4.2. Exclusion criteria

Patients were excluded from the study, if they refused to provide consent, were seriously ill (status epileptics) and unable to complete the interview including, psychiatric illness, or had incomplete medical records.

4.5. Sample Size determination and sampling technique

The sample size was calculated using simple population proportion sample size estimation formula

$$n= \frac{\left(z_{1-\alpha/2}\right)^2 P(1-P)}{d^2} = \frac{(1.96)^2 0.65(1-0.35)}{0.05^2} = 351$$

Where, n = sample size, Z = confidence interval (1.96), d = Margin of error to be tolerated (0.05), and the prevalence (P). The sample sizes were calculated separately for each outcome variable based on prior studies, resulting in 269 for HRQoL (113), 350 for medication adherence (69), and 351 for seizure remission. Thus, the sample with the largest value was obtained from a retrospective cohort study on treatment response and predictors in epileptic patients, in which seizure remission was reported in 64.6 % (100). Considering 5% of the contingency value, the total calculated sample size was 369. The patient registration book was used as a sample frame to select the study participants, and 1100 epileptic patients met the inclusion criteria. Dividing the sample frame to the calculated sample size (369), yielding a sampling interval of 2.98. Therefore, every third patient on the list was selected using stratified systematic random sampling, proportionally from the three selected hospitals. The sampling procedure is provided in Figure 2.

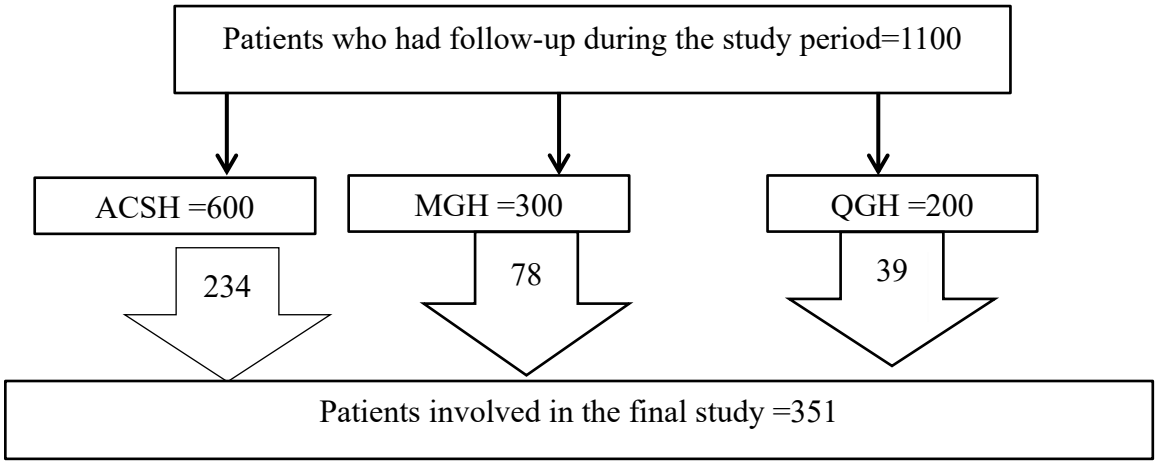

Figure 2. Sampling technique and procedures of the study participants at three selected hospitals in Mekelle City, Tigray, Ethiopia, 2023 (N=351)

4.6. Study variables

4.6.1. Dependent variable

HRQoL, treatment outcomes, and level of AED adherence.

4.6.2. Independent variables

Participant's socio-demographics (age, sex, religion, place of residence, marital status, educational background, and current occupation), disease-related factors (family history of epilepsy, type of seizure, age at onset of seizure diagnosis, number of seizures before treatment, co-morbid disease condition and history of status epileptics) and drug-related factors (number of AEDs, AED related ADEs, type of AED prescribed, medications for comorbid disease conditions and source of AEDs) were independent variables in this study.

4.7. Data Collection Tools and Procedures

4.7.1. Data collection tools

The data collection tool has 3 components. Data abstraction format, validated Euro-QoL questionnaire, and the MMAS-8 were used to collect the data.

Data abstraction format

The data abstraction format was developed following a thorough review of related literature (23, 114-116) and was used to extract data about the socio-demographic and clinical characteristics of the study participants. Information related to the patient's treatment outcomes was retrieved through the patient follow-up sheet.

EQ-5D-5L, EQ-VAS

Euro-QoL is a generic, preference-based, multi-dimensional questionnaire used to determine HRQoL. It is used in the assessment of health technology (HTA) by different nations like the National Institute for Health and Care Excellence (NICE) and other European countries' economic evaluations, which gives a clue and helps in making decisions about resource allocation and policy making. EQ-5D-5L can summarize the overall health state of a patient in a single score known as the utility (26, 42, 77, 117-120). The tool comprises of EQ-5D-5L descriptive system and EQ-VAS. The EQ-5D-5L descriptive system has five dimensions of health status: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with five levels: no problems, slight problems, moderate problems, severe problems, and extreme (unable), indicating the severity of the problems for each dimension (118, 121, 122).

Eight-item Morisk medication adherence scale (MMAS-8)

The MMAS-8 is a self-reported tool commonly used to evaluate patients' adherence to their medication and physician consultations (123). This tool is favored for its affordability, ease of administration, and ability to extract valuable information regarding participants' attitudes and beliefs. It consists of eight questions, with each item assessing medication-taking behaviors. The response options for the first seven questions are dichotomous, requiring a simple yes or no response, while the final question utilizes a 5-point Likert scale (124).

4.7.2. Data collection procedures

The data collection tool was initially developed in English language and translated into the local language (Tigrigna) by two native speakers for data collection and then backtranslated into English maintaining its consistency and accuracy. The data collection process had two phases; data socio-demographic profile, HRQoL, and medication adherence were collected through face-to-face interviews, and the clinical

characteristics were assembled from the medical chart review and smart care using the data abstraction format.

In the EQ-5D-5L descriptive system, study participants were kindly asked to choose the preferred level that reflects their current health status for each health dimension, and then tick their preference on the box provided. The second component of the instrument is the EQ-VAS, which is a quantitative measure of health outcomes that can reflect overall patient preference. It records the patient's self-rated health on a 20-cm vertical bar, with endpoints labeled "100 as the best imaginable health state" and "0 as the worst imaginable health state". The study participants were kindly requested to judge the health status of the data collection from 0 to 100 and mark it on the vertical graph. Medication adherence of the study participants was evaluated by asking the patients about their medication-taking habits over the preceding two weeks.

4.8. Data quality control and assurance

Data quality was ensured through the use of validated and structured data collection tools. The tool was pretested in 5% (18) of the study participants from the three hospitals for its completeness and consistency, and any necessary modifications were made before the actual data collection commenced. Pretest respondents were not involved in data analysis. A total of three data collectors, two senior neurology clinic nurses, one BSC pharmacist, and one supervisor were involved in the data collection process. The data collectors and supervisor were trained about the purpose of the study, data collection tools and terminologies, way of data extraction from the medical records and interviews, and ethical issues of the study participants. The supervisor provided daily supervision throughout the data collection process.

4.9. Data processing and analysis

The data was cleaned for discrepancies and missing values before being coded and entered into the EPI data manager and entry client. The data entered into the EPI data manager was exported into STATA version 14 and data analysis was done through this software. Descriptive statistics such as frequency mean (±SD) and median (IQR) were used to summarize participants' socio-demographic and clinical profiles. Assumptions were checked, and binary logistic regression was employed to identify factors associated with treatment outcome and medication adherence. Variables with a p-value of ≤ 0.25 were selected for inclusion in multivariate regression. Statistical significance was declared at 95% CI; p-value of < 0.05.

The utility value was calculated using Microsoft Excel 2018. Patient health profiles from EQ-5D-5L were converted into a single value (utility) based on the preference of the general population of Ethiopia. Utility values were figured out using coefficients that represented level-specific disutility values obtained from the general population via a hybrid regression model (125). Four dummies were prepared for each dimension, using level one as a reference to represent a decrease in utility when moving from one level to the next higher level (for example, moving from SC_1 to SC_2 resulted in a 0.0235 utility decrement).

$$\text{Utility value} = 1 - (\text{MO2} \times 0.0337341 + \text{MO3} \times 0.0644715 + \text{MO4} \times 0.2276493 + \text{MO5} \times 0.3598963) + (\text{SC2} \times 0.0235125 + \text{SC3} \times 0.0394815 + \text{SC4} \times 0.1419238 + \text{SC5} \times 0.2223553) + (\text{UA2} \times 0.0323013 + \text{UA3} \times 0.0482993 + \text{UA4} \times 0.1573934 + \text{UA5} \times 0.2721253) + (\text{P/D2} \times 0.0360808 + \text{P/D3} \times 0.0515949 + \text{P/D4} \times 0.2703189 + \text{P/D5} \times 0.4063984) + (\text{A/D2} \times 0.0258862 + \text{A/D3} \times 0.0848133 + \text{A/D4} \times 0.2987388 + \text{A/D5} \times 0.4577938 \quad \ldots\text{(Equation…1)}.$$

©M0-mobility; ©SC-self-care; ©UA-usual activity; ©P/D-pain/discomfort; ©A/DAnxiety/depression

The data for the HRQoL (EQ-5D-5L utility value and EQ-VAS score) was checked for normality using the Kolmogrov-Simirnor and Shapiro Wilk test (p-value < 0.005) and histogram inspection revealed skewed and kurtotic. The Mann-Whitney U test and the Kruskal Wallis H test were used to compare the significant difference in utility value between study participants' subgroups. Multivariate tobit regression model was used to determine factors significantly associated with HRQoL and statistical significance was declared at 95% CI and p-value less than 0.05.

4.10. Ethical clearance

The ethical clearance for this study (Ref. No; ERB/SOP/246/13/2021) was obtained from the ethical review committee of the School of Pharmacy, College of Health Science, Addis Ababa University, and also the School of Pharmacy wrote a letter of support to the three hospitals of the study settings, and a formal approval letter was obtained from the study setting's administration before commenced the data collection. Informed consent was obtained from individual study participants after the purpose and rationality of the study were briefly clarified. Data collection questionnaires were labeled with numerical codes to maintain the study participant's anonymity and confidentiality. The findings did not disclose the names of patients or healthcare providers.

4.11. Operation definitions

In this study, epilepsy was defined based on the International League Against Epilepsy published in 2014 (126). Accordingly, epilepsy was defined by (a) at least two unprovoked (or reflex) seizures occurring >24 h apart; (b) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (c) Diagnosis of an epilepsy syndrome.

The health-related quality of life (HRQoL) in this study was evaluated using the EQ-5D-5L utility value. Patients with a utility value below the median score were considered to have poor HRQoL.

The treatment outcomes in this study were measured by the achievement of a one-year seizure remission. Patients were classified as having either "good" or "poor" seizure control. Good seizure control was defined as being seizure-remission for at least one year after the initiation of anti-epileptic drug (AED) treatment. Those who had not achieved a one-year seizure remission were considered to have poor seizure control. Seizure-remitting relapse was defined as experiencing a seizure after having been seizure-free for at least one year.

The MMAS-8 was utilized to assess medication adherence in this study. Patients with an MMAS-8 score of eight were considered highly adherent, medium adherent if their MMAS-8 score was between 6 and 8 (6, 8), and low adherent with an MMAS-8 score of less than 6. Overall, patients were classified as either adherent or non-adherent. Those with medium or high adherence (MMAS-8 score > 6) were considered adherent, while those with low adherence (MMAS-8 score < 6) were considered non-adherent.

5. Result

5.1. Socio-demographic characteristics of the study participants

A total of 351 study participants were involved in the final study with a response rate of 95.12%. The mean (±SD) age of the study participants was 37.98 ±14.27 years, with more than two-thirds (248,70.7%) of them being between the ages of 18 and 44. Males accounted for more than half 191 (54.4 %) of the study participants, and nearly two-thirds (230, 59.8%) of them were urban residents. Approximately half of the study's participants (170, 48.4%) were unemployed, and more than one-third of them had informal education (35.1%). Substance use was reported by 64 (18.2%) of the respondents, with regular alcohol consumption and cigarette smoking were reported in 33 (9.4%) and 25 (7.1%), respectively (Table 1).

Table 1. Study participant's socio-demographic characteristics among the study participants at three selected hospitals in Mekelle City, Tigray, Ethiopia, 2023 (N=351)

Variables	Category	Frequency N(%)
Age in year	18-30 year	139 (39.6)
	31-44 year	109 (31.1)
	45-60 year	71 (20.1)
	> 60 years	32 (9.1)
Sex	Male	191 (54.4)
	Female	160 (45.6)
Place of residence	Urban	210 (59.8)
	Rural	141 (40.2)
Marital status	Single	148 (42.2)
	Married	169 (48.1)
	Divorced	14 (4.0)
	Widowed	20 (5.7)
	No formal education	124 (35.3)
Level of education	Elementary (1-8)	97 (26.7)
	Secondary (9-12)	109 (31.1)
	Diploma and above	21 (6.0)
	Unemployed	170 (48.4)
Current occupation	Farmer	30 (8.5)
	Housewife	46 (13.1)
	Government employed	22 (6.3)
	Student	58 (16.5)
	Private sector	25 (7.1)
Substance use/abuse	Yes	64 (18.2)
	No	280 (81.8)
Habit of use/abuse	Khat chewing	13 (3.7)
	Smoking cigarette	25 (7.1)
	Alcohol	33 (9.4)

5.2. The clinical characteristics of study participants

The mean age at seizure diagnosis of the study participants was 23.61±14.06 years. Only 34 (9.7%) have a family history of epilepsy. Of the total, two-fifths of 150 (42.7%) of the study participants had co-morbid disease. Among these, schizophrenia (8%), hypertension (5.7%), and lower back pain (4.8%) are the most reported co-morbidities. The most common type of epilepsy was GTCS which accounts for 227 (64.7%). Half (177, 50.4%) of the study participants had a history of > 5 episodes of seizure episodes before AED treatment was started. Two hundred eighty-three (80.6%) of the respondents began their treatment with a single AED. Phenobarbitone was the commonly prescribed AED at initiation followed by phenytoin, and then carbamazepine which accounts for 128 (36.5%), 75(21.4%), and 46 (13.1%), respectively. Among the participants, 100 (28.5%) individuals experienced adverse drug events, gingival hyperplasia (8.5%), behavioral changes (5.1%), and cerebral ataxia (4.8%), which were commonly reported ADEs (Table 2)

Table 2. Clinical characteristics of study participants among the study participants at three selected hospitals in Mekelle City, Tigray, Ethiopia, 2023 (N=351)

Variable	Category	Frequency (%)
Family history of epilepsy	Yes	34 (9.7)
	No	317 (92.3)
Comorbidity	Yes	150 (42.7)
	NO	201 (57.3)
Type of comorbidity	Schizophrenia	28 (8.0)
	Hypertension	20 (5.7)
	Pain	17 (4.8)
	Anxiety	6 (1.7)
	Depression	9 (2.6)
	Major depressive disorder	10 (2.8)
	HIV/AIDS	6 (1.7)
	Migraine headache	4 (1.1)
	Anxiety and depression	3 (0.9)
	Others©	15 (4.3)
Etiology of epilepsy	Idiopathic	254 (72.4)
	Structural	65(18.5)
	Infectious	28(8.0)
	Genetics	4(1.1)

Table 2. continued.

Variable	Category	Frequency (%)
Age at onset of a seizure	<30 years	220 (68.8)
	31-44 years	62 (19.4)
	45-60 years	32 (10.0)
	>60 years	6 (1.9)
Source of medication	Free	202 (57.5)
	Charge	149 (42.5)
Type of epilepsy	Generalized	227 (64.7)
	Focal onset	61 (16.4)
	Unclassified	63 (17.9)
Seizure episodes before treatment	Less than 5	174(49.6)
	Greater than 5	177(50.4)
Treatment at initiation	Monotherapy	283 (80.6)
	Two drugs	66 (18.8)
	Three drugs	2 (0.6)
AEDs at initiation	Phenobarbital	129 (36.75)
	Phenytoin	75 (21.4)
	Carbamazepine	46 (13.1)
	Valproic acid	28 (8.0)
	Phenytoin+ phenobarbitone	9 (2.6)
	Phenytoin +Carbamazapine	6 (1.7)
	Phenytoin +valproic acid	8 (2.3)
	Phenobarbiton+Carbamazapine	25 (7.1)
	Phenobarbitone +Valproic acid	17 (4.8)
	Valproic acid +Carbamazapine	6 (1.7)
	Valproic acid +Carbamazapine + Phenytoin	2 (0.6)

Variable	Category	Frequency (%)
Adverse drug events	Yes	100 (28.5)
	No	251 (71.5)
The type of ADEs	Skin lesions and rash	9 (2.6)
	Gingival hyperplasia	30 (8.5)
	Cerebral ataxia	17 (4.8)
	Drowsiness	2 (0.6)
	Headache	6 (1.7)
	Behavioural change	18 (5.1)
	Irritability and tremor	4 (1.1)
	Not reported	14 (3.9)

ADE: Adverse drug events, AED: antiepileptic drug

5.3. Health-Related Quality of Life of study participants

In the EQ-5D-5L descriptive system, anxiety/depression (342, 97.4%) was the most frequently reported health problem followed by pain/discomfort (335, 95.4%) Figure 3). More than half (179, 51%) of epileptic patients in this study had poor HRQoL, with a median (IQR) EQ-VAS score of 65 (65-80), and the median EQ-5D-5L utility value was 0.77 (0.56-0.85). On the other hand, the mean (SD) of the EQ-VAS score and EQ-5D-5L utility value were 64.7 ± 18.36 and 0.68 ± 0.23, respectively.

The difference in HRQoL between subgroups of the study participants was evaluated, and age, marital status, co-morbid disease condition, use of medication for the co-morbidities, and ADEs reported were among the socio-demographic and clinical profiles that showed statistically significant differences in the median (IQR) of EQ-5D-5L utility value and EQ-VAS score (Table 4).

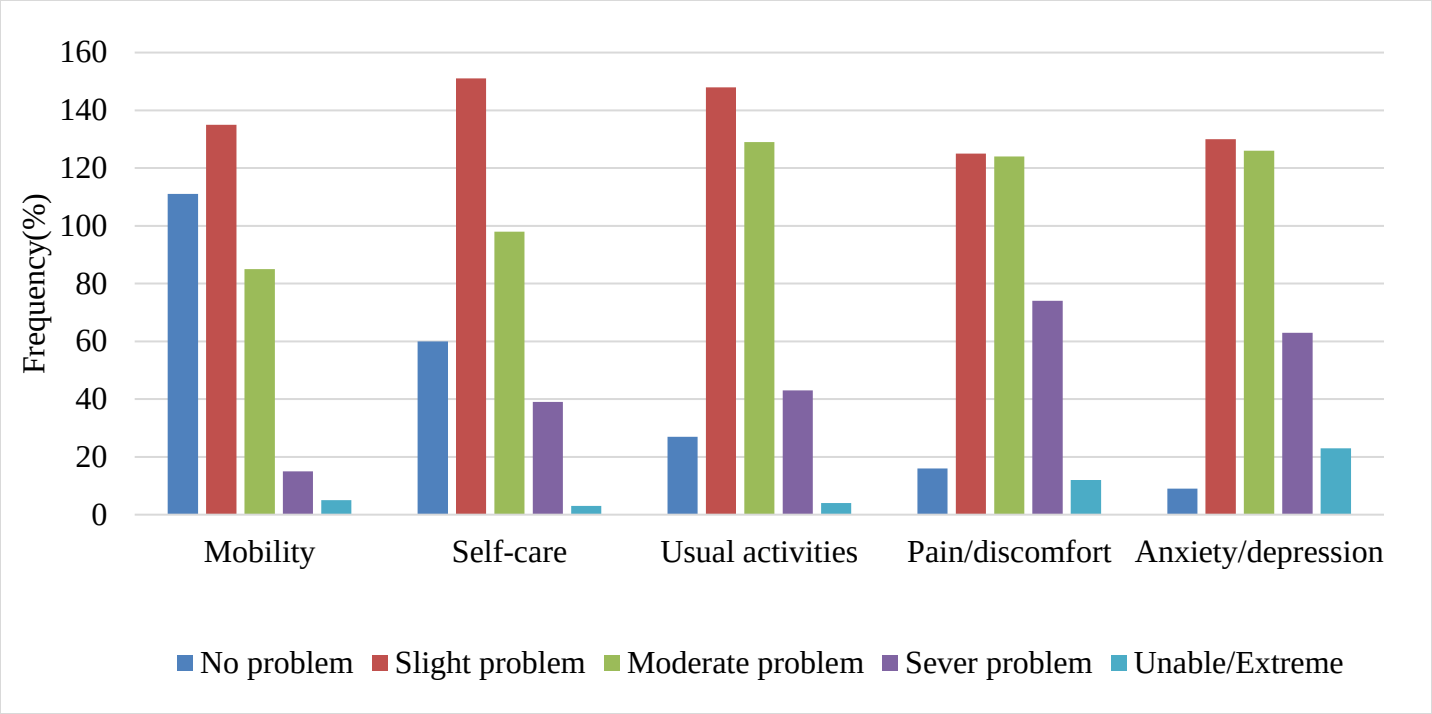

Figure 3. Self-reported health problems, EQ-5D-5L descriptive system among the study participants at three selected hospitals in Mekelle City, Tigray, Ethiopia, 2023 (N=351)

Table 3. The difference in Median (IQR) difference of EQ-5D-5L utility value and EQ-VAS score among the study participants at three selected hospitals in Mekelle City, Tigray, Ethiopia, 2023 (N=351)

Variables	EQ-VAS score median(IQR)	Mean rank	P value	EQ-5D-5L utility score median(IQR)	Mean rank2	P-value
Age in year						
18-30	74(60-85)	213.44	**0.001**	0.82(0.442-0.818)	205.69	**0.001**
31-44	67(53-67)	179.21		0.75(0.669-0.876)	174.51	
45-60	60(45-60)	142.72		0.70(0.614-0.849)	156.01	
>60	42.5(34.3-42.3)	78.29		0.57(0.675-0.849)	96.44	
Residence						
Urban	67(50-67)	175.91	0.985	0.77(0.73-0.849)	173.4	0.55
Rural	63(50-63)	176.13		0.76(0.56-0.849)	179.87	
Marital status						
Single	72 (60-82)	208.1	**0.001**	0.81(0.468-0.845)	200.96	**0.001**
Married	62 (50-78)	165.3		0.75(0.605-0.856)	164.65	
Divorced	46(36.5-58.5)	96.82		0.75(0.704-0.849)	137.93	
Widowed	47(33.5-59.3)	84.98		0.66(0.649-0.857)	113.83	
Substance use/abuse						
Yes	63 (50.0-80.0)	172.1	0.13	0.76(0.54-0.855)	172	0.12
No	70 (51.5-81.5)	193		0.79(0.568-0.849)		
Level of education						
No formal education	55.5(42.25-70.0)	138.55	**0.001**	0.75(0.71-0.85)	148.65	**0.004**
Primary	70.0(54.0-80.0)	191.25		0.82(0.568-0.849)	196.12	
Secondary	70.0(54.5-85.5)	201.35		0.81(0.438-0.849)	188.39	
Diploma	69.0(59.0-85.0)	201.44		0.80(0.56-0.841)	186.32	

Table 3. Continued

Variables	EQ-VAS score median(IQR)	Mean rank	P value	EQ-5D-5L Utility Median (IQR)	Mean rank	P-value
Current occupation						
Unemployed	63.0(43.75-78.0)	166.43	0.055	0.76(0.568-0.849)	173.88	0.392
Farmer	66.0(51.0-83.0)	178.37		0.76(0.573-0.85)	171.80	
Housewife	61.5(47.25-80.0)	162.50		0.77(0.645-0.874)	175.32	
Gov't employed	70.0(54.5-82.75)	195.98		0.79(0.572-0.852)	194.14	
Student	71.5(60.0-83.25)	211.13		0.82(0.408-0.812)	192.67	
Private sector	60.0(50.0-80.0)	161.10		0.70(0.541-0.857)	142.08	
Family history of epilepsy						
Yes	65(50-80)	173.16	0.161	0.79(0.591-0.848)	192.3	0.32
No	75(52.75-88.25)	199.26		0.75(0.560-0.850)	174.2	
Source of medication						
Free	65(65.0-80.0)	178.90	0.687	0.75(0.566-0.849)	172.66	0.423
Charged	65(65.0-80.0)	173.42		0.78(0.568-0.850)	180.52	
Number of seizures before treatment started						
<5	66.(51.5-80.0)	181.06	0.314	0.80(0.608-0.849)	189.1	**0.016**
>5	64.(45.0-54.5)	170.86		0.75(0.495-0.782)	163.11	
Comor Yes	54.(50.0-80.0)	121.46	**0.001**	0.58(0.521-0.849)	129.55	**0.001**
No	75(50.0-80.0)	216.70		0.83(0.571-0.850)	210.66	

Variables	EQ-VAS score median (IQR)	Mean rank	P value	EQ-5D-5L utility score median(IQR)	Mean rank	P-value
Medications for co-morbidity						
Yes	55(42.0-65.0)	120.60	**0.001**	0.59(0.560-0.849)	121.53	**0.001**
No	71(60.0-84.0)	208.99		0.82(0.568-0.850)	206.05	
Number of AEDs taking						
One	63(50.0-80.0)	174.5	0.80	0.76(0.575-0.85)	173.1	0.56
Two	67(40-78.25)	181.6		0.78(0.534-0.849)	188.1	
Three	70(60.0-80.0)	207.3		0.68(0.501-0.835)	182.5	
Adverse drug events						
Yes	60(47.25-77.75)	159.01	**0.048**	0.75(0.560-0.849)	163.01	0.130
No	67(52.0-80.0)	182.77		0.77(0.576-0.849)	181.18	
Medication adherence						
Adherent	66(51.0-80.0)	176.19	0.97	0.79(0.576-0.850)	180.27	0.389
Non-adherent	65(50.0-80.0)	175.77		0.76(0.546-0.849)	170.90	
Seizure status						
Good	65(50-80)	177.92	0.659	0.78(0.601-0.85)	176.42	0.950
Poor	64(42.0-77.25)	173.03		0.77(0.521-0.848)	175.73	

CI, Confidence Interval, EQ-5D-5L. Euro-QoL life five dimensions with five levels, EQ-VAS, Euro-QoL-Visual Analog Scale, IQR, Inter Quartile Range, and Bold numbers indicate there is a statistically significant association.

5.4. Factors associated with health-related quality of life among the study participants

In this study, advanced age (> 60 years) (β = -0.21, 95% CI = -0.402, -0.017), being widowed (β = -0.14, 95% CI = -0.256, -0.028), five and more seizure episodes before treatment (β =-0.0054, 95% CI: -0.0102-0.006) were significantly negative associated with HRQoL. Conversely, the absence of co-morbidities (β = 0.095, 95% CI: 0.012 -0.178) and not experiencing seizure remitting-relapsing (β = 0.062, 95% CI: -0.0007- 0.125) were positively associated with HRQoL (Table 5).

Table 4. Health-related quality of life and associated factors among the study participants at three selected hospitals in Mekelle City, Tigray, Ethiopia, 2023 (N=351)

	EQ-5D-5L utility score		EQ-VAS score	
Patient characteristics	β-Coefficient [95% CI]	P-value	β-Coefficient [95% CI]	P-value
Age of participant (18-30 years ©)				
31-44 years	-0.0227(-0.079,0.032)	0.417	-2.821(-7.964, 2.322)	0.281
45-60 years	0.0060(-0.168,0.0466)	0.266	4.454(-12.494, 3.587)	0.276
>60 years	-0.209(-0.402,-0.017)	**0.007**	0.545(-25.736,-3.359)	**0.011**
Type of epilepsy (GTCS ©)				
Focal onset	-0.042(-0.104,0.208)	0.191	-4.490(-8.83,-0.166)	**0.043**
Unclassified	-0.0001(-0.062,0.061)	0.985	-2.902(-1.352, 7.16)	0.180
Marital status (Single ©)				
Divorced	-0.120(-.250, 0.009)	0.07	-18.37(-27.57, -9.166)	**0.001**
Widowed	-0.142(-0.256,-0.028)	**0.015**	-5.251(-14.85,4.353)	**0.001**
Number of seizure episodes before treatment (< 5 seizures ©)				
> 5 seizures	-0.0054(-0.0102, 0.006	**0.0027**	-1.369(-4.87, 2.13)	0.442
Seizure remitting-relapsing (yes©)				
No	0.062(-0.0007,0.125)	**0.03**	3.11(-1574,7.799)	0.192
Co-morbidity (yes ©)				
No	0.095(0.012,0.178)	**0.025**	12.63(6.650, 18.612)	**0.001**

5.5. Treatment outcomes among study participants

Out of the total study participants, 214 (61%) of them were seizure-free for at least one year, with 75 (21.4%) achieving their seizure-remission status within six months of AED treatment. Seizure remission-relapse was reported in 20.8% of study participants (Figure 4).

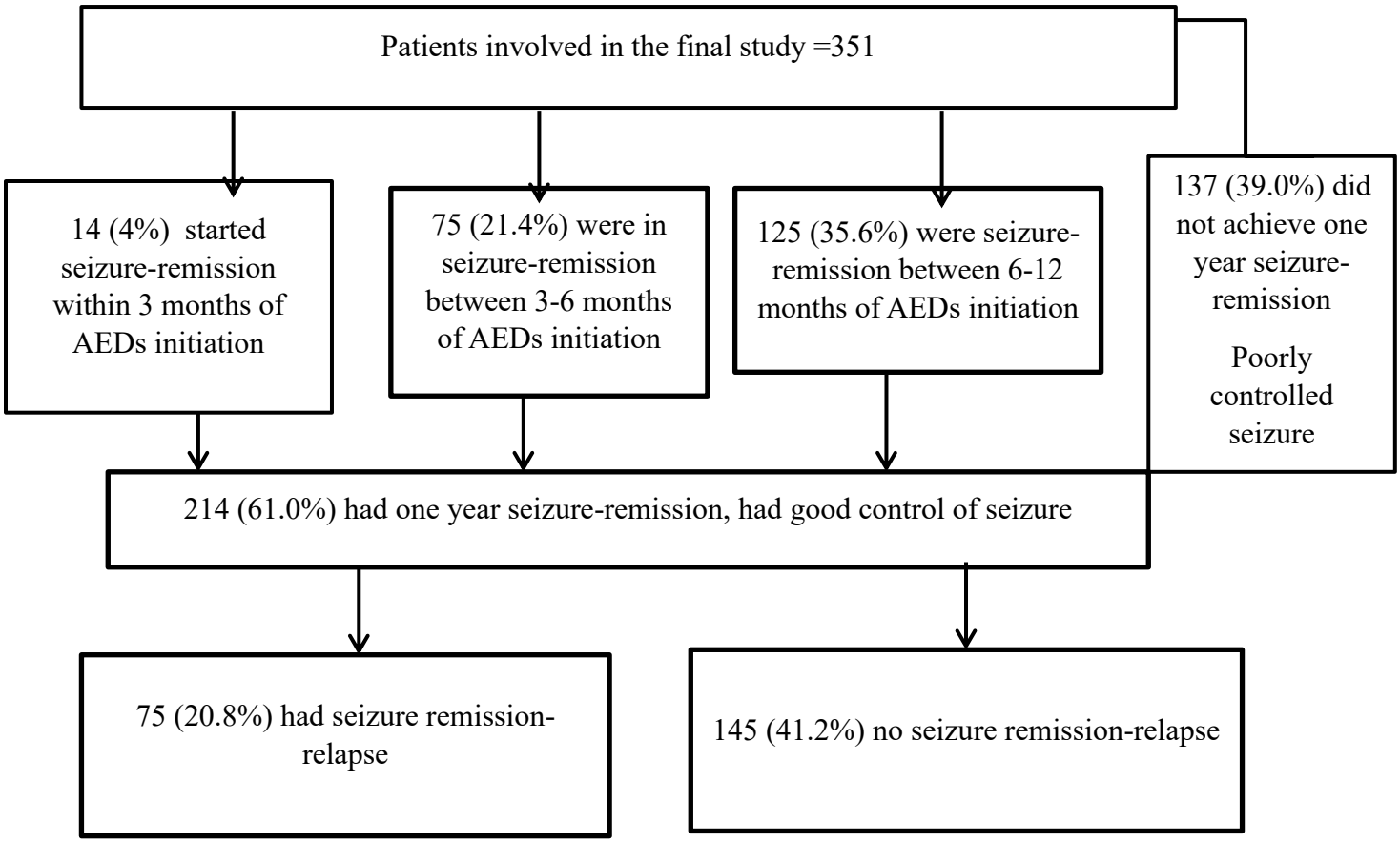

Figure 4. Treatment outcome among the study participants at three selected hospitals in Mekelle City, Tigray, Ethiopia, 2023 (N=351)

5.6. Factors associated with treatment outcome among study participants

In this study, living in urban areas (AOR=3.36, 95% CI; 1.1-10.4, p=0.037), being government-employed (AOR= 4.0, 95% CI; 1.1-14.5, p=0.035), and a student (AOR=4.0, 95% CI; 1.1-14.5, p=0.035) were significantly associated with good seizure control in our study. On the other hand, frequent seizure episodes (> 5 seizures) before AED treatment (AOR= 1.64, 95% CI; 1.03-2.51), p=0.029) was the only factor significantly associated with poor seizure control (Table 6).

Table 5. Factors significantly associated with treatment outcomes among the study participants at three selected hospitals in Mekelle City, Tigray, Ethiopia, 2023 (N=351)

Variables	Category	Seizure control N (%)		COR (95% CI)	AOR 95% CI	P-values
		Good	Poor			
Residence	Rural	95 (67.9)	45(22.1)	1		
	Urban	118 (56.2)	92 (43.8)	1.61(1.03-2.51)	1.64(1.03-2.51)	**0.029**
Current occupation	Unemployed	102 (60)	68 (40)	1		
	Farmer	19 (63.3)	11(36.7)	2.67(0.96-7.45).	2.6(0.96-7.5)	0.06
	Housewife	25 (54.3)	21 (45.7)	2.31(0.7-7.92)	2.31(0.7-7.92)	0.181
	Gov't	11(50.0)	11(50.0)	3.36(1.07- 10.46)	3.36(1.1-10.47)	**0.037**
	Student	36 (62.1)	22(37.9)	4.0(1.10-14.50)	4.0(1.1-14.5)	**0.035**
	Private sector	20 (80.0)	5(20).0	2.44(0.8-7.45)	2.4(0.8-7.4	0.12
Seizures before treatment	<5	127 (73)	47(27)	1		
	>5	85 (48.3)	91 (51.7)	2.89 (1.83-4.87)	0.22(0.05-0.97)	**0.045**

COR: Crude Odds Ratio; AOR: Adjusted Odds Ratio; CI: Confidence Interval and Bold number indicate there is a statistically significant association.

5.7. Level of medication adherence and associated factors

Out of the total study participants, only 28% of the respondents were highly adherent to their AED treatment, while half of the participants (177, 49.6%) were non-adherent to their treatment. The most commonly reported reasons for medication non-adherence were feeling hassled to stick with the treatment plan (45.58%), unavailability of AEDs (45.3%), and forgetfulness (41.3%). Several factors demonstrated a significant association with AED treatment adherence. Being a farmer (AOR=4.2, 95% CI: 1.5-11.3, p=0.005), housewife (AOR=4.9, 95% CI: 1.4-17.2, p=0.012), free of seizure-triggering factors (AOR=3.7, 95% CI: 2.34-6.06, p<0.001), absence of co-morbidities (AOR=1.8, 95% CI: 1.11-11.28, p=0.008), and good seizure control (AOR=2.38, 95% CI: 1.55-3.71, p<0.001) were factors significantly associated with AED treatment adherence (Table 7).

Table 6. Factors associated with medication adherence among study participants at three selected hospitals in Mekelle City, Tigray, Ethiopia, 2023 (N=351)

Variables	Adherence N (%)		COR (95% CI)	AOR 95% CI	P-values
	Adherent	Non-adherent			
Current occupation					
Unemployed	94(55.3)	76(44.7)	1		
Farmer	17(56.7)	13(43.3)	3.4 (1.36-8.6)	4.2 (1.5-11.3)	**0.005**
Housewife	29(63.0)	17((37)	5.14 (1.62-16.36)	4.9 (1.4-17.2)	**0.012**
Government	12(54.5)	10(45.5)	2.8 (0.98-8.00	2.9 (0.9-8.6)	0.06
Student	32(55.2)	26(45.8)	0.57 (0.14-2.3)	0.54 (0.11-2.6)	0.44
Private sector	11(44.0)	14(56.0)	1.95 (0.70-5.38)	1.4(0.9-2.)	0.05
Seizure triggering factor					
Yes	76(39.8)	115 (61.2)	1		
No	57(35.6)	103 (64.6)	3.71 (2.34-5.88)	3.71 (2.34-6.06)	**0.001**
Comorbid disease					
Yes	77(51.3)	73(48.7)	1		
No	73(45.6)	87(54.4)	1.70 (1.11-2.61)	1.81 (1.11-2.81)	**0.008**
Seizure control					
Poor	72(52.2)	66(47.8)	1		
Good	119(55.9)	94(44.1)	2.77(2.77-2.82)	2.38(1.55-3.7)	**0.001**

COR: Crude Odds Ratio, AOR: Adjusted Odds Ratio, CI: Confidence Interval and Bold number indicated there is a statistically significant association.

6. Discussion

This is a multicenter observational study aimed at assessing the HRQoL, treatment outcome, level of medication adherence, and associated factors among epileptic patients at three selected hospitals of neurology clinics in Mekelle City Hospitals, Tigray, Ethiopia.

More than half of the epileptic patients in this study had poor HRQoL, with a median utility score below the median (IQR) score of 0.77 (0.56-0.85). The mean (±SD) in EQ-5D-5L utility value and EQ-VAS score of the study participant were 0.68 ± 0.230, and 64.7 ± 18.36 respectively. These findings were lower as compared to the general population of Ethiopia, which had a mean (±SD) utility of 0.94 (±0.10) and a mean (±SD) EQ-VAS score of 87.27 ±13.63 (125), suggesting epileptic seizures have a significant impact on the HRQoL of epileptic patients. People living with epilepsy have multiple factors that attenuate the HRQoL as compared to the general population and other chronic disorders (127, 128). Uncertainty about seizure frequency and pattern, common co-morbidities like anxiety and depression, high unemployment rate, and longer treatment duration are among the factors that reduce the HRQoL in epileptic patients (15, 129). In addition, AEDs exhibit diverse pharmacokinetic profiles and are associated with ADEs mainly cognitive impairment which can further influence the HRQoL of epileptic patients (130, 131). This implies the HRQoL of epileptic patients in the study area was poor, suggesting the importance of recognizing epilepsy as a significant public health concern that demands more attention to augment the HRQol of epileptic patients.

The mean± SD EQ-VAS (64.7 ± 18.36) score of this study was similar to a study done in the United Kingdom and Malaysia, which reported 66, and 68.9 ±15.9) respectively (90, 132). However, respondents in this study had slightly better HRQoL in comparison to studies done in Ethiopia (55.6±20.9), Uganda (58.0±13), and the global mean score (59.8±8) (90, 91, 133). The difference in HRQoL scores may be attributed to the fact that the previous studies included patients who had been taking medications for at least 3 months and could have had poor seizure control and poor HRQoL compared to the participants in this study. Additionally, the previous studies were conducted in a single health facility, and used different tools, such as QOLIE-31 and WHOQOL-BREF, to evaluate the HRQoL, which may have contributed to the variation in the results.

In the EQ-5D-5L descriptive system, anxiety/depression was a highly reported health dimension (342, 97.4%) followed by pain/discomfort (335, 95.7%). The findings of the study were in agreement with the

study done in the general population of Ethiopia, where anxiety/depression was the most frequently reported problem, accounting for 43.29% of the population (125), and a study in Dessie Referral Hospital (93). This suggested that epileptic seizures have a significant effect on the psychological aspect of patients' HRQoL. Factors such as excessive worry about seizure patterns and frequency, stigma and discrimination, and medication-related side effects are some factors contributing to the poor psychological aspect of HRQoL in people living with epilepsy (134). Additionally, anxiety and depression are common co-morbidities in individuals living with epilepsy, which may increase the risk of suicide and feelings of stigmatization that may negatively affect the HRQoL (135, 136).

The current study also attempted to determine the factors that have a significant impact on the HRQoL of epileptic patients. Similar to previous studies (90, 137-139), this study found a significant negative association between the number of seizure episodes (>5 episodes) and HRQoL of people with epilepsy. Frequent seizure attacks have a manifold detrimental effect on HRQoL. They are associated with excessive fear, unemployment, and psychological distress (90). The uncertainty of seizure patterns and frequency in epileptic patients predisposes them to live in discomfort and be restricted from doing routine tasks such as driving, cooking, swimming, and engaging in social interactions (140, 141). This finding emphasizes the need for optimal seizure control protocols like effective AED treatment, building public awareness, and social support to improve the HRQoL of epileptic patients.

Another factor that adversely affected the HRQoL in our study was the age of the study participants, and elders (age >60 years) had relatively lower EQ-5D-5L utility values than patients aged 18-30 years. This finding was consistent with studies done in Ethiopia, and Italy (142, 143). One possible explanation for the poor HRQoL in elder epileptic patients could be because they are affected by various co-morbidities, which predispose them to polypharmacy, frequent hospitalization, and increased healthcare costs (144, 145). They also have delayed drug metabolism and clearance, which results in prolonged drug exposure in the body and increases their risk of ADEs (146, 147). Additionally, most of the AEDs have a significant effect on cognitive functioning, fatigue, and memory, which further decline their HRQoL (144, 148). Our finding suggested that elderly epileptic patients have poor HRQoL, and their treatment should be individualized, and AEDs having minimal impact on cognitive functioning, memory, and energy are preferred to decrease the burden of drug-related side effects on HRQoL (149, 150).

The presence of co-morbidities was also another factor that negatively affected the HRQoL of epileptic patients in the current study. Participants without co-morbidities had good HRQoL in both EQ-5D-5L

utility value and EQ-VAS score as compared to those who have co-morbidities, convergent to studies done in the United States, Australia, Nigeria, and Ethiopia (87, 93, 151-153). This might be due to co-morbidities, particularly psychiatric illnesses are associated with disability, stigma, and higher suicidal rates, which can result in poor medication adherence, poorly controlled seizures, and frequent hospitalizations (76, 154). Likewise, AEDs especially the conventional ones, have potential interactions with co-morbidities and other medications, thereby augmenting ADRs such as cognitive impairment, fatigue, sleep disturbances, and restlessness, contributing to repeated hospital visits and further decline in HRQoL (153, 155-157). This finding implies that epileptic patients should be screened for co-morbidities and the treatment goal of epileptic patients should not solely target controlling the seizures; it should be individualized and must address the co-existing co-morbidities.

Assessment of seizure control and associated factors was another goal of our study. In our study, we found that 61% of the study participants achieved a one-year seizure remission, which is comparable with studies done in Ethiopia 64.6% (100), Nigeria 62.8% (99), China 61.3% (98), and Scotland 63.7% (95), that demonstrates substantial proportion of patients had not achieved seizure remission. However, the rate of the seizure-free period observed in this study was significantly lower than studies done in China 80% (158), and Ethiopia 78% (101). In contrast, the seizure control achieved in our study was superior to other studies conducted in Ethiopia (159), Nigeria (160), and rural areas of China (161), where the proportion of seizure control in those studies was 39.2%, 43%, 43.6%, and 45% respectively. Discrepancies in seizure control rates across these studies could be attributed to factors such as sample size, methodology, the inclusion of newly diagnosed epileptic patients, variations in healthcare access, AEDs used and availability, and possibly genetic variability.

In this study, 20.8% of the study participants had seizure remission- relapse which is lower than in other studies 36.6% (98), 40% (162), and 28.7% (100). This finding implies that there is a high probability of experiencing seizures after seizure remission is achieved. The American College of Neurology (ACN) showed most of the seizure recurrence happened within the first year of seizure occurrence, but the cumulative incidence of seizure recurrence increases over time (163). Therefore, it is important to have a sufficient follow-up period including patients who achieved seizure remission, and the patient's neurological, cognitive, and EEG should be evaluated before deciding to discontinue an AED treatment in epileptic patients (164, 165).

Many factors determine the treatment outcomes in people living with epilepsy. According to the findings of this study, place of residence, employment status, and number of seizure episodes before the initiation of AED treatment were significantly associated with seizure control. Interestingly, these findings diverged from previous studies (95, 101), where treatment duration, number of AEDs used, medication adherence, and number of seizure episodes before treatment initiation were predictors of seizure control.

Previous studies reported that epileptic patients living in urban areas had better seizure control than those living in rural areas (79, 166, 167), also supported by findings of this study, where urban dwellers were 1.64 times more likely to be seizure-free than those living in rural areas. This could be because patients living in urban areas have good access to healthcare services which allows them to discuss with their healthcare providers easily and are more aware of their medical condition and medications than rural residents. In addition, rural residents have more affiliation with religious and traditional medicine which might affect their healthcare-seeking behavior and result in poor seizure control (168, 169). This implies the expansion of epilepsy care services to primary healthcare facilities and providing comprehensive training to healthcare professionals working in rural areas is important to optimize healthcare service and seizure control.

Consistent with the findings of previous studies (170-172), a significant proportion (48.6%) of epileptic patients in this study were unemployed and had poor seizure control. Government-employed patients and students were 4 and 3.5 times more likely to achieve a one-year seizure-free period than those unemployed. The unpredictable and visible nature of seizures in epileptic patients often leads to significant barriers and social discrimination, unlike other disease conditions (170). Many employees refuse to hire people living with epilepsy due to the concern of workplace accidents and frequent workplace absenteeism (173, 174). Moreover, the presence of co-morbid mental disorders, low educational background, and qualifications also contribute to the high unemployment rate in this population. Efforts should focus on improving awareness about epilepsy, changing misconceptions, and promoting equal job opportunities for individuals living with epilepsy (16, 69).

The frequency of seizures before the initiation of AED treatment emerged as a significant factor that influences seizure control in the current study. Epileptic patients who experienced >5 episodes of seizures before starting AED treatment were less likely to achieve seizure remission as compared with those having infrequent seizure episodes. This finding was consistent with other studies (100, 175). One possible explanation is that prolonged and frequent seizure attacks can lead to additional structural and neurological

damage, potentially contributing to the development of new epileptic foci, which ultimately may result in poor seizure control (176, 177). Additionally, multiple seizure episodes before AED treatment may inherently alter the target receptors for AEDs and exacerbate the severity of the disease, which can compromise the response to AEDs (178). Studies suggested that early identification and immediate treatment of epileptic seizures are associated with a low probability of seizure relapse and good seizure remission (38, 179).

The other aim of this study was to assess medication adherence and associated factors. Only 174 (49.6%) of the study participants were adherent to their medications, which closely aligns with studies conducted in Pakistan, Malaysia, and China, which reported adherence rates of 50%, 50.7%, and 51.9% respectively (33, 106, 180). However, AED adherence in the current study was significantly lower than in studies conducted in India 70% (181), and Pakistan 73.33% (182). Variations in sample size, duration of treatment, healthcare access, insurance coverage, and socio-demographic factors could be potential contributing factors to the inconsistent results among the studies. Additionally, the internal crisis within the current study area may contribute to a lower rate of adherence, particularly as it affects the availability and type of AEDs.

Multiple factors influence treatment adherence in epileptic patients (183). In this study, unavailability of AEDs 160 (45.58%), feeling hassled to stick with the treatment plan 159 (45.3%), and forgetfulness 145 (42%) were the most reported reasons for non-adherence. This was congruent to other studies (184), (185) in which forgetfulness, running out of AEDs, and missing medication were commonly reported in patients with poor AED adherence. In contrast to this study, previous studies (186, 187), showed that forgetfulness (64.5%), use of alternative therapies (10%), younger age (≤35 years), recent episodes of seizure (≤1 month), drug-related fatigue, and being away from home were significantly associated with AEDs non-adherence. The possible justifications for such inconsistency might be the difference in methodology and tool used to assess medication adherence, healthcare accessibility, medication availability, and socio-demographic factors.

Identifying the barriers to AED non-adherence is one strategy to improve the level of medication adherence in people living with epilepsy(188). In the current study, occupational status, co-morbidity, and seizure control were factors significantly associated with AED adherence (Table 7), which were different from studies done in Sudan (189), and Ethiopia (102).

In this study, nearly half of the study participants were unemployed, and farmers and housewives were more adherent to AED treatment than unemployed patients. The visible and unpredictable pattern of seizure attacks makes epileptic patients isolated from the social environment and affects their daily tasks, which is associated with a significant rate of unemployment and underemployment as compared to the general population and people living with other disease conditions (190, 191).

Patients without co-morbidities were about twice more adherent to their AEDs prescribed as compared to their counterparts in the current study, which was similar to other studies (102, 184). Common co-morbidities in epileptic patients like anxiety, depression, and other neurodegenerative disorders are significantly related to low mood, poor interest, fatigue, and cognitive impairments which decrease the motive of epileptic patients to adhere to their AEDs (139, 192, 193). Additionally, many medications used to treat these comorbidities and AEDs have multiple drug-drug interactions and overlapping ADEs, which can be an additional contributing factor to treatment discontinuation (102). This finding suggests that the treatment of epilepsy should be individualized and special attention should be given to epileptic patients with co-morbidities.

7. Limitations of the study

This study aimed to evaluate HRQoL, treatment outcomes, AED adherence, and related factors across multiple centers, utilizing a reasonable sample size and validated assessment tools. However, this study was not without limitations. Had a cohort study design with longer follow-up been employed, the strength of association among the factors might have been good. Additionally, the exclusion of newly diagnosed and pediatric epileptic patients limits the applicability of the findings to these specific patient groups.

8. Conclusion

In this multicenter observational study, more than half of epileptic patients had poor HRQoL, with the anxiety/depression dimension being the most commonly reported health problem. Age, status of employment, co-morbidity, number of seizure episodes before AED treatment, treatment outcome, and seizure-remitting relapse were the factors significantly associated with HRQoL. More than two-thirds of epileptic patients had poor seizure control, with one out of five epileptic patients experiencing seizure remission-relapse. Living in rural areas, unemployment, and frequent seizure episodes before treatments were factors associated with poor treatment outcomes. In addition, half of the study participants had low adherence to their AEDs. Unemployment, frequent seizure episodes before AED treatment, co-morbidity, and poor seizure control were factors significantly associated with medication non-adherence in our study.

9. Recommendations

- Throughout the follow-up period, it is essential to assess the health-related quality of life of individuals with epilepsy, with particular emphasis on older patients, those with co-morbidities, and frequent seizure episodes.
- Timely identification of epileptic seizures by healthcare providers is crucial, and personalized treatment with AEDs should be initiated promptly, taking into account factors such as seizure type, underlying cause, neurological assessments, and imaging results to optimize treatment outcomes and minimize the occurrence of future seizure episodes.
- Regular screening for co-morbidities and appropriate treatment should be provided to individuals living with epilepsy.
- Encouraging active participation of individuals with epilepsy and their caregivers in the treatment process, along with implementing strategies like utilizing a follow-up checklist and regularly discussing medication adherence during follow-up visits, can promote adherence to AEDs.
- There is a need for additional research studies that employ longitudinal designs, longer durations of follow-up, and larger participant populations to investigate the effects of poor medication adherence and frequent seizure episodes on health-related quality of life and related costs. These studies should also incorporate newly diagnosed individuals and pediatric patients with epilepsy. Researchers should also investigate the prevalence, treatment outcomes, and predictors of drug-resistant epilepsy to address this significant public health challenge.

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Annexes I

Consent form of study participants

Dear study participant,

My name is _____, and I am collecting data for a study titled "Assessment of Health-related Quality of Life, Treatment Outcome, Medication Adherence, and Associated Factors among epileptic patients." The study is being carried out by G/Michael G/yohanns, a Master's student in Pharmacy Practice at Addis Ababa University, College of Health Sciences, School of Pharmacy, Department of Clinical Pharmacy and Pharmacology.

The main objective of this study is to evaluate the HRQoL, seizure control, medication adherence, and related factors in epileptic patients in Tigray, Mekelle, Ethiopia. The findings from this study will play a crucial role in shaping healthcare policies and strategies that aim to improve the quality of life, medication adherence, and treatment outcomes for epileptic patients. Additionally, the results will provide valuable insights for healthcare providers to reflect on their current practices and strive for better patient care.

Your participation in this study is highly appreciated, and we kindly request your honest and genuine responses to the study questionnaires. Please be assured that there is no immediate payment or direct incentive for participating in this study. However, the information obtained from this study will contribute to enhancing the quality and type of healthcare services provided to you and others in similar situations.

Participating in this study will not incur any costs for you, except for approximately 30 minutes of your time for data collection. Your selection as a participant in this study is random, as you happened to be at the hospital during the designated time for the study. There is no specific targeting of individuals; it is purely based on chance. Your involvement in this study will not cause any harm to you.

It is important to emphasize that your participation in this study is entirely voluntary. You have the right to choose whether or not to participate, and you can withdraw from the study at any time without any consequences. Your decision to participate or decline will not affect the healthcare services you receive at the hospital.

We want to assure you that your privacy will be strictly protected throughout the study. Your personal information will be kept confidential using unique identifiers, and access to the data will be limited to the principal investigator and those directly involved in the research.

If you have any questions or require further information about the study, please feel free to contact any of the following responsible individuals:

Personal contacts

G/Micheal G/yohannes kahsay, phone number:+251975271763

Email address: gebrmichealgebreyohanns@gmail.com,

Or my advisor

Alemseged Beyene(Associate professor, clinical pharmacy)

Email address: alemseged.beyene@aau.edu.et

Consent: I read the consent form, it has been read to me by the data collector, and I understood all the content of the document. Henceforth

I agree to participate in the study, and I can confirm my consent through my signature-------

Name of the interviewer: _____Sign. _____ , Date of interview_____

Name of the supervisor: _____ Sign. _____ Date_____

Thank you for being involved in the study and for your valuable time!!!

Annex II

Data collection tool

Questionnaire number---------- Code----------

Patient ID number---------- Health institution---------

Data collector name---------- Signature……

Part I. Participant Socio demographics (please encircle your letter of choice)

1. Sex A. Female ❑ B. Male ❑

2. Age (years) ❑----------
3. Residence A. Urban ❑ B. Rural ❑
4. Marital status
   A. Single ❑ C. Married ❑
   B. Divorced ❑ D. Widowed ❑
5. Religion

A. Orthodox ❑ B. Muslim C. Protestant ❑ D. Catholic ❑

6. Educational status
   A. No formal education ❑ C. Primary ❑
   B. Secondary ❑ D. Diploma and above ❑
7. Employment
   A. Unemployed ❑
   B. Government Employed ❑ C. Working in the private sector ❑
   C. Student ❑ D. Farmer ❑
   E. Housewife ❑ F. Daily laborer ❑
   F. Others ❑
8. Source of your medication A. Free ❑ B. Fee❑
9. History of Social drug use/abuse A. Yes ❑ B. No ❑

9.1. If yes, please specify …….

Part II. Clinical characteristics of study participants

1. Family history of epilepsy A. Yes ❑ B. No ❑ C. N/A❑
2. Etiology of seizure
   A. Genetic ❑ C. Structural/metabolic ❑
   B. Infectious ❑ D. Idiopathic (unknown cause) ❑
3. Seizure type
   A. Focal onset seizure ❑ B. Generalized onset seizure ❑ C. Unclassified seizure❑
4. Age at onset seizure diagnosis(years) ❑
5. Number of seizures before starting treatment ❑
6. One year seizure-free period A. Yes ❑ B. No ❑ C. N/A❑
7. When was the seizure-free period achieved
   A. Immediately after treatment started ❑
   B. 3-6 months after AED treatment ❑
   C. Between 6-12 months after AED treatment ❑
   D. After one year of AED treatment ❑
   E. Not achieved ❑
8. Any seizure triggering factor A. Yes ❑ B. No ❑

8.1. If yes please specify ----------.

9. Prior brain injury A. Yes ❑ B. No ❑

9.1. If yes, time of brain injury occurred A. Before seizure ❑ B. After seizure ❑ C. N/A❑

10. Any imaging technique A. Yes ❑ B. No ❑ C. N/A❑

10.1.If yes please specify ……..

11. Report the result of the imaging /EEG----------
    A. Normal ❑ B. Abnormal ❑
12. Any history of status epileptics A. Yes ❑ B. No ❑ C. N/A ❑

12.1.If yes was medication given? A. Yes ❑ B. No ❑ C. N/A ❑

12.2.Medication order for the condition(status epileptics) ❑------

13. Comorbid disease condition/s A. Yes ❑ B. No ❑ C. N/A ❑

13.1.If yes; what type of comorbid condition?

A. HIV and OIs ❑ C. CRVHD/❑
B. CHF ❑ D. Major depressive disorder ❑

E. Migraine headache ❑ F. Mental retardation ❑ G. HTN ❑

H. Stroke ❑ I. Others ❑

13.2.Are you taking any medication for the condition

A. Yes ❑ B. No ❑

13.3.If yes specify----------

The patient seizure follows-up checklist form during the study period

Follow-up date	AEDs	Months	Number of seizures recorded	Remark
		1		
		2		
		3		
		6		
		9		
		12		
		15		
		18		
		21		

Part III. Prescribing Pattern of AEDs among epileptic patients

AED treatment initiation	A. Monotherapy (one drug) ❑ C. Triple therapy (3 drugs) ❑ B. Quadruple therapy(4 drugs) ❑ D. Dual therapy (2 drugs) ❑
Type of AED prescribed at initiation	A. Phenobarbitone (PHB) ❑ C. Phenytoin (PH) ❑ B. Valproic acid (VA) ❑ D. Carbamazepine(CBZ) ❑ E. PHB+PHT ❑ F. PHB+VA ❑ G.PHT+VA ❑ H. PHB+CBZ ❑ I. PHT+CBZ ❑ J. Other, Specify……
Any ADR/s detected specify A. Yes ❑ B. No ❑ C. N/A ❑	

Dosing of Antiepileptic drugs

AED name	Follow date of follow-up	Dose at initiation	Current dose	Max dose	Dose side effects reported	Dose-seizure free period achieved
Phenobarbitone (PHB)						
Phenytoin (PHT)						
Valproic acid						
Carbamazepine						
PHB+PHT						
PHB+VA						
PH+VA						
VA+CBZ						
CBZ+PHB						
PHT+CBZ						
Others specify--------						

Part IV. 8-Item Morisky Medication adherence(AEDs) scale (MMAS-8)		Yes	No
1	Do you sometimes forget to take your AED/s?	❑	❑
2	People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your AED/s?	❑	❑
3	Have you ever cut back or stopped taking your AED/s without telling your doctor because you felt worse when you took it?	❑	❑
4	When you travel or leave home, do you sometimes forget to bring along your mAED/s?	❑	❑
5	Did you take all your AED/s yesterday?	❑	❑
6	When you feel like your symptoms are under control, do you sometimes stop taking your AED/s?	❑	❑
7	Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	❑	❑
8	How often do you have difficulty remembering to take all your AED/s? A) Never/rarely❑ B) Once in a while ❑ C) Sometimes ❑ D) Usually ❑ E) All the time ❑		

V. Health Questionnaire (EQ-5D-5L) UK (English) © 2009 Euro Qol.

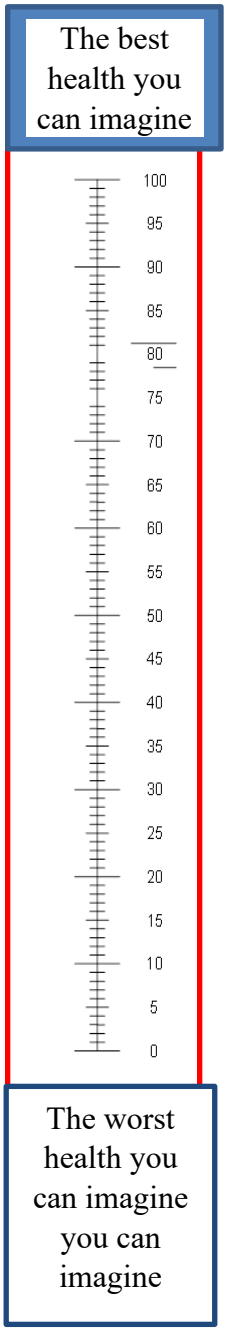
MOBILITY	
I have no problems walking about	❑
I have slight problems in walking about	❑
I have moderate problems in walking about	❑
I have severe problems in walking about	❑
I am unable to walk about	❑
SELF-CARE	
I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑
USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	
I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑
PAIN / DISCOMFORT	
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑
ANXIETY / DEPRESSION	

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

Health Questionnaire (EQ-5D-5L) UK (English) © 2009 EuroQol

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
- 0 means the worst health you can imagine.
- Mark an X on the scale to indicate
- How your health is today
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY ☐



ኣብ ትሕቲ ሕድሕድ ርእሲ ንናይ ሎምዓንት ጥዕነኦም/እን ብደንቢ ዝገልፅ ዝሓዘ ሓደ መማረፂ ብምርኣይ ኣብ ቅድሚቱ ዘሎ ሳፁን ይኣርሙ/ማ

ምንቅስቓስ

ብእግረይ ንምጉዓዝ ፀገም የብለይን ❑

ብእግረይ ንምጉዓዝ ንእሽተይ ፀገም ኣለኒ ❑

ብእግረይ ንምጉዓዝ ማእኸላይ ፀገም ኣለኒ ❑

ብእግረይ ንምጉዓዝ ብርቱዕ ፀገም ኣለኒ ❑

ብእግረይ ምጉዓዝ አይክእልን ❑

ዓርሰ-ምንክብኻብ

ዓርሰይ ንምሕፃብ ወይ ክዳነይ ንምክዳን ፀገም የብለይን ❑

ዓርሰይ ንምሕፃብ ወይ ክዳነይ ንምክዳን ንእሽተይ ፀገም ኣለኒ ❑

ዓርሰይ ንምሕፃብ ወይ ክዳነይ ንምክዳን ማእኸላይ ፀገም ኣለኒ ❑

ዓርሰይ ንምሕፃብ ወይ ክዳነይ ንምክዳን ብርቱዕ ፀገም ኣለኒ ❑

ዓርሰይ ንምሕፃብ ወይ ክዳነይ ምክዳን አይክእልን ❑

ዝውቱራት ተግባራት (ንኣብነት ስራሕ፣ መጽናዕቲ፣ ስራሕቲ-ገዛ፣ ቤተሰብ ወይ መዝናነይቲ ተግባራት)

ዝውቱራት ተግባራተይ ኣብ ምትግባር ፀገም የብለይን ❑

ዝውቱራት ተግባራተይ ንምትግባር ንእሽተይ ፀገም ኣለኒ ❑

ዝውቱራት ተግባራተይ ንምትግባር ማእኸላይ ፀገም ኣለኒ ❑

ዝውቱራት ተግባራተይ ንምትግባር ብርቱዕ ፀገም ኣለኒ ❑

ዝውቱራት ተግባራተይ ምትግባር አይክእልን ❑

ቃንዛ/ ስእነት-ምኞት

ቃንዛ ወይ ስእነት-ምኞት የብለይን ❑

ንእሽተይ ቃንዛ ወይ ስእነት-ምኞት ኣለኒ ❑

ማእኸላይ ቃንዛ ወይ ስእነት-ምኞት ኣለኒ ❑

ብርቱዕ ቃንዛ ወይ ስእነት-ምኞት ኣለኒ ❑

ብጣዕሚ ከቢድ ቃንዛ ወይ ስእነት-ምኞት ኣለኒ ❑

ጭንቀት / ዝን-ምባል

ጭኦኞ ወይ ዝን-ዝበልኩ ኣይኮንኩን ❑

ንእሽተይ ጭኦኞ ወይ ዝን-ዝበልኩ እየ ❑

ብማእኸላይ ጭኦኞ ወይ ዝን-ዝበልኩ እየ ❑

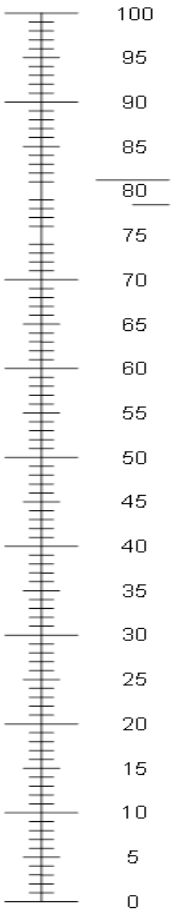
ብርቱዕ ጭኦኞ ወይ ዝን-ዝበልኩ እየ ❑

ብጣዕሚ ከቢድ ጭኦኞ ወይ ዝን-ዝበልኩ እየ ❑

- ጥዕነኡም/አን ሎምዓንቲ ክንደየናይ ፅቡቕ ወይ ሕማቕ ከምዘሎ ክንፈልጥ ንደሊ ኢና።
- እዚ መለክዒ ካብ 0 እስካብ 100 ‘ቁፅሪ ተውሂብዎ ኣሎ።
- 100 ማለት እቲ ብሓሳብኩም/ክን ዝበለፀ ኢልኩም/ክን ትሓስብዎ/ኦ ጥዕና እዩ።
- 0 ማለት እቲ ብሓሳብኩም/ክን ዝኾፍአ ኢልኩም/ክን ትሓስብዎ/ኦ ጥዕና እዩ።
- ናይ ሎምዓንቲ ጥዕነኡም/አን ከመይ ከምዝኾነ ንምምልካት ኣብቲ መለክዒ ናይ X ምልክት የቐምጡ/ጣ።
- ሕዚ በይዘኡም/አን እቲ ኣብቲ መለክዒ ዘቐመጥዎ/ኦ ቁፅሪ

  - 0 ማለት እቲ ብሓሳብኩም/ክን <u>ዝኾፍአ</u> ኢልኩም/ክን ትሓስብዎ/ኦ ጥዕና እዩ።

እቲ ብሓሳብኩም/ክን ዝበለፀ ኢልኩም/ክን ትሓስብዎ/ኦ ጥዕና



እቲ ብሓሳብኩም/ክን <u>ዝኾፍአ</u> ኢልኩም/ክን ትሓስብዎ/ኦ ጥዕና

ናይ ሎምዓንቲ ጥዕነኡም/አን =

ናይ ተሓከምቲ ናይ መድሓኒት ኣዎሳስዳ ዝምልከት

ሕቶታት	መልሲ
ሓደ ሓደ ጊዜ መድሓኒት ምውሳድ ረሲያም ይፈልጡዶ ?	1. እዎ ❑ 2. ኣይፋሉን❑
ሓደ ሓደ ጊዜ ሰባት ካብ ምርሳዕ ወጻኢ መድሓኒት ከይወሰዱ ይተርፉ እዮም። ኣብዝሓለፈ ክልተ ሰሙን መድሓኒት ከይወሰዱ ዘሕለፍዎ መዓልቲ ነይሮም ዶ?	1. እወ ❑ 2. ኣይፋሉን/ኣይኮነን ❑
ሕማሞም ስለ ዝተባኣኣሰ ሓኪሞም ከየማኸሩ መድሓኒቶም ኣቓሪጾም ዶ ይፈልጡ	1. እወ ❑ 2. ኣይፋሉን/ኣይኮነን❑
ኣብ መገሻ ጊዜ መድሓኒቶም ብትክክል ዶ ይዎስዱ ?	1. እወ ❑ 2. ኣይፋሉን/ኣይኮነን ❑
ትማሊ መድሓኒትካ/ኪ ብዝተኣዘዘልካ/ኪ መሰረት ዶ ወሲድካ/ኪ?	1. እወ ❑ 2. ኣይፋሉን/ኣይኮነን ❑
መድሓኒት ዘይምዉሳድ ናይ ሓደ ሓደ ሰባት ፀገም እዩ። መድሓኒቶም ብትእዛዝ መሰረት ንምዉሳድ ይሰላቸዉ ዶ ?	1. እወ ❑ 2. ኣይፋሉን/ኣይኮነን ❑
ሕክምናኻ/ኺ ንምቅ ክትሓስብ እንከለኻ/ኺ ናይ ምንዳድ ስምዒት ይስምዐካ/ኪ ዶ?	1. እወ ❑ 2. ኣይፋሉን/ኣይኮነን ❑

. ኩሉ መድሓኒቶም ንምዉሳድ ዝኸበደኩም ክንደይ ጊዜ እዩ ?	1 በፍጽም❑	2 ብዝኾነ ጊዜ ሓደ ጊዜ ❑	3 ሓሃሓደ/ሳሕቲ / ጊዜ ❑	4 መብዛሕቱኡ ጊዜ ❑	5 ኩሉ ጊዜ ❑

በ ፋርማሲ ት/ቤት
የኢቲካል ሪቪው ኮሚቴ

አዲስ አበባ ዩኒቨርሲቲ
Addis Ababa University

School of Pharmacy
Ethical Review Committee

ቀን Date: March 08, 2021

ቁጥር Ref. No.: ERB/SOP/246/13/2021

To: **Gebremicheal Gebreyohannes Kahsay**
School of Pharmacy

Re: Ethical Clearance

It is to be recalled that you submitted a research proposal entitled "**Assessment of treatment outcome and prescribing pattern of antiepileptic drugs among epilepsy patients, multicenter prospective observational study, Mekelle, Northern Ethiopia**". The committee thoroughly reviewed the proposal based on its operational guidelines and found that it fulfills all ethical requirements stipulated in the guidelines. This is, therefore, to inform you that the proposal is ethically approved for implementation.

With best regards,

Shemsu Umer (PhD)
Chairperson, ERC
School of Pharmacy
College of Health Sciences
Addis Ababa University

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