Assessment of Medication Therapy Management Service outcome among Epilepsy Patients on Follow-up care at Ambulatory Clinic of Tikur Anbessa Specialized Hospital

BY: Meaza Bulbula (B. Pharm)

A Thesis Submitted to the Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University in Partial Fulfillment for the requirements of Master of Science Degree in Pharmacy Practice

May, 2020

Addis Ababa, Ethiopia

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This is to certify that the thesis prepared by Meaza Bulbula entitled "Assessment of Medication Therapy Management Service outcome among Epilepsy Patients on Follow-up care at Ambulatory Clinic of Tikur Anbessa Specialized Hospital", and submitted in partial fulfillment for the requirements of the Degree of Master of Pharmacy in Pharmacy Practice complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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Abstract

Background: The provision of medication therapy management services aims to prevent, identify and resolve drug-related problems (DTPs), thereby reducing morbidity and mortality as well as helping patients achieve improved clinical outcomes. Epilepsy is one of the most common neurological diseases affecting about 45.9 million people globally. However, about 90% of them are not receiving appropriate treatment due to lack of prioritization, poor health care system, and inadequate supply of antiepileptic drugs.

Objective: This study aimed to assess the outcome of medication therapy management service among epileptic patients on follow up care at Tikur Anbessa Specialized Hospital.

Methods: A pre/post study design and systematic random sampling technique were utilized. Data was collected through patient interview, medical charts and electronic data record review. Cipolle's DTP classification, Treatment Satisfaction with Medicine Questionnaire, and Morisky Medication Adherence Scale were used as data collection tools. Data were entered and analyzed using statistical package for social science version 21. Descriptive statistics were used to summarize patients' characteristics and paired sample t –test and McNamara's was performed to examine the effect of intervention in the pre- and post-intervention phases. Inferential statistics (independent t-tests and logistic regression analysis) were used to examine the influences of different variables on outcome. $P<0.05$ was set as a level of significance.

Results: From the total of 336 epileptic patients, generalized tonic-clonic seizure was the most common diagnosis (53.9%) followed by focal to bilateral (14.9%) and unclassified (14%). Majority of the study patients (57.7%) were on mono-therapy and phenobarbital (22.6%) was the most frequently prescribed antiepileptic drug. A total of 451 DTPs had been identified during the study and a significant reduction in the number of DTPs was noted in the post-intervention compared to the pre-intervention phase ($t(335) = 10.79$, $p < 0.005$). Non-adherence, adverse drug reaction and dose too low showed significant reduction ($p < 0.05$) from pre to post study. Duration of seizure, number of comorbidities, total number of medications and seizure control status were significantly associated with DTPs ($p<0.05$). In the post-intervention phase 61% of the patients were adherent to their medication and the general treatment satisfaction was 72.1(SD ± 12.3).

Conclusion: Implementation of medication therapy management service in the neurology clinic is associated with better patient outcomes, as revealed by reduction in the total number of DTPs and the number of patients with DTPs. Moreover, majority of the study patients were adherent to their medication and the general treatment satisfaction was good in the post-intervention phase.

Key words: Medication therapy management, Epilepsy, Tikur Anbessa Specialized Hospital, Drug related problems.

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Abbreviations/Acronyms

ACEIs	Angiotensin Converting Enzyme Inhibitors
ADAs	Antidiabetic agents
ADR	Adverse drug reaction
AEDs	Anti-epileptic drugs
ANOVA	Analysis of variance
AOR	Adjusted odds ratio
APhA	American Pharmacists Association
CBZ	Carbamazepine
CLONA	Clonazepam
CMR	Comprehensive medication review
COR	Crude odds ratio
DM	Diabetes mellitus
DRP	Drug-related problem
DTP	Drugs therapy problem
EEG	Electroencephalograph
GBD	Global burden of disease
GTCS	Generalized tonic clonic seizure
ILAE	International League against Epilepsy
LAMO	Lamotrigine
MAP	Medication related action plan
MMAS	Morisky Medication Adherence Scale
MTM	Medication therapy management
MTR	Medication therapy review
NICE	National Institute for health and Care Excellence
PHB	Phenobarbital
PHT	Phenytoin
PMR	Personal medication record
SATMED-Q	Satisfaction with Medicines Questionnaire

SD	Standard deviation
TASH	Tikur Anbessa Specialized Hospital
UK	United Kingdom
USA	United States of America
USD	United States dollar
VPA	Valproic acid
WHO	World Health Organization

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1. Introduction

1.1. Background

Epilepsy is one of the chronic non-communicable neurologic diseases or conditions, usually with cardinal manifestations of unpredictable, unprovoked recurrent seizures that affect a variety of mental, social and physical functions (disability and socioeconomic burden). The epileptic seizures are manifested by an abnormal, excessive, and hypersynchronous electrical discharge of neurons in a group of brain cells. Several diseases and injuries are implicated in the origin of epileptic seizures. Although many underlying disease mechanisms can lead to epilepsy, the cause of the disease is still unknown in about 50% of global cases (Bromfield *et al.*, 2006; Goldenberg, 2010; Feigin *et al*., 2019).

It is one of the most common neurological diseases affecting about 45.9 million individuals with active epilepsy (idiopathic or secondary nature) globally and nearly 80% of the people with epilepsy live in low- and middle-income countries (Aliand Nabi, 2014; WHO, 2017; Feigin *et al.*, 2019). In Ethiopia, a large community-based epidemiological study revealed the prevalence of epilepsy to be 5.2/1000 population and the annual incidence of 64/100,000 population (Tekle-Haimanot *et al*., 1990; 1997).

International League Against Epilepsy (ILAE) defines epilepsy as a disease of the brain with the following conditions: (i) At least two unprovoked (or reflex) seizures occurring > 24 h apart; (ii) 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 ever in the next 10 years; and (iii) diagnosis of an epilepsy syndrome (Fisher *et al*., 2014). The characteristic signs and symptoms of seizures vary and depend on where in the brain the disturbance first starts, and how far it spreads. Temporary symptoms occur, such as loss of awareness or consciousness, and disturbances of movement, sensation (including vision, hearing, and taste), mood, or other cognitive functions. People with seizures tend to have more physical problems (such as fractures and bruising from injuries related to seizures), as well as higher rates of psychological conditions, including anxiety and depression. Similarly, the risk of premature death in people with epilepsy is up to 3 times higher than the general population, with the highest rates found in low- and middle-income countries and rural versus urban areas (WHO, 2019).

Fisher *et al*. (2017) categorize seizure types into three subgroups: partial, generalized and unknown on-set. Focal seizures are confined to discrete areas of the cerebral cortex; only a certain area of the body is usually involved, at least at the start. Generalized seizures are, however, distinguished by the involvement of the entire brain simultaneously. A partial seizure is further subdivided into focal aware and focal impaired awareness (Banerjee *et al.,* 2009; Brodie *et al.,* 2018 and Pack *et al.,* 2019).

The diagnosis of epilepsy is made primarily by a clinical judgment based on clinical history that requires a witness. Also, it can be further supported by EEG patterns, lesions detected by neuro-imaging, detection of anti-neuronal antibodies, and Gene mutations (Fisher *et al.,* 2017).

The goals of treatment for epilepsy are to eliminate seizures or reduce the frequency, to avoid the adverse effects associated with long-term treatment, and to aid patients in maintaining or restoring their usual psychosocial and vocational activities, and maintaining a normal lifestyle (Goldenberg, 2010; Fisher *et al.,* 2017). Its management includes pharmacological, non-pharmacological (vagal nerve stimulation & ketogenic diet), and surgical (Lobectomy and lesionectomy) approach. The principle of epilepsy management should be individualized and the selection of treatments should aim to control symptoms as well as to prevent other complications (Kerr *et al*., 2009). The treatment goal of epilepsy is a cost-effective approach to eliminate seizures or a reduction in their number and frequency while avoiding drug interactions and side effects and to achieve the best possible quality of life (Rout and Kar, 2010).

Treatment should be started with a single (monotherapy) conventional antiepileptic drugs (AED). The dose should be slowly built up until seizure control is achieved or side effects occur. If the initial treatment is ineffective or poorly tolerated, then another AED can be tried. The dose of the second drug is slowly increased until the adequate or maximum tolerated dose is reached. The first drug is then tapered off slowly. Combination therapy can be considered when two attempts at monotherapy with AEDs have not resulted in seizure freedom (Viktil and Blix, 2008). Factors favoring successful withdrawal of AEDs include a seizure-free period of 2 to 5 years, complete seizure control within 1 year of onset, an onset of seizures after age 2 years and before age 35 years, normal neurological examination and normal I.Q and a normal EEG after treatment (Dipiro *et al*., 2008). When AED treatment is being discontinued, it should be carried out slowly (at least 2−3 months) it may take up to 6 months or longer for benzodiazepines and

barbiturates to avoid drug-related withdrawn symptoms and one drug should be withdrawn at a time (Goldenberg, 2010; Meyer, *et al.*, 2010 and Appleton *et al.*, 2012).

Even though medications are key for epilepsy management, they are also associated with drug therapy problems (DTPs). DTP is any undesirable event experienced by a patient that involves or is suspected to involve drug therapy, and that interferes with achieving the desired goals of therapy and requires professional judgment to resolve (Blume, 2003). Most of AEDs are complex, especially because of varied pharmacokinetic properties between and within individuals, which makes the dosing and monitoring difficult in most of the epileptic patients. The complexity of medical problems and polypharmacy for the management of co-morbidity result in an increased likelihood of drug-related problems (DRPs), which in turn can affect seizure control (Perucca, 2006). Patient medications involving problem can be categorized into seven types of DTPs. These include unnecessary drug therapy, need for additional drug therapy, ineffective drug, dosage too low, adverse drug reaction, dosage too high and noncompliance (Cipolle *et al.*, 2012).

Medication therapy management (MTM) is a range of services provided to individual patients by optimizing therapeutic outcomes (get the most benefit from their medications) (Burns, 2008). The service has five core elements (medication therapy review (MTR), a personal medication record (PMR), a medication action plan (MAP), intervention and referral, and documentation and follow-up) included may increase patient satisfaction and reduce DTPs. It is rendered by pharmacists with the strategic aim of reducing DRPs working collaboratively with physicians and other healthcare professionals to optimize medication use following evidence-based guidelines (Traynor, 2015).

MTM service encompasses a systematic process of reviewing patient's medical history and medication profile, improving patient's understanding of the disease state and patient drug therapy, helping patients to self-monitor both desirable and undesirable medication-related effects, and collaboration with other members of the health care team to optimize drug therapy (Smith *et al.*, 2010). Any patient using prescription and non-prescription medications, herbal products, and other dietary supplements could potentially benefit from MTM services especially if a potential or actual DRP is discovered or suspected, regardless of the number of medications

they use, their specific disease states, or their health plan coverage (Burns, 2008; Di Pietro and Bright, 2014).

This study aimed to provide MTM services and assess the outcome of the provided intervention for epilepsy patients on follow up at the ambulatory neurology clinic of Tikur Anbessa Specialized Hospital (TASH).

1.2. Statement of the Problem

Epilepsy is one of the most common neurological diseases affecting about 45.9 million people globally and associated with 126,055 deaths and 13.5 million disability. About 90% of epileptic patients are not receiving appropriate treatment due to the cultural attitude, lack of prioritization, poor health care system, economic problem and inadequate supply of AEDs. Nearly 80% of the people with epilepsy live in low- and middle-income countries (Scott, 2011; Ali and Nabi, 2014; Gurshaw *et al.*, 2014; WHO, 2017; Feigin *et al*., 2019).

AEDs are a cornerstone of treatment in epilepsy though they are characterized by a narrow therapeutic index, high inter- and intra-individual variability, a large number of interactions and side effects, and some follow zero-order kinetics, which makes difficult to predict their outcome. Besides, inappropriate use, lack of follow-ups, and lack of reassessment of therapeutic outcomes may lead to DTPs (Goldenberg, 2010; Talati *et al*., 2011; Shareef *et al.*, 2015 and Beretta, 2017).

DTPs becomes a public health issue worldwide and have been significantly increased over the past few decades. It can occur at all stages of the medication usage process starting from prescribing to a user (IDF, 2015). A study done by Zhu *et al.*, (2019) and Kanjanasilp et al., (2008) reported a total of 111 and 410 DRPs respectively with an average of 2.5 DTPs per patient. Similarly in a study conducted at TASH, Ethiopia also showed a high prevalence (70.4%) with a total of 352 DTPs among 205 study participants (Nasir *et al.*, 2020).

DTPs can be triggering factors for recurrence and breakthrough seizures, leading to a poor quality of life (increased loss of seizure control, a decrease in productivity, emergency department visits, hospitalizations) being endured by epileptic patients and mortality (Koshy, 2012). All contribute to increased direct and indirect healthcare costs related to epilepsy. That may become a burden to the patient or government or third parties. In the US an estimated 100,000 deaths occur annually due to DTPs (Ombengi *et al.*, 2016) and the economic burden arising from drug-related morbidity and mortality was estimated to be $177.4 billion per annum, which is twice as much money as spent on the drug themselves (Koshy, 2012).

Low treatment satisfaction may cause poor compliance, which further reduces effectiveness, especially among patients with chronic diseases, and might ultimately lessen patients' health-related quality of life (Weaver *et al.,* 1997). Since patients having better satisfaction tend to adhere more to their medication and have improved treatment outcomes. Patient satisfaction assessment done in Palestine showed patients with well-controlled epilepsy scored significantly higher in the effectiveness and global Satisfaction domains than those with poorly controlled epilepsy (Sweileh *et al*., 2011).

MTM service is ideally suited to provide pharmaceutical care and overcome drug therapy-related issues to attain targeted therapeutic outcomes. The service encompasses an intervention package on DRPs that may lessen drug-related morbidity and mortality. Even though limited studies indicate the role of Pharmacists in addressing DTPs, interventional based studies related to the provision of pharmaceutical care and patient satisfaction are scarce globally and there are no studies in Ethiopia, especially in a neurologic disorder like epilepsy. Therefore, this study could highlight the benefits of MTM services in the identification and prevention of DTPs as well as patient satisfaction that influence patient adherence and treatment outcome. The study could also serve as evidence for convincing hospital managers on the role of clinical pharmacists in the management of epilepsy and the need for the continuation of MTM service. On top of that, the work may be useful to other researchers as a baseline while conducting further studies on related topics. The findings of this study could also help in influencing stakeholders during the development of guidelines and policies for the prevention and management of DTPs to improve the quality of care, patient satisfaction, and treatment outcomes.

1.3. Literature review

Epilepsy is the most common complex neurological disorder upsetting approximately 50 million people worldwide. It has deep physical, social, emotional, and economic repercussions for patients and their environment. Patients with epilepsy have poor health outcomes both psychological distress (depression, anxiety and work restriction), and physical injuries (fractures and burns) that are associated with increased mortality. Besides epileptic seizures result in devastating social consequences which result in poor quality of life (Meyer *et al.,* 2010; WHO, 2019).

The prevalence of epilepsy is slightly higher in male than female and generalized type of epilepsy to be the most common among other types of epilepsies (Ali and Nabi, 2014; Biru *et al.,* 2016; Rishe *et al.,* 2015), although other studies reported focal seizure to be the predominant one (Naddad *et al.,* 2016). The pattern of AED prescription was found to be different among studies but most of them used older anticonvulsants. Carbamazepine (CBZ) was the most frequently prescribed drug in Bangladesh (Habib *et al.*, 2013), while Phenobarbital took over in Ethiopia (Rishe *et al.,* 2015; Biru *et al.,* 2016; Getinet *et al.,* 2016).

Kanjanasilp *et al,* (2008) identified 111 DRPs before provision of pharmaceutical care and this number came down to 61 after the care was provided. Using MTM as an intervention, average DRPs per patient in the periods before and after provision of pharmaceutical care were 2.25 and 1.33, respectively. It is of note that the frequency of seizure free and seizure attack was 46.15% and 28.9% before pharmaceutical care, and this rate was changed to 71.2% and 13.5%, respectively, after pharmaceutical care, indicating the contribution of pharmaceutical care in improving patient outcomes. Another study in TASH, Ethiopia, on diabetic patients showed reduction of DTPs from 578 (72.9% patients) in the pre-intervention to 128 (26.2% patients) in the post-intervention phase (Wakijira *et al*., 2020). Regarding the change in the number of DRPs types, better achievement was found in subtherapeutic dosage 11 (9.40%) to 4 (5.80%) and over dose 5(4.27%) to 0, while drug interactions 31(26.50%) to 27 (39.13%), failure to receive drugs 24 (20.51%) to 7(10.14) and adverse drug reactions 24 (20.51%) to 20 (28.99%) had minimal variation (Kanjanasilp *et al.,* 2008).

A prospective interventional study conducted in Gonder, Ethiopia on MTM reported that 30.5% patients had need of additional drug therapy and unnecessary drug therapy (29.5%). Similarly, a prospective cohort study that assessed pharmaceutical care issues on hospitalized epilepsy patients in Malaysia identified medication non-adherence (64.6%), inadequate dose (51.9%), under reporting of adverse effects (76.2%), under-utilization of therapeutic drug monitoring services (41.5%), and inappropriateness of therapy in patients with liver disease (6.1%) (Manan *et al.,* 2014). The baseline study for MTM by Nasir *et al.* (2020) also showed that ADR (146, 41.5%) as the leading DTPs followed by ineffective drugs (98, 27.8%), drug interaction (45, 12.8%), and inappropriate dose (42, 11.9%). All the above studies clearly recommend that pharmacists need to address the DRPs in order to optimize drug therapy and achieve the desired treatment.

ADR is the inherent to most of AEDs of which Headache (39, 13.4%), depression (36, 12.4%), epigastric pain (35, 12%), and hypersomnia (28, 9.6%) were the most reported by Nasir *et al.* (2020). This finding was similar with Rishe *et al.* (2015) and Getachew *et al.* (2014).

A RANSOM study performed on epileptic patients to assess non-adherence and mortality found that non-adherence was associated with a threefold increased risk of mortality compared to adherence. Time periods of non-adherence were also associated with a significantly higher incidence of emergency department (ED) visits, hospital admissions, motor vehicle accident (MVA) injuries, and fractures than periods of adherence. This study suggested that non-adherence to antiepiletic drugs could have serious or fatal consequences for patients (Faught *et al.,* 2008). Different studies done to assess non-adherence to AEDs have reported varied rates. An Ethiopian study conducted in Gondar reported a rate of 37.8% (Getinet *et al.,* 2016) and TASH, 42.7% (Nasir *et al.,* 2020), which was similar with a US study (39%) (Chapman *et al.,* 2014). However, higher non-adherence rates were also reported in Jimma, Ethiopia (63%) (Getachew *et al.,* 2014), and Malaysia (64.6%) (Mananet *et al.,* 2014).

There are various factors associated with the occurrence of DTPs. A study by Nasir et al, (2020) shows that the total number of medications taken by the patient was risk factor for DTPs. Patients who were on more than 2 medications were 3.8 times more likely to develop DTPs as compared on single medication (AOR = 3.810 CI 1.409–10.30). In addition in wakijira et al,

(2020) study patients who do not get their medication free (AOR= 2.27, 95%CI: 1.08-4.77), and male gender (AOR=3.06, 95% CI: 1.54-6.07) were significant predictors of DTPs.

Patients' treatment satisfaction is an important component to achieve goal of drug therapy. Therefore, determining the treatment satisfaction level is central for improving health care. The patient satisfaction assessment performed in the same clinic as a baseline study for MTM by Nasir *et al,* (2020) showed that the global satisfaction scores as 67.4 ± 17.5 and the general satisfaction as 70.2 ± 12.5 (Nasir *et al.*, 2020). Patient satisfaction scores in Palestine with respect to effectiveness, side effects, convenience, and global satisfactions were 73.6%, 82.4%, 69.5%, and 68.4%, respectively. This study reported that patients with well-controlled epilepsy scored significantly higher in the Effectiveness and Global Satisfaction domains than those with poorly controlled epilepsy (Sweileh *et al.,* 2011). Satisfaction studies carried out in other chronic diseases reported more or less similar scores. A study carried out in diabetic patients by Wakjira *et al,* (2020) with respect to the six-dimension side effects, effectiveness, convenience, impact, medical follow up and global satisfactions reported a score of 8.8 %, 87.1%, 91.6%, 91.3%, 88.3% and 91.1%, respectively. A Palestine study on hypertensive patients also reported an overall satisfaction of 72.1(SD ± 23.1) (Sa'ed *et al.,* 2013).

1.4 Conceptual framework

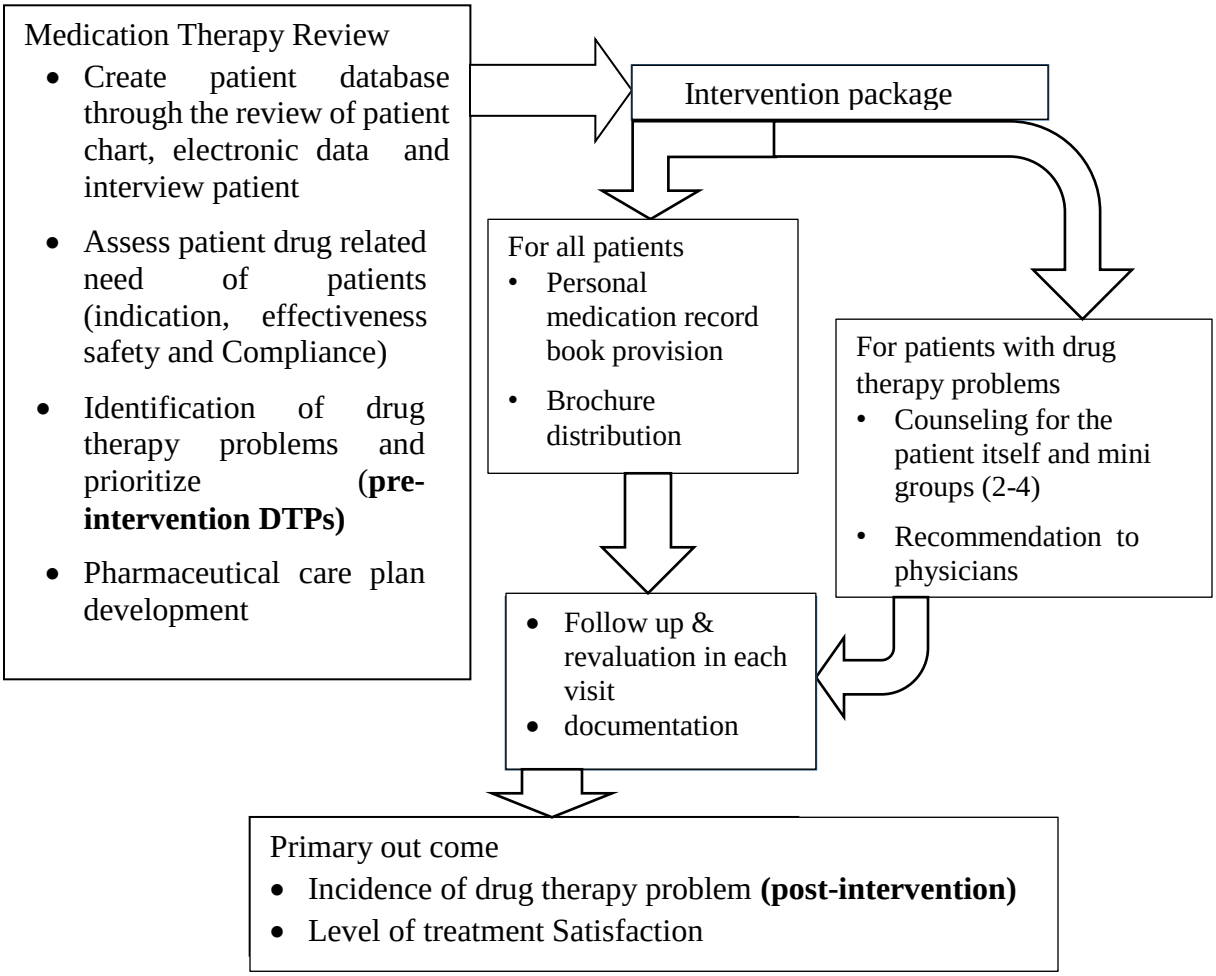


Figure 1-1: Conceptual framework for implementation of MTM services in adult epileptic patients on follow up at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018/19.

2. Objectives

2.1. General Objective

- The general objective of this study was to assess the outcome of introducing medication therapy management services to epileptic patients attending at the neurology clinic of TASH, Addis Abeba, Ethiopia, 2018/19.

2.2. Specific Objectives

- To identify drug therapy problems before and after providing medication therapy management service among epilepsy patients;
- To identify predictors for the occurrence of drug therapy problems before and after providing medication therapy management service among epilepsy patients;
- To assess treatment satisfaction after the provision of medication therapy management service among epilepsy patients.

3. Methods

3.1. Study Setting

The study was carried out at TASH, which is the largest referral hospital in the country, with a total bed capacity of 700. It was established in 1972 and run by Federal Ministry of Health. In 1998, TASH was transferred to Addis Ababa University and it has since become a University teaching specialized hospital. TASH is now the main teaching specialized hospital for both clinical and preclinical training for undergraduate and postgraduate health science (medical, dentistry, nursing, midwifery, pharmacy, medical laboratory technology, and radiology technology) students, who shoulder the health problems of the community and the country at large. It is also an institution where specialized clinical services that are not available in other public or private institutions are rendered to the whole nation (http://www.aau.edu.et/chs/tikur-anbessa-specialized-hospital/background-of-tikur-anbessa-hospital/). Among the specialty clinics in TASH, neurology is the one that provides a comprehensive neurologic service (epilepsy, stroke, movement disorder, peripheral neuropathy, disk prolapse etc...). In the neurology department, there are around 15 neurologists and 6 nurses with fluctuating number of residents. The clinic works throughout the week but epilepsy patients are served once per week (every Monday) even though some patient come on Tuesdays and Thursdays. On average 105 patients are served per week.

3.2. Study Design and Period

This was quasi-experimental study design (single group pretest posttest and posttest only) undertaken from August 2018 to August 2019 for a total of 12 months. The study period had three phases (4 months for pre intervention phase, 6-month for intervention and the last 2-months for assessment of intervention).

3.3. Source and Study Population

The source population includes all epileptic patients who were on follow-up at neurology clinic of TASH. The study population involved all patients visiting TASH during the study period and fulfilling the inclusion criteria.

3.4. Eligibility Criteria

3.4.1. Inclusion criteria

- All adult (age grater 14 years) patient attending neurology clinic for the management of epilepsy
- A known epilepsy patient and on follow-up for at least three months
- Epilepsy patient with at least on one antiepileptic medication

3.4.2. Exclusion criteria

- Patients planning to change the follow-up clinic to other setups
- Patients who were not willing to participate in the study

3.5. Sample Size and Sampling Technique

Sample size was computed based on single proportion formula assuming a prevalence (p) of change in drug therapy problems 50%, as there was no research conducted on this topic in Ethiopia and neighboring countries.

$$n = \frac{Z^2\ p\ (1-p)}{d^2} = \frac{(1.96)^2 x\ (0.5)\ (0.5)}{(0.05)^2} \quad = 384.16$$

- Confidence level of 95% chosen with z-value of 1.96
- Margin of error (d) = 5%
- n = 384 (sample size without adjustment and with p = 50%)
- The total population of epileptic patients who have follow-up at TASH (N) was around = 1600

Corrected sample size = $(n \times N)/(n \pm N)$=310

With the adjustment for 10% contingency, the total sample size was found to be 341.

Systematic random sampling technique was applied for recruitment of patients as the number of patients attending the follow-up clinic per week was approximated to be 105 (around 85 patients on Monday and the remaining on Tuesdays and Thursdays). Taking these three periods, patients

who had an appointment during these days were used as a sampling frame and then sampling fraction was calculated (Table 4-1). The predetermined sample of patients per day was calculated by using total sample size (341) divided by the number of days scheduled per four months (48 days) of the recruitment period. Based on their proportion, 17, 2 and 2 patients were sampled on Monday, Tuesday and Thursday, respectively.

Table 3-1: Summary of proportion of studied epilepsy patients and K value

Appointment Days	Monday	Tuesday	Thursday
Total number of patients per each day	85	8	12
Total number of patients per week			105
Proportion of patients attending on each day	0.809524	0.07619	0.114286
Sample size			341
Studied patient per day	17	2	2
Number of studied patients over the study period	276	26	39
K^{th}	N/n = 1600/341		4.692082 ≈ 5

As depicted in Table 4-1, K value was 5 and every 5^{th} patient's medical card number (ID) was taken for comprehensive chart review. Chart review and other relevant activities were performed a day before the appointment date. At the day of appointment, recruited patients were interviewed for additional information and provided with MTM services after they got usual physician services. All patients recruited for the intervention were used for post MTM assessment study.

3.6. Study Variables

3.6.1. Dependent variables

- Change in DTPs
- Patient satisfaction

3.6.2. Independent variables

Age, sex, marital status, education, occupation status, cost (free or paying), family history, type of epilepsy, comorbid conditions, number of comorbid conditions, number of medications, duration with the disease, and availability of medication.

3.7. Data Collection and Management

3.7.1. Data collection instruments

Four data collection instruments had been used in order to gather data:
1) Data abstraction format (Annex I), which was adopted from baseline assessment, pre-tested and modified to fit for intervention phase. It includes sociodemographic data, health information and lifestyle factors, clinical characteristics, past and current medication history with dose and frequency and duration including OTC and herbal medications; 2) Cipolle DTP identification tool (Annex II) to record DTPs in the intervention as well in the post-intervention phase; 3) Morisky 8 adherence assessment questionnaire (Annex III); and 4) SATMED-Q (Annex IV) for treatment satisfaction. The latter two tools were used during the post-intervention phase only as baseline assessment was done in the same study population (Nasir *et al*. 2020).

Cipolle drug therapy problem identification tool

DTPs were identified and classified using the Cipolle's DTP classification tool. The tool classifies the DRPs in to seven (unnecessary drug therapy, need for additional drug therapy, ineffective drug, dosage too low, adverse drug reaction, dosage too high and non-adherence), which are derived from the four categories of drug related need of patients (indication, effectiveness, safety, and compliance). Further the tool provides a list of cause for each DTPs (Cipolle *et al.*, 2012).

Medication adherence

Modified Morisky Medication Adherence Scale (MMAS 8) assessment questionnaire was used to assess the self-reported adherence after the intervention was given to see the impact of MTM intervention. It is an eight item self-report measure of adherence. The single composite measure was scored according to the developers' instructions so that lower scores indicate higher

adherence. Individuals had identified several issues regarding their medication taking behavior. Each question was based on their personal experience with the medication taking behavior. The first seven questions are scored with "yes = 1" and "No = 0". Question eight concerning the difficulty to remember taking medications is scored as Never = zero, and one for the remaining response (rarely once in a while, sometimes, usually and all the time). During calculation the value were exchanged according to the tool and classified as sum of all value <6 low adherence; 6-8 middle adherence; 8 high adherences (Bener *et al.*, 2014).

Treatment satisfaction

A self-administered Treatment Satisfaction with Medicines Questionnaire (SATMED-Q) 17 was used to measure patients' treatment satisfaction. It is a brief, feasible and easy to self-administer multidimensional generic questionnaire with good metric properties of reliability and validity. The SATMED-Q is designed to assess treatment satisfaction in persons with any chronic disease treated with medicines. The SATMED-Q has 17 items, assessing six treatment satisfaction domains; undesirable side effects (3 items), treatment effectiveness (3 items), convenience of use (3 items), impact on daily activities (3 items), medical care (2 items) and global satisfaction (3 items), each of which was computed as a score. In addition, a total satisfaction score is computed. Each item in the scale uses a five-point Likert scale; overall and domain scores range from zero to 68 or zero to 100 (after transformation), with higher scores indicating greater levels of treatment satisfaction (Rejas *et al.,* 2011; Ruiz *et al.*, 2008).

3.7.2. Recruitment and training of intervention providers and data collectors

Three clinical pharmacists (two for provisions of MTM service and one for pre- and post-intervention phase data collection) and two nurses (for facilitating both the intervention and data collection) were recruited after making sure they were interested and showed commitment for the service. They were provided with a 2-day intensive theoretical and practical based training. The training was provided by senior clinical pharmacists about the general information on medication therapy management, procedure followed during pharmaceutical intervention, ways of delivering and implementing intervention package, and resolving challenge as well as how to communicate with physicians and patients for intervention. The training was supervised by principal and co-investigators.

3.8. Intervention Development and Implementation

The MTM service was launched by creating patient database through reviewing patient medication therapy that start from reviewing patient chart and electronic data for patient characteristics, laboratory results, current medications, co-morbidities, duration of illness and treatment, relevant previous medical and medication histories, and other pertinent findings. Patients were also interviewed for additional information that are not included in the chart or electronic data (any medications taken including recreational drug, over-the-counter (OTC) medications, supplements, herbal products, medications used to treat acute conditions or used for a limited time period (e.g., antibiotics, analgesics), adverse drug events, adherence etc…) and were documented.

During the first face to face contact with patients the clinical pharmacists provided a ten page personal medication record book that contains different information (counseling on emergency situation, patient contact information, medication history, current medication, medication action plan, plain pages (for recording action under taken during seizure attack, number of seizure episode and duration), pertinent laboratory and self-monitoring data, and MTM providing pharmacist contact information). The other material provided to patient was brochure that was written in English and translated to Amharic language to increase patients' as well caregiver's awareness about epilepsy and way of management. The clinical pharmacists identified medication related need of patients including indication, effectiveness, safety, and adherence. This was followed by evaluation of the appropriateness of medical therapy using various references and guidelines like Up-to-date, National Institute for Health and Care Excellence guideline (NICE), pharmacotherapy text book (Joseph DiPiro, 2017), Epocratus and Micromedex and Medscape. Micromedex and/or Medscape drug interaction checker were used to identify drug-drug interactions. Eventually, medication related problems were listed and prioritized leading to development of a care plan.

Pharmaceutical intervention was provided for individual patients as well as for groups based on the pharmaceutical care plan developed. If the identified DTPs were like non–adherence and problems associated with recreational drug use, counseling were provided for each patient and general information about the disease was given in mini groups (2-5 patients). If the plan

involves physicians, the attending pharmacist communicated with the physician and provided recommendation with ultimate goal of optimizing medication therapy to improve treatment outcomes using the aforementioned reference materials. The interventions were provided for newly recruited patients in the first four months and continued for the remaining six months for those on MTM follow-up considering the maximum lag time for appointment for patients recruited at the end of the fourth month.

During the recruitment phase, based on Cipolle's (Cipolle *et al.,* 2012) DTP classification tool, DTPs were identified and recorded, which were used as baseline DTP. After each visit, patients were interviewed for progress, any new DTP, and counseled on their disease state and medications use. Unresolved issues from the prior sessions were also discussed. The pharmacist carried out an assessment of the treatment care plan to monitor the patient's adherence to the medication action plan and to establish new therapy goals when required. New lab values, updates on the patients' progress and primary outcome (type of intervention given, DTP status, and reassurance) were assessed and recorded simultaneously in each visit.

Finally, after six months' follow-up, outcomes of the pharmaceutical care provided for each patient were assessed. The assessment included DTP identification and Treatment Satisfaction.

3.9. Data quality assurance

Pre-test was done on 5% of the sample at the neurology clinic of TASH for the intervention phase, before starting patient recruitment and data collection in order to check completeness of the instruments. Based on the finding obtained from the pre-test, adjustment was made on the assessment tools especially inclusion of some information (I care number, appointment date etc…) and ways of providing intervention. After each day (recruitment, intervention, post intervention phase), the principal investigator checked the completeness and quality of recorded information and/ or filled questionnaire to ensure accuracy and consistency. Any missed information was readdressed. After data collection was completed, the PI carefully cleaned and entered the data into SPSS. The data analysis was performed under the supervision of a biostatistician.

3.10. Data Analysis

Data were analyzed using statistical package for social science (SPSS) version 21. Descriptive statistics are presented as means with standard deviations for continuous variables and frequencies with percent were used for categorical variables. To summarize patients' characteristics tables or chart were used. To examine the influence of different variables and control potential confounders on DTPs and adherence, both binary and multiple logistic analyses were performed. Independent variables having p-value <0.25 in the univariate logistic regression analysis were entered into multivariable logistic regression analysis. Paired sample t –test and McNemar's test was performed to examine the effect of intervention in the pre- and post-intervention phases for the number of DTPs and type of DTPs respectively. In order to determine the relationship between treatment satisfaction (mean scores of SATMED-Q) and sociodemographic characteristics of patients, independent t-test was used for mean values of two continuous variables and one-way analysis of variance (ANOVA) with post hoc analysis for mean value of more than two continuous variables. A 95% CI and p-value of <0.05 were considered statistically significant.

3.11. Ethical Consideration

The data collection process was started after getting approval from School of Pharmacy, College of Health Sciences, AAU Institutional Review Board (IRB) (Ref. No.: 002/17/SPharma) and written consent from each patient before starting the data collection. Patients were informed about the objective of the study and they had full right to withdraw from the study at any time. They were informed that their participation was completely voluntary. Privacy and confidentiality were maintained by avoiding use of identifiers and restriction of data access. Individual identifiers like name were not used instead card number and I care number were used and accessed by the intervention team only. Finally, the card and/or I care number was changed to code number.

3.12. Operational Definitions

- Adverse drug reaction (ADR): Any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy

of disease, or for the modification of physiological function (Adusumilli and Adepu, 2014).

- Comorbidity: The presence of one or more additional diseases co-occurring with epilepsy
- Controlled seizure: Patient without any type of seizure episode for the last 2years
- Drug-therapy problem: Any undesirable event experienced by the patient that involves or is suspected to involve drug therapy and that actually or potentially interferes with desired health outcomes (Cipolle *et al*., 2012).
- Informal education- A person not certified with any grade level of education but can read and write.
- Medication adherence: The extent to which a person's behavior in taking medicines corresponds with the agreed recommendations from a health care provider.
- Poly-pharmacy: The daily consumption of 5 or more medications (Fulton and Riley Allen, 2005).
- Poorly controlled seizure: Patient having repeated seizure attack within the past months
- Uncontrolled seizure: Patients having seizure attack at list once in the past two years.
- Unemployed: Patients who do not have a job that provides money.
- Well controlled seizure: Patients without seizure attack at least for the past six months but less than 2 years

4. Results

4.1. Socio-Demographic Characteristics

Socio-demographic characteristics of the study population are presented in Table 4-1. A total of 336 epileptic patients were included in the study. The median age of patients was 28 with an interquartile range of 21 to 40 years. Female patients accounted for 159 (47.5%) of the study subjects. One hundred thirty-six (40.5%) patients were married, 32.1% completed high school, and 36% were unemployed. Majority of the study subjects (59.2%) received their medication free of charge. Half of the patients drink coffee while only 7 (2.1%) patients drink alcohol.

Table 4-1: Socio-demographic characteristics of epileptic patients attending at neurology clinic of Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, 2018/19.

Variables		Frequency	Percent
Age	<18	45	**13.4**
	18-30	140	**41.7**
	31-60	124	**36.9**
	>60	27	**8.0**
Sex	Female	159	**47.3**
	Male	177	**52.7**
Marital status	Single	184	**54.7**
	Married	136	**40.5**
	Divorced	8	**2.4**
	Widowed	8	**2.4**
Educational level	unable to write and read	44	**13.1**
	informal education	19	**5.7**
	primary school	101	**30.1**
	secondary school	108	**32.1**
	College diploma and above	64	**19.0**
Occupation	Unemployed	121	**36.0**
	Employed	111	**33.0**
	Private	19	**5.7**
	Student	85	**25.3**

Source of medication	Free	199	**59.2**
	Buying	137	**40.8**
Alcohol use	Yes	7	**2.1**
	No	329	**97.9**
Caffeine intake	Yes	168	**50.0**
	No	168	**50.0**
Personal assistance	Yes	66	**19.4**
	No	270	**80.4**
Family history	Yes	41	**12.2**
	No	295	**87.8**

4.2. Clinical Characteristics

Most of the patients had generalized onset epilepsy. Of these, generalized tonic-clonic was the most common diagnosis (53.9%) followed by focal to bilateral (14.9%) and unclassified (14%) epilepsy. About 95 (28.3%) of the patients had seizure duration lasting 1-5 years (Table 4-2).

Table 4-2: Clinical characteristics of adult epilepsy patients on follow-up at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018/19.

Clinical characteristics			**Frequency**	**Percent (%)**
Seizure category	Generalized	Tonic clonic	181	53.9
		Myoclonic	5	1.5
		Absence	7	2.1
	Focal	Focal aware	35	10.4
		Focal impaired	11	3.3
		Focal to bilateral	50	14.9
	Unclassified	Unclassified	47	14.0
Duration of seizure		≤ 1 year	37	11.0
		1-5 years	95	28.3
		5-10 years	65	19.3
		≥ 10 years	93	27.7
		Since childhood	46	13.7
Comorbid illnesses		Yes	139	41.4
		No	197	58.6
Number of comorbidities		One	85	25.3
		Two	36	10.7
		Three	14	4.2
		Four	3	.9
		Five	1	.3
Number of follow-up		Two	133	39.6

	Three	149	44.3
	Four	44	13.1
	Five	9	2.7
	Six	1	0.3

One hundred thirty-nine patients had comorbid diseases and the majority of them (25.3%) had only one comorbidity. Table 4-3 shows comorbidities among epileptic patients. The most common comorbidity in the patients was HIV (7.8%) followed by major depressive disorder (6.8%) and stroke (6.5%).

Table 4-3: List of Comorbidities among adult epilepsy patients on follow-up at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018/19.

Comorbid disease	Frequency	Percent (%)
Human immunodeficiency virus	27	7.8
Major depressive disorder	23	6.8
Stroke	22	6.5
Malignancy*	20	6
Hypertension	16	4.8
Heart failure	16	4.8
Migraine	10	3
Diabetes mellitus	9	2.7
Schizophrenia	4	1.2
Intellectual disability	4	1.2
Chronic Low Back Pain	3	0.9
Asthma	3	0.9
Osteoarthritis	3	0.9
Peripheral neuropathy	2	0.6
Pangastropathy	2	0.6
Benign prostatic hyperplasia	2	0.6
Others**	43	12.8

**pituitary adenoma, astrocytoma, meningioma, cavernoma; **generalized anxiety disorder, agoraphobia, tuberculoma, Bell's palsy, post-traumatic stress disorder, autism, fatty liver, Parkinson, dyslipidemia, chronic kidney disease , Systemic lupus erytromatus, hypothyroidism, severe malnutrition , toxoplasmosis, attention deficit hyperactive disorder, Adjustment disorder, abdominal aortic syndrome, acute kidney injure, dyspepsia, Bipolar disorder, broncholtiasis, hiccups, alcoholic liver disease.*

4.3. Pattern of Antiepileptic Drug Use

Both mono-therapy and combined AEDs were prescribed to patients with a mean of 1.5 (SD ±0.7) drugs/patient. Majority of patients (57.7%) were on mono-therapy. The most frequently prescribed antiepileptic drug for monotherapy was phenobarbital (22.6%) followed by carbamazepine (13.1%). Phenobarbital plus Phenytoin (8.6%) was the most repeatedly prescribed combination (Table 4-4).

A total of 730 medications were prescribed for the management of comorbid illnesses and epilepsy, with a mean of 2.17 (SD ±1.37) drugs/patient and with a maximum of twelve medications (Figure 4.1).

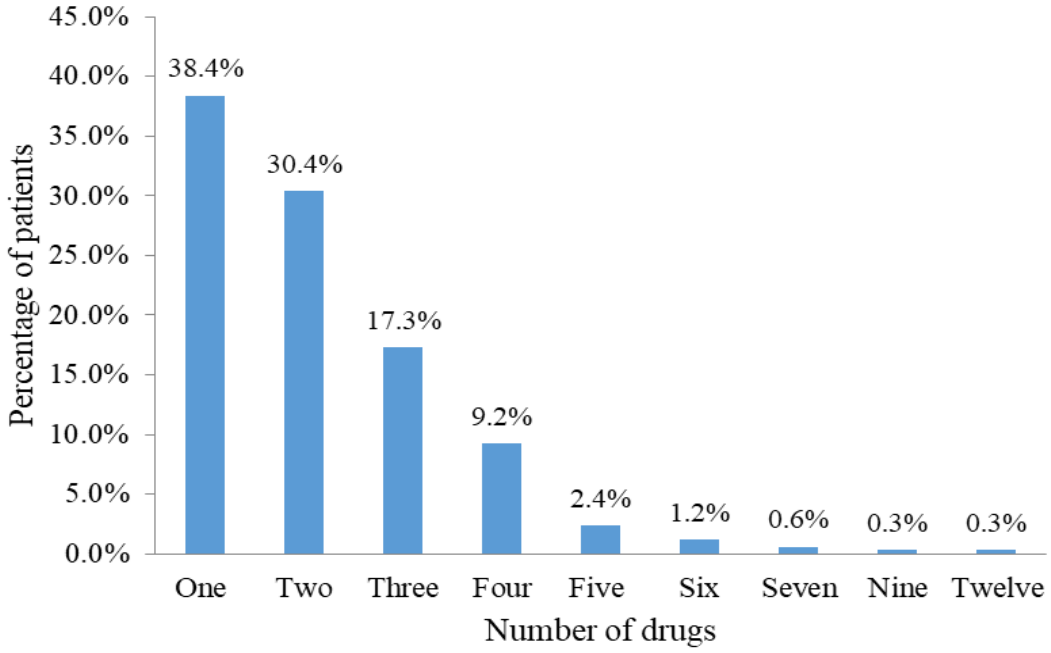


Figure 4-1: Frequency distribution of total number of drugs among epilepsy patients attending at neurology clinic of Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, 2018/19.

Table 4-4: Types of prescribed medications, Number of prescribed medications and type of epilepsy among adult epilepsy patients on follow-up at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018/19

Antiepileptic drugs	Type of epilepsy							Total Frequency (%)
	Tonic-clonic	Myoclonic	Absence	Focal aware	Focal impaired	Focal to bilateral	unclassified	
PHB	50	0	2	4	2	7	11	76 (22.6)
CBZ	13	1	1	12	1	9	7	44 (13.1)
PHT	20	0	0	3	1	6	4	34 (10.1)
VPA	14	1	0	3	1	5	5	29 (8.6)
LAMO	2	0	1	1	1	0	0	5 (1.5)
CLONA	0	0	0	1	0	0	1	2 (0.6)
PHB + PHT	22	0	1	1	0	0	5	29 (8.6)
PHB + VPA	11	2	0	1	0	2	2	18 (5.4)
PHB + CBZ	4	1	0	2	1	5	2	15 (4.5)
PHT+ CBZ*	7	0	0	1	3	2	2	15 (4.5)
PHT+ VPA	10	0	0	0	0	2	1	13 (3.9)
CBZ + VPA*	1	0	1	3	0	3	2	10 (3.0)
PHB + LAMO*	2	0	1	2	0	1	1	7 (2.1)
PHY + LAMO*	3	0	0	0	0	0	0	3 (0.9)
CBZ + LAMO*	0	0	0	0	0	1	0	1 (0.3)
CLONA + PHB*	1	0	0	0	0	0	0	1 (0.3)
PHB + PHY+ VPA	4	0	0	1	0	3	1	9 (2.7)
CBZ + PHB + VPA*	5	0	0	0	1	1	1	8 (2.4)
CBZ + LAMO + VPA*	3	0	0	0	0	2	0	5 (1.5)
CBZ + PHT+ PHB*	4	0	0	0	0	0	0	4 (1.2)
CBZ + LAMO + PHB*	1	0	0	0	0	0	2	3 (0.9)
CBZ + LAMO + PHY*	2	0	0	0	0	0	0	2 (0.6)
CBZ + CLONA + PHT*	0	0	0	0	0	1	0	1 (0.3)
CLONA+LAMO + PHT + VPA*	1	0	0	0	0	0	0	1 (0.3)
CBZ + PHB + PHT + VPA*	1	0	0	0	0	0	0	1 (0.3)
TOTAL	181	5	7	35	11	50	47	336 (100)

Abbreviations: PHB, phenobarbital; PHT, Phenytoin; CBZ, carbamazepine; VPA, Valproic acid; LAMO, Lamotrigine; CLONA, Clonazepam.

Table 4-5 displays drugs prescribed for treating the comorbidities of epileptic patients. Since the major comorbidity was HIV, most epilepsy patients (23 (6.3%)) were on ART (ART 1st and 2nd line). Comparably about 23 (6.8%) patients were also on ASA.

Table 4-5: Drugs prescribed for treating comorbidities adult epilepsy patients on follow-up at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018/19.

Medications	Frequency	Percent (%)
Antihypertensive drugs	27	4.2
Aspirin	23	6.8
ART 1st line**	22	5.4
Statins	18	5.4
Selective serotonin reuptake inhibiters	14	4.2
Vitamins	14	4.2
Beta Blockers	13	3.9
Amitriptilne	12	3.6
Anti-psychotic	11	3.3
Antidiabetics	5	1.5
ART 2nd line*	5	1.5
Warfarin	4	1.2
others ***	32	9.5

zidovudine/lamivudine/atazanavir/ritonavir, tenofovir/lamivudine/atazanavir/ritonavir, abacavir/lamivudine/atazanavir/ritonavir; **tenofovir/lamivudine/efavirenz, tenofovir/lamivudine/nevirapine, zidovudine/lamivudine/efavirenz;** ***indomethacin, metoclopramide, omeprazole, antacids, digoxin, alfuzocine, B. penicillin, anti-TB, chloquine, beclomethasone puff, prednisolone, salbutamol puff, thyroxine and sumatriptan.*

4.4. Pattern and type of DTPs during the Intervention and Post-Intervention Phase

A total of 309 (0.92 ± 0.91) DTPs were identified during institution of the MTM service among 205 patients, out of which 21 of them were identified during the follow up period. In the post-assessment period, 142 (0.42 ± 0.6) DTPs were identified in 129 epilepsy patients. There was significant reduction in the mean number of DTPs from M=0.85 in the pre-intervention phase to M=0.42 the post-intervention phase ($t(335) = 10.79$, $p < 0.005$). The percentages of patients who had at least one DTP before and after the period of the provision of pharmaceutical care were 58.6% and 38.3%, respectively (Figure 4-2).

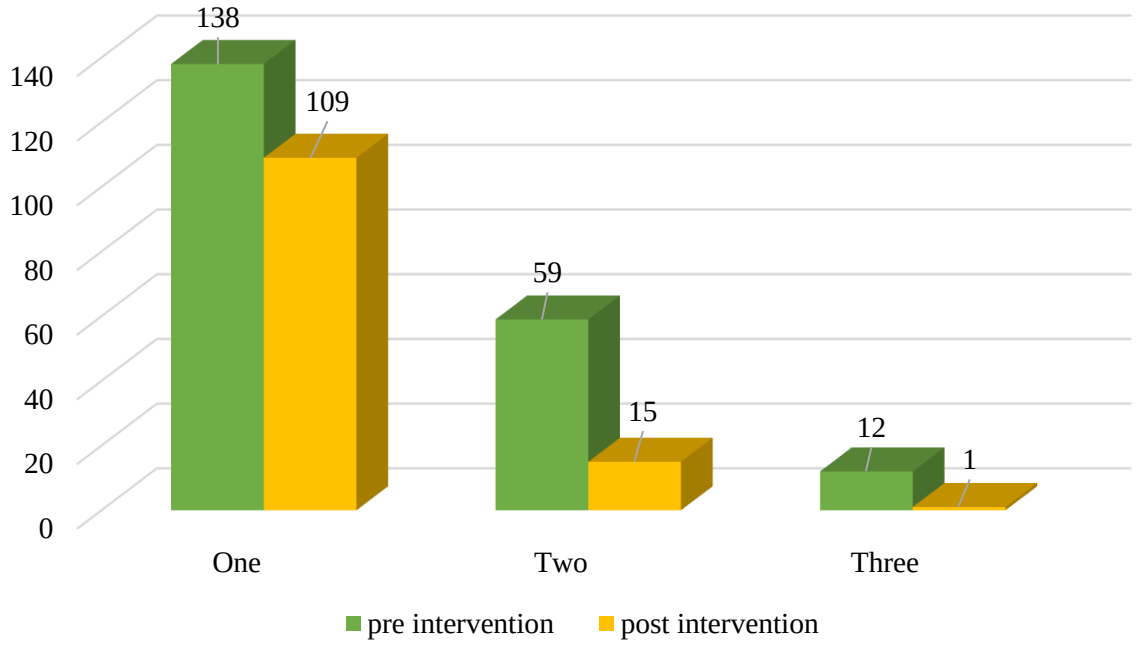
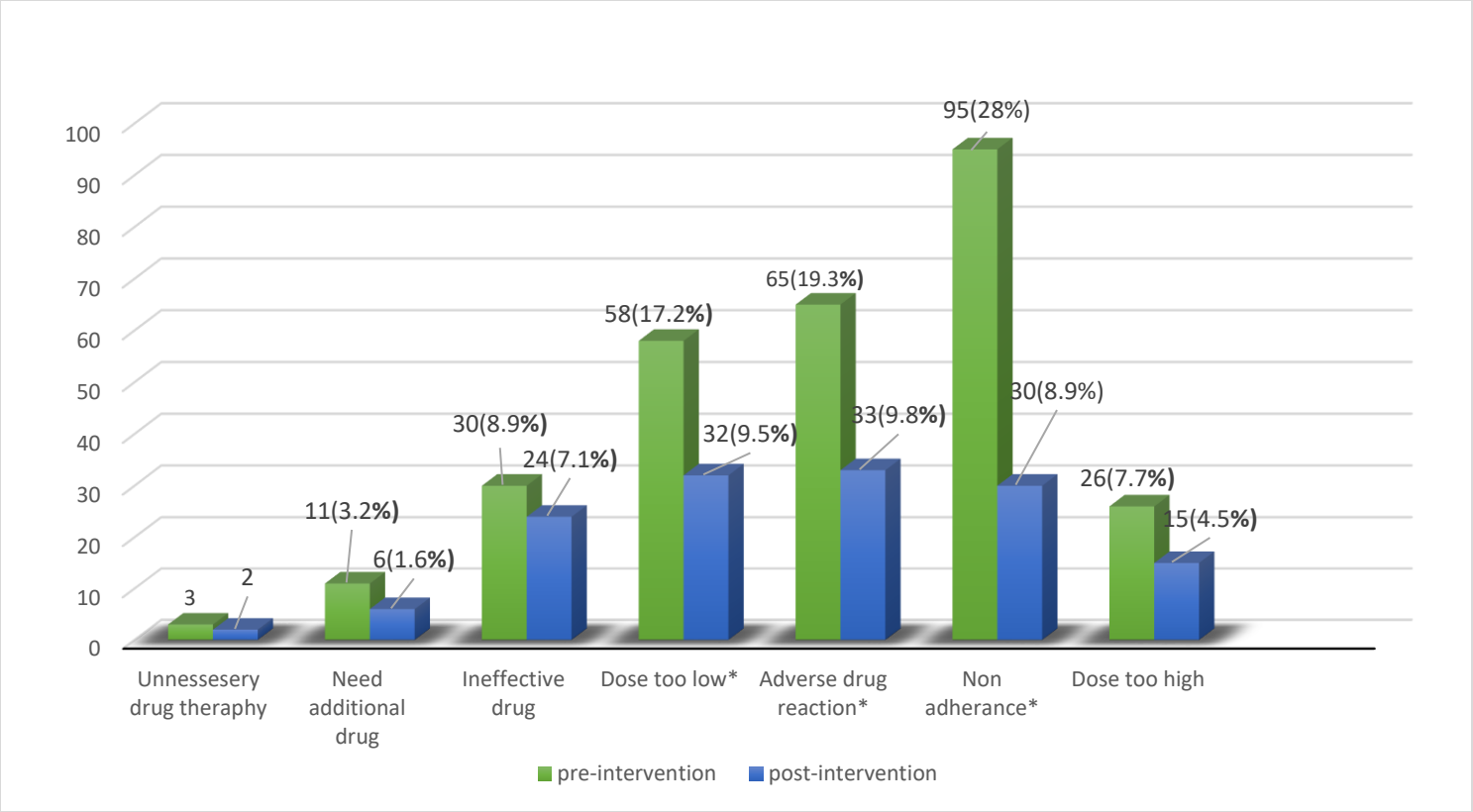


Figure 4-2: Frequency of number of drug therapy problems/patient among epilepsy patients attending at neurology clinic of Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, 2018/2019.

Among the DTPs identified, 79.2% and 68.2% of them were actual in the pre-intervention phase and post-assessment phase, respectively. The most encountered DTPs in the pre-intervention phase were non-adherence (95, 33%) followed by adverse drug reaction (65, 22.6%) and ineffective drug selection (30, 10.4%), whereas in the post-assessment phase the most encountered DTP were dose too low (32, 22.57%) followed by adverse drug reaction (33, 22.3%) and non-adherence (30, 20.3%). The change in the incidence of DTPs types from pre to post intervention phase is displayed in Figure 4.3. Using the McNemars test there was a statistically significant change in proportion of three DTPs categories (non- adherence from 28 to 8.9%, ADR from 19.3 to 9.8%) and dose to low from 17.2 to 9.5%) from pre- to post-intervention phase, $p<0.01$.



*statistically significant based on McNemars test.

Figure 4-3: Type of drug therapy problems among epilepsy patients attending at neurology clinic of Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, 2018/2019.

4.5. Predictors of Occurrence of Drug Therapy Problems

To identify factors contributing to the occurrence of DTPs, binary logistic regression was employed. Socio-demographic (age, gender, marital status, educational status, and occupation) and clinical characteristics (type of epilepsy, duration of disease, presence of comorbidity, number of antiepileptic drugs and source of medication) were used for both pre- and post-assessment, but clinical outcome and number of follow-up that had been compiled in post-assessment phase were used only for post-intervention phase DTPs predictor in binary logistic analysis (Table 4-6).

In the pre-intervention phase, the only variable that significantly associated with DTPs was age. Accordingly, patients with the age group of 18-30 had 2.3 times (AOR=2.3, 95% CI: 1.1-4.8) more likely to develop DTPs. During the post-intervention phase, factors such as seizure duration, total number of medications, and seizure control status were significantly associated with DTPs ($p<0.05$). The only factor that was associated negatively with the occurrence of DTP was duration of seizure, as the duration of seizure increases, patients were less likely to develop DTP. Patients who had seizure duration of 1-5 years were 2.5 times less likely to develop DTPs (AOR= 0.4, 95% CI: 0.2-0.9). Patients with three and more drugs were found to be 2.9 times more likely to develop DTPs than patients taking one AED (AOR=2.9, 95%CI: 1.4-5.8). Patients with uncontrolled seizure had 3.2 times fold probability to develop DTPs than patients with controlled seizure (AOR= 3.2, 95% CI: 1.76-5.73).

Table 4-6: Predictors of occurrence of drug therapy problems in epileptic patients attending at neurology clinic of Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, 2018/19.

Variables categories		Pre intervention phase DTP		Odds ratio with 95% C.I		Post intervention phase DTP		Odds ratio with 95% C.I	
		Yes	No	COR	AOR	Yes	No	COR	AOR
Age	<18	21 (46.7)	24 (53.3)	1	1	17 (37.8)	28 (62.2)	1	1
	18-30	89 (63.6)	51 (36.4)	**2.3 (1.1-4.5)**	**2.3 (1.1-4.8)**	56 (40)	84 (60)	0.9 (0.56-2.31)	0.7 (0.3-1.5)
	30-60	71 (57.3)	53 (42.7)	1.7 (0.8-3.4)	1.8 (0.9-3.9)	43 (34.7)	81 (65.3)	1.1 (0.56-2.31)	0.9 (0.4-2)
	>60	16 (59.3)	11 (40.7)	2.3 (0.8-6.3)	1.4 (0.7-5.1)	13 (45.1)	14 (51.9)	0.6 (0.24-1.7)	0.4 (0.1-1.2)
Sex	Female	93 (58.5)	66 (41.5)	1	1	58 (36.5)	101 (63.5)	1	1
	Male	104 (58.8)	73 (41.2)	1 (0.6-1.5)	0.9 (0.5-1.4)	71 (41.1)	106 (59.9)	1.2 (0.75-1.8)	1.2 (0.7-2)
Employment status	Employed	127 (61.7)	79 (38.3)	1	-	44 (35.7)	128 (64.3)	1	1
	Unemployed	70 (53.8)	60 (46.2)	1.4 (0.9-2.1)	-	85 (41.3)	121 (58.9)	1.3 (0.9-2.2)	1.4 (0.8-2.4)
Source of medication	Buying	77 (56.2)	60 (43.8)	1	-	71 (35.7)	128 (64.3)	1	1
	Free	120 (60.3)	79 (39.7)	1.9 (0.7-1.8)	-	58 (42.7)	79 (57.7)	1.3 (0.8-2.1)	1.4 (0.9-2.4)
Seizure duration	Less than one year	22 (59.5)	15 (40.5)	1	1	17 (45.9)	20 (54.1)	1	1
	One – five	56 (58.9)	39 (41.1)	1.02 (0.5-2.2)	1.1(0.5-2.5)	30 (31.6)	65 (68.4)	0.5 (0.2-1.2)	**0.4 (0.2-0.9)**
	Five - ten years	39 (60)	26 (40)	0.9 (0.4-2.2)	1(0.42.5)	21 (32.3)	44 (67.7)	0.6 (0.2-1.3)	0.4 (0.2-1.1)
	Above ten years	80 (57.6)	59 (42.4)	1.1 (0.5-2.2)	1.2(0.5-2.7)	61 (43.9)	78 (56.1)	0.9 (0.4-1.9)	0.7 (0.3-1.6)

(Table 4-6 continued)

Variables categories		Pre intervention phase DTP		Odds ratio with 95% C.I		Post intervention phase DTP		Odds ratio with 95% C.I	
		Yes	No	COR	AOR	Yes	No	COR	AOR
Comorbidity	Yes	88 (63.7)	51 (36.7)	1	1	62 (44.6)	77 (55.4)	1	1
	No	109 (55.3)	88 (44.7)	1.5 (0.9-2.4)	0.7 (0.2-2.3)	67 (34)	130 (66)	0.6 (0.4-1)	0.9 (0.3-3)
Total no of medication	One	72 (55.8)	57 (44.2)	1	1	42 (32.6)	87 (67.4)	**1**	**1**
	Two	54 (52.9)	48 (47.1)	1.1 (0.6-1.8)	1 (0.6-1.8)	31 (30.4)	71 (69.6)	0.9 (0.5-1.6)	0.9 (0.5-1.7)
	More than three	71 (67.6)	34 (32.4)	1.9 (0.9-2.6)	1.8 (0.9-3.7)	56 (53.3)	49 (46.7)	**2.4 (1.4-4)**	**2.9 (1.4-5.8)**
clinical status (pre and post)	Controlled	44 (53.7)	38 (4.3)	1	1	20 (21.5)	73 (78.5)	1	**1**
	uncontrolled	153(60.3)	101(39.8)	0.8(0.5-1.3)	1.8(1.1-3.1)	109(44.9)	134(55.1)	**2.9(1.7-5.1)**	**3.2(1.76-5.73)**

COR, crude odds ratio; AOR, adjusted odds ratio; CI, confidence interval.

4.6. Level of adherence Status

By using the MMAS, 131 (39%) of the patients were found to be low adherent. For interpretation purpose, the adherence was re-categorized into two by merging high and medium adherence as adherent and low adherence as non-adherent. Thus, 205 (61%) of the patients were adherent to their medication (Figure 4-4).

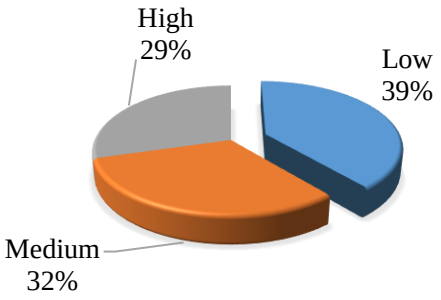


Figure 4-4: Level of medication adherence status among epilepsy patients attending at neurology clinic of Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, 2018/2019.

4.7. Predictors of medication non-adherence

For predictor of non- adherence, variables such as age, gender, marital status, education status, occupation, source of medication, personal assistance, family history, type of epilepsy, duration of seizure, presence of comorbidity, adverse drug reaction, number of MTM visits, and post clinical status were considered. But age, education status, occupation, source of medication, personal assistance, type of epilepsy, duration of seizure, number of MTM visits, and post clinical status fulfill the criteria for multivariate logistic analysis. From the mentioned variables age, personal assistance, source of medication and seizure control status were significant in multivariable logistic regression (Table 4-7).

Patients with age group greater than 60 were found to be 12.3 times more likely to be adherent (AOR=12.3, 95% CI: 2.8-53). Patients who got their medication by purchase and had personal assistants were found to be 2.9 times more likely to be adherent than who got freely and who did not have assistance ((AOR=2.9, 95% CI: 1.7-4.9), (AOR=2.9, 95% CI: 1.4-5.9)). A significant association was found between adherence and seizure control status. Patients with controlled seizure and well controlled seizure had had 5.2 and 3.1 times adherent than patients with poorly controlled respectively ((AOR=5.2, 95% CI: 1.6-5.7), (AOR=3.1, 95% CI: 2.5-11.1)).

Table 4-7: Factors associated with medication adherence among epilepsy patients on follow-up at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018/2019.

Variables	Categories	Level of adherence		Odds ratio (95% C.I.)	
		Adherent N (%)	Non-adherent N (%)	COR	AOR
Age	<18 Years	24(53.3)	21 (46.7)	1	1
	18-30 Years	88(62.8)	52(37.1)	1.48(0.751-2.919)	2.1(0.9-4.8)
	30-60 Years	70(56.4)	54(43.6)	1.13(0.572-2.250)	1.2(0.5-2.7)
	>60 Years	23(85.2)	4(14.8)	**5.03(1.49-16.9)**	**12.3(2.8-53)**
Educational level	Unable read and write	23(51.1)	22(48.9)	1	1
	Informal Education	7(36.8)	12(63.2)	0.55(0.19-1.67	0.4(0.1-1.5)
	Primary School	63(63)	37(37)	1.63(0.799-3.318)	1.0(0.4-2.4)
	Secondary School	63(61.1)	42(38.9)	1.51(0.75-3.03)	0.5(0.2-1.3)
	Collage And Above	46(71.9)	18(28.1)	**2.44(1.09-5.43)**	0.4(0.2-1.2)
Employment status	Employed	117(56.8)	89(43.2)	1	1
	Unemployed	88(67.7)	42(32.3)	**0.63(0.39-0.99)**	0.6(0.3-1.0))
Source of medication	Free	107(53.8)	92(46.2)	1	1
	Buying	98(71.5)	39(28.5)	**2.16(1.35-3.43)**	**2.9(1.7-4.9)**
Personal assistance	No	162(58.3)	116(41.7)	1.000	1
	Yes	43(74.1)	15(25.9)	**2.6(1.4-4.8)**	**2.9(1.4-5.9)**
Duration of seizure	> 10 years	86(61.9)	53(38.1)	1	1
	< 1 Year	30(81.1)	7(18.9)	**2.64(1.03-6.44)**	3.2(0.9-10.7)
	1-5 Years	53(55.8)	42(44.2)	0.78(0.458-1.321)	0.6(0.2-1.4)
	5-10 Years	36(55.4)	29(44.6)	**0.76(4.21-1.39)**	0.5(0.1-1.1)
Seizure control status	Poorly Controlled	32(41.6)	45(58.4])	1	1
	Well Controlled	104(62.4)	62(37.3)	**2.3(1.3-4.1)**	**3.1(1.6-5.7)**
	Controlled	69(74.2)	24(25.8)	**4(2.1-7.7)**	**5.2(2.5-11.1)**
Number of Follow-up	Four And Above	24(47.1)	27(52.9)	1	1
	Two Times	82(60.3)	54(39.7)	1.7(0.89-3.27)	1.1(0.5-2.4)
	Three Times	99(66.4)	50(33.6)	**2.2(1.17-4.25)**	1.7(0.8-3.6)

4.8. Treatment Satisfaction (Post-MTM)

According to the SATMED-Q score tool of treatment satisfaction, there are six domains of score (undesirable side effects, the efficacy of the medicine, convenience and ease of use of the medicine, impact of the medicine on everyday life, medical follow-up and overall opinion of the medicine and health). The general satisfaction was found to be 72.1 (SD, ± 12.3). The score for undesirable side effects was 66.9 (SD ± 26.11) and the overall mean score of treatment satisfaction was 76.75 (SD, ± 25.75) (Figure 4-5).

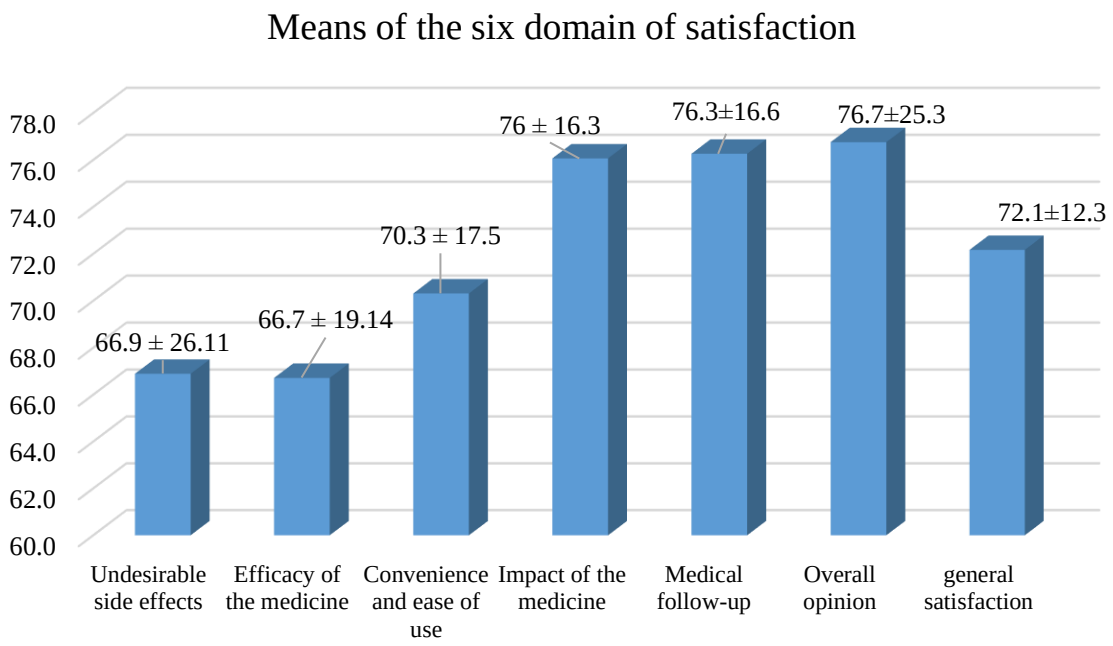


Figure 4-5: Treatment satisfaction among epilepsy patients on follow-up in the post assessment phase at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018/19.

There was no statistical difference in general treatment satisfaction among the age group, marital status, education, occupation, type of seizure, duration of seizure, presence of comorbidity, number of comorbidities, number of medications, presence of DTPs, number of DTPs, the type of regimen, and clinical status. The two significant variables were sex and level of adherence.

Table 4-8: Relationship between treatment satisfaction and different characteristics of epilepsy patients on follow-up at neurology clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

Variables	Category	N	Mean	F	P
Age	<18	44	71.53± 10.36	0.674	0.569
	18-30	140	71.89± 13.59		
	30-60	124	72.14± 11.70		
	>60	26	75.45± 11.41		
Sex	Female	157	73.99± 13.33	2.515	**0.013**
	Male	177	70.64± 11.20		
Marital status	Single	183	72.19± 13.25	0.969	0.407
	Married	135	71.65± 11.18		
	Divorced	8	77.17± 12.20		
	Widowed	8	77.26± 8.54		
Educational status	Unable to write & read	44	70.77± 12.24	2.205	0.068
	Informal education	18	74.46 ± 13.80		
	Primary school	100	72.80 ± 12.05		
	Secondary school	108	70.06 ± 11.70		
	College diploma	64	75.29 ± 13.02		
Employment Status	Unemployed	129	72.88 ± 12.10	0.042	0.435
	Employed	205	71.79 ± 12.50		
Personnel assistance	Yes	66	72.37 ± 17.10	3.991	0.930
	No	268	72.18 ± 10.89		
Source of medication	Free	197	71.26 ± 12.03	0.105	0.091
	Buying	137	73.58 ± 12.68		
Comorbidity	Yes	138	72.78 ± 13.84	3.718	0.486
	No	196	71.82 ± 11.18		
Seizure type	General	192	72.76 ± 11.12	1.419	0.243
	Focal	95	70.46 ± 12.07		
	Unclassified	47	73.54 ± 16.79		

(***Table 4-9*** *continued)*

Variables	Category	N	Mean	F	P
Number of Antiepileptic drugs	1	193	72.59 ± 13.41	0.438	0.646
	2	104	71.28 ± 11.15		
	3	37	72.86 ± 9.47		
Total number of medications	One	128	71.39 ± 13.10	0.916	0.401
	Two	102	71.89 ± 11.18		
	Three and above	104	73.54 ± 12.46		
DTP (post)	Yes	129	72.02 ± 11.44	0.451	0.866
	No	207	72.28 ± 12.65		
ADR (post)	Yes	32	70.90 ± 10.83	0.231	0.527
	No	302	72.35 ± 12.49		
Adherence level	Non-Adherent	130	67.82 ± 9.29	7.119	**0.001**
	Adherent	206	75.05 ± 13.22		
Clinical status (post)	Poorly controlled	96	71.01 ± 11.69	1.248	0.288
	Well controlled	156	72.06 ± 12.28		
	Controlled	82	73.92 ± 13.12		

4.9. Examples of Drug Therapy Problems Identified in the Study Subjects

Table 4-10 depicts examples of DTPs identified during the pre-and post-intervention phase. The patients were selected based on the type, number and presentation (pre-post) of DTPs among epilepsy patients attending at neurology clinic of TASH, Addis Ababa, Ethiopia, 2018/2019.

No	Patient presentation	Pre-intervention phase	Post-intervention phase	Identified drug related problem
1.	A 45 years old female patient with a known diagnosis of GTC, HTN, dyslipidemia, old stroke, severe fatty liver, and post-stroke Parkinson was taking phenytoin 100 mg PO TID, carbamazepine 800 mg PO BID, enalapril 5 mg PO /day, atorvastatin 20 mg PO/day and clonazepam 1.5 mg PO/day. She presented with recurrent abnormal body movement, tiredness, polyuria (five to eight times at night) and loss of balance. Because of her illness, she sometimes misses her medication. Laboratory test has done a month back shows an FBS value of 280 mg/dl and SrCr=1mg/dl. During the post-intervention assessment, she complains of one abnormal body movement over the past month, and also she had indigestion and stomach fullness.	✓	×	Need additional drug therapy
		✓	×	Non-adherence
		✓	✓	Dose too low (DDI)
2.	A 16 years old male patient with a known diagnosis of GTC + myoclonic seizure was taking phenobarbital 100/50 mg PO BID and carbamazepine 400/300 mg PO BID. He presented with recurrent abnormal body movement (4-6/week) and he forgets to take his medication especially the morning dose. On his last visit, he states that the seizure frequency was reduced to 1-2 /month and most of them were provoked by stress.	✓	×	Non-adherence
3.	A 21 years old female patient with the diagnosis of GTC for the past two years was on phenobarbital 100 mg PO/d and	✓	×	Non adherence

	Valproic acid 400/200 mg PO BID. Her seizure was well controlled for the last 6 months. She didn't get Valproic acid and discontinued for 3 weeks due to unavailability. She encountered 4 seizure attacks after discontinuation. During the post-intervention assessment, she states that on her previous appointment carbamazepine 200 mg BID was added because she wasn't able to get lamotrigine. She escalated CBZ to 200/400 mg PO BID by herself because her seizure was not controlled.	×	✓	Ineffective drug
		×	✓	Dose too low
4.	A 28 years female patient with a known diagnosis of GTC on phenobarbital 100 mg PO/d for the last 7 years. The last episode of abnormal body movement was 6 months back. She has a history of two miscarriages because of this event she prefers not to take medication. She is not using any contraceptive and plans to be pregnant. During the post-assessment phase, she has not had a period for the last 6 weeks. She is very afraid of taking the medication and discontinued for a week because of her previous events.	✓	×	Need additional drug therapy
		✓	✓	ADR
		×	✓	Non adherence
5.	An 18 years old male patient with a known diagnosis of mixed seizure (GTC + myoclonic seizure) and congestive heart disease (ASD) was taking phenytoin 150 mg PO TID, phenobarbital 130/100 mg PO bid, and risperidone 1mg PO/d. Currently, he presented with frequent episodes of abnormal body movement (5 times over the past month) and gingival hyperplasia. His family reported that he sometimes becomes aggressive and refuses to take his medication. On his last visit, the dose of phenytoin was reduced to 50 mg PO/day.	✓	✓	ADR
		✓	×	None adherence
		✓	✓	Dose too low
6.	A 27 years old male patient with a known diagnosis of focal seizure and T1DM was taking phenobarbital 100/200 mg PO BID, Valproic acid 500 mg PO BID, and NPH 22/15 IU subcutaneously BID. He reported that the seizure episode	×	✓	Non adherence

	was reduced since valproic acid was added to his regimen and the last seizure attack was two months back. On his last visit, he presents with 2 episodes of abnormal body movement after discontinuation of Valproic acid due to unavailability.			
7.	A 63 years old female patient with a known diagnosis of GTC, RVI, HTN, and CNS toxoplasmosis taking phenytoin 100 mg PO BID, ART(TDF-3TC-EFV PO/d), nifedipine 20 mg PO BID, enalapril 10 mg PO BID, ASA 81 mg PO/d, and atorvastatin 40 mg PO/d. She has a history of difficulty in keeping balance and very tired for the past two weeks. She also states that she has been taking nifedipine 40 mg PO BID and phenytoin 150 mg PO BID. She discontinued both medications two days back. On her last visit, she states a history of raised blood pressure but during the physical examination, her blood pressure was 130/80. She has no abnormal body movement for the past 2 years. She denies a history of taking salt-containing foods and she was taking all her medications.	✓	×	Dose too High
		✓	×	Non adherence
8.	A 39 years old male patient with a known diagnosis of focal seizure with secondary generalization for the past 8 years. He was on phenytoin 100 mg PO/day, phenobarbital 50/100mg PO BID, Valproic acid 200 mg PO BID, and amitriptyline 25 mg PO/d. He is married and has three children. He presented with erectile dysfunction of the past 2 years that get worse after he started the fourth medication (amitriptyline) that were added before one month. He also states sometimes misses his medication thinking that his problem was due to his medications. On his last visit, the amitriptyline was discontinued and valproic acid was changed to lamotrigine. He states that he was not able to get	✓	✓	ADR
		✓	×	Non adherence
		✓	×	Inappropriate drug selection

	lamotrigine and discontinued for a week that provokes the seizure (2x).			
9.	A 22 years old male patient with a known diagnosis of focal seizure was on phenytoin 100 mg PO TID and carbamazepine 400/200/200 PO TID. He complains of abnormal body movement three days back and he has been taking carbamazepine 200 mg PO TID stating that was what he was told by the pharmacist. On his last visit, he was taking 400 mg PO TID carbamazepine and he has two episodes of abnormal body movement over the past month. TDM was not done because he can't afford it.	×	✓	Dose too low (DDI)
		✓	×	Non-adherence (due to poor communication)
10.	A 21 years old male patient with a known diagnosis of mixed (GTC+ myoclonic) was taking lamotrigine 50 mg PO/d, clonazepam 0.5 mg PO/d, Valproic acid 400 mg PO TID, and phenytoin 100 mg PO TID. He presented with 2 episodes of abnormal body movement a week back. On his last appointment, he was diagnosed as Juvenile myoclonic epilepsy.	✓	×	Dose low
		×	✓	Ineffective drug product

5. Discussion

AEDs are the mainstay therapy for epilepsy and the ultimate goal of drug therapy is to achieve definite therapeutic outcomes and improve quality of life while minimizing patient risks. Nevertheless, they are known to have several inherent limitations that could potentially lead to DTPs (Goldenberg, 2010; Beretta, 2017). Besides, over half of the patients fail to take their medicine correctly (WHO, 2019). Therefore, identification and resolution of common types of DTPs contribute to the reduction of drug-related hospitalizations, morbidity, and mortality (Shareef et al., 2015). Hence, this study was aimed to investigate the outcome of introducing MTM services in epilepsy patients in TASH.

The majority of the study patients fell in the age group of 18-30 years with a median age of 28 and ICR of 21-40; this finding was in line with Manan et al., (2014) and Nasir, et al., (2020). The prevalence of epilepsy by gender was slightly higher in males (177, 52.7%) than females although the difference was not significant, which was in line with other studies (Birru et al., 2016; Rishe et al., 2015). However, it was found to be lower as compared to the study by Manan et al., (2014). This might be due to the difference in the study setup and cause of epilepsy.

Generalized onset (193, 57.4%) epilepsy was found to be the most diagnosed type of epilepsy, of which GTC (177, 53.9%) was the predominant one. Our result was congruent with a study conducted in Saudi Arabia (65%) (Gabr and Shams, 2015), East Shoa, Ethiopia (48.6%) (Rishe *et al.,* 2015) and TASH, Ethiopia (66.3%) (Nasir, *et al.,* 2020). On the contrary, a study in Qatar reported focal seizure to be the commonest one (65.5%) (Naddad *et al.,* 2016). The difference might be due to differences in the qualification of expertise and availability of diagnostic tools used for classification of seizure type.

In the pharmacological management of epilepsy, monotherapy is a preferred treatment modality as compliance is better, side effects are less, and drug-drug interaction is not an issue. This study revealed that 194 (57.7%) of patients were on monotherapy, which was in line with many studies, including Jimma referral hospital (54.5%) (Gurshaw *et al*., 2014), Malaysia (47.7%) (Manan *et al.,* 2014), and India (62%) (Sebastian *et al.,* 2013). Higher rates had also been reported in Bishoftu hospital (88%) (Rishe *et al.,* 2015) and Gondar referral hospital (80.35%) (Birru *et al*., 2016). This discrepancy might be due to differences in the study settings as the present study was conducted

in a tertiary care hospital, where complicated and uncontrolled seizures that might need combination therapy are referred.

The most widely used anticonvulsant agent in our study was phenobarbital with a total prescription of 171 (50.9%) followed by Phenytoin (107, 31.8%) and CBZ (104, 31.7%). This finding was consistent with various studies in Ethiopia, Gondar, (62.47%) (Birru *et al*., 2016), East Shoa, (90.7%) (Genet *et al.*, 2016), Bishoftu (92.8 %) (Rishe *et al*., 2015) and Jimma, (97.9%) (Gurshaw *et al.*, 2014). However, the most frequently prescribed AEDs was VPA (59.6 %) in a study conducted in Saudi Arabia (Gabr and Shams, 2015) and CBZ (67%) in Bangladesh (Habib *et al*., 2013) and PHT (42%) in India (Sebastian *et al.,* 2013). This might be due to the availability of medication, cost and the difference in standard treatment guidelines used in a different setup.

The percentages of patients who had at least one DTP before and after the provision of pharmaceutical care were 197 (59%) and 145 (39%), respectively. The change in the percentages of patients with DTP was 20% (from 59% to 39%) which is higher than the study in Thailand (90.38% to 75.00 %) (Kanjanasilp *et al.,* 2008). This disparity might be due to the specific type of medication used (where it only recruits patients on Phenytoin), the small sample size (52), and the presence of a low number of actual DTPs (53.85% and 46.38%). In this study, a total of 288 DTPs were identified during the pre-intervention, and 142 in the post-intervention phase. The change in the number of DTP showed a significant reduction from pre-intervention to post-intervention condition; $t\ (335) = 10.79$, $p < 0.005$. This finding was in line with a study by Kanjanasilp *et al.* (2008), where 111 DTPs were identified in the pre-intervention phase and 61 in the post-assessment phase and the change was significant. However, the reduction was found to be lower than that observed with other chronic diseases, including diabetes (Wakijira *et al.,* 2020). Regarding the mean DTP, our finding was lower (1.79 vs 1.7) than Kanjanasilp *et al*. (2008) but higher than the study in India (0.29) (Dahal *et al.,* 2013). This discrepancy might be due to the difference in study design, study setup (hospitalized), type of medication used and the number of patients.

The most encountered DTPs in the pre-intervention phase was non-adherence (95, 33%) followed by adverse drug reaction (65, 22.6%) and ineffective drug selection (30, 10.4%), whereas, in the post-assessment phase adverse drug reaction (33, 22.3%) followed by dose too low (32, 22.57%) and non-adherence (30, 20.3%). This inconsistency between the pre-post findings might be due to

the intervention package (brochure distribution, counseling, PMR use, and mini-group discussion) given specially to increase patient awareness on the need of absolute adherence, the nature of the antiepileptic drug (high level of DDI) and the presence of a lesser acceptance rate during the intervention phase for dose too low (58-36) as TDM was not performed for the majority of the patients. But, in the Kanjanasilp *et al.*, (2008) in Thailand study, the most frequent DTPs in pre-intervention phase was drug-drug interactions (26.50%) followed by failure to receive drugs (20.51%) and adverse drug reactions (20.51%) and while after the provision of pharmaceutical care, the most frequent DTPs were drug interactions (39.13%) and adverse drug reactions (28.99%). This difference across studies is due to variation on the DTP classification instrument used (modified Cipolle) and the type of antiepileptic drug used (patients on Phenytoin).

ADR was the second (70, 24-22%) most encountered DTP among patients, in which depression, headache, and somnolence were the most commonly reported ADRs. Unfortunately, ADR was still the second most encountered DTP in the post-assessment phase, this lower achievement with ADR might have to do with the nature of the disease or antiepileptic drugs. Most patients experience depression and were already on antipsychotic medication. As it is very difficult to know whether depression was caused by the disease or the AEDs, seeing small change in both phases is not surprising. Nevertheless, the present finding is consistent with the previous study in the same setting (Nasir *et al.,* 2020) but different from the one in Thailand (Kanjansalip *et al.,* 2008), where gingival hyperplasia was the most reported ADR, as a result of phenytoin use.

In the pre-intervention phase, the only variable that significantly associated with DTPs was age. Patients within 18-30 age group had 2.3 times (AOR=2.3, 95% CI: 1.1-4.8) more chance to develop DTPs. This might be due to the fact that 84 (60%) of the patients from this age group and 40 % among all patients were taking more than 2 drugs. In the post-assessment phase, variables such as the number of comorbidities and total number of medications were significantly associated with DTP. The shift of predictors from age to others (number of comorbidity and medication) might be due to the fact that majority of the patients in the pre-intervention phase (56%) had DTPs but less (38.3%) in the post-intervention phase, that might have given the true causes of DTPs.

Another factor associated with the occurrence of DTP was the duration of seizure. As the duration of seizure increased, patients were less likely to develop DTPs. This might be because the majority (79, 83%) of patients with 1-5 years seizure duration had no comorbidity or only one comorbidity.

Patients with uncontrolled seizure had 3.2 fold more probability to develop DTPs than patients with controlled seizure. This might be due to patients with controlled seizures are more likely to be adherent 4 (2.1-7.7) than patients with an uncontrolled seizure that might contribute to DTPs.

Non-adherence is associated with an over threefold increased risk of mortality compared to adherence. Periods of non-adherence were also associated with a significantly higher incidence of ED visits, hospital admissions, MVA injuries, and fractures than periods of adherence which suggested that non-adherence to antiepileptic drugs can have serious or fatal consequences for patients (Faught *et al.*, 2008). By using the MMAS-8, the rate of adherence to antiepileptic medication was 61%, whereas using the Cipolle *et al.* (2012) DTP classification, adherence in the pre-intervention phase was 69.1%, and post-assessment was 91%. This discrepancy between the two post-assessments of adherence might be due to high efforts made to reduce non-adherence based on the pre-intervention adherence finding of Cipolle's DTPs classification especially on problems associated with understanding instructions, forgetfulness, and drug product availability as well as the freedom of expressing feelings in self-administered questioners.

Even though the change is minimal (5.3%), our finding by using the MMAS-8 was better (61%) than the baseline study in TASH, (55.7%) (Nasir, *et al.*, 2020), this change might be brought due to pharmaceutical intervention provided to enhance patient's adherence to their medication but lower because of the strictness of MMAS-8 instruments that at least a patient should respond correctly for at list seven questions. But our finding was lower than the findings in India (98.6%) (Sebastian *et al.*, 2013) and USA (71%) (Hovinga *et al.*, 2008). This variation might be due to patient characteristics (more 1.8 ± 0.7 antiepileptic used) differences in culture and belief, unavailability of drugs (stockouts), and study set up.

Patients older than 60 years were found to be 12.3 times more likely to be adherent (AOR=12.3, 95% CI: 2.8-53) and patients with controlled seizure were 5.2 times more likely to be adherent (AOR=5.2, 95% CI: 1.6-5.7). This finding was in line with Sweileh *et al*., (2008) at which older patients and patients with controlled seizure had higher adherence rates. This may be due to the patients' realization of the benefits of adherence to their medications through time.

Patients who got their medication through purchase were more likely to be adherent (AOR=2.9, 95% CI: 1.7-4.9). This result was in line with a study done by Nasir *et al.*, (2020), where patients

who got their medication for free were 2.3 times more likely to be non-adherent. But, a study done by Getnet *et al.* (2016) showed that paying patients were more likely to be non-adherent. This discrepancy might be due to frequent stockouts of antiepileptic drugs especially valproic acid (26.8%) and lamotrigine (7.1%) and the majority of free patients cannot buy their medication because of the high cost. Getnet *et al.,* (2016) also states that patients with poor social support were 1.88 times more likely to be non- adherent, which was in line with our study that patients with personal assistance were more likely to be adherent (AOR=2.9, 95% CI: 1.4-5.9).

Treatment satisfaction is an important factor believed to influence patient's health-related decision making especially in treating chronic diseases. In this study, using the SATMED-Q satisfaction score tool general satisfaction was 72.1 (SD±12.3). This finding shows change when compared with the baseline study (67.4%) Nasir *et al.* (2020), this might be due to the positive impact of the intervention but, the achievement was lower due to side effect (66.9±26.11) and efficacy of medicine domain (66.7±19.14) lower accomplishment that could be associated with less success in reducing the incidence of ADR type of DTPs. But was in line with a study conducted among hypertensive patients in Palestine (72.1 ± 23.1) (Sa'ed *et al.,* 2013). The scores for side effects (66.9 ± 26.11), convenience & ease of use (70.3 ± 17.5), efficacy (66.7 ± 19.4) were lower than reported by Sweileh *et al.* (2008) study, 73.6%, 82.4%, and 69.5% respectively. This discrepancy might be due to the type of medication frequently used (phenobarbital vs carbamazepine) and presence of comorbidity (41.4% vs 13.7%).

Regarding factors affecting treatment satisfaction, gender and level of adherence were significant. Male gender (73.99 ±13.33) had a lower treatment satisfaction score than females. This is in contradistinction to the findings of Bener *et al.* (2014), where females were reported to have less satisfaction than males. This variation might be due to the difference in medication adherence behavior between females 101(63.5) and males 104(58.7), although not statistically significant. Treatment satisfaction may be associated with medication adherence for several reasons, including patients' attitudes or beliefs towards taking medications (Krousel-Wood *et al.,* 2004). Similarly, in this study, non-adherent patients (75.05 (SD, ± 13.22)) were less satisfied than adherent patients, which was also supported by a study done by Sweileh *et al.,*(2008), who reported that patients with a high adherence had the highest satisfaction scores compared with those with low or medium adherence. Moreover, Molugulu *et al.* (2016) demonstrated adherence as a predictor of patient

healthcare satisfaction particularly in the overall patient satisfaction domain (P = 0.043). This was further confirmed by Sa'ed *et al.* (2013).

6. **Limitation**

- ✓ Historical control group, who were used for ethical reasons, creates difficulty to ascertain that the cause was only the intervention
- ✓ Difficult to make generalization because of the short intervention period
- ✓ Self-reporting methods are not considered as a trusted way to assess medication adherence.
- ✓ Being a single-center study

7. Conclusion

The implementation of medication therapy management service showed a reduction in the number of patients with DTPs and the total number of DTPs. In addition, the service showed a significant reduction in the incidence of non-adherence, dose too low, and ADR types of DTP from pre to post-intervention phase. Non-adherence and adverse drug reaction were the most frequently seen DTPs both in the pre-intervention and post-assessment phase. Age, seizure duration, number of comorbidities, total number of medications, and seizure control status were significantly associated with DTPs. In the post-assessment majority of the patients were adherent to their medication and age, personal assistance, source of medication, and seizure control status were determinate for adherence. Overall, the general treatment satisfaction of patients was found to be good.

8. Recommendation

- The hospital management and the school pharmacy should facilitate the initiation MTM service to serve epileptic patients at TASH.
- TDM should be done for all patients in need (potential DTPs and DDI).
- Frequent unavailability was the common reason for non-adherence on patients who acquire drugs free of charge, so the responsible body (Hospital management and Ethiopia pharmaceutical supply agency) should take appropriate action.
- The minsters of health should perform a large-scale national study to design policies and increase patient's access to MTM services.

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Annex

Annex I

Data collection tools

Pharmacy Contact Information Here

Pharmacist:

_____

I. Patient socio-demographics

Age (year):_____ Sex: ____

Marital status:	Single ☐	Married ☐	Divorced ☐ Widowed ☐
Educational status	Unable to write & read ☐	Informal education ☐	Secondary school ☐
		primary school ☐	College diploma and above ☐

Residence(current): _____

Occupation Employed ☐ Unemployed ☐ Private ☐ Student ☐

Other(specify) ☐_____

How do get your medication? Buying ☐ Free ☐ Company ☐ Third Party Coverage ☐

II. Health Information and Lifestyle Factors

Inquiry	Yes/No	Details/ comments
a. Allergies	◯ Y N ◯	Reaction
b. Smoker	◯ Y N◯	Cigarettes/day:
c. Alcohol Consumption	◯ Y N ◯	Drinks/week:
d. Caffeine Intake	◯ Y N ◯	Cups/day:
e. Physically Active	◯ Y N◯	Type of activity: Hours/week
f. Recreational/Other Drug Use	◯ Y N◯	Specify:

g. Do you have person assist you in medication use	◯ Y N ◯	
h. Aids, Alerts, Devices, etc.	Others	

Past medical history (relevant illnesses, hospitalizations, surgical procedures, injuries, pregnancies). _____

Past medication(s)_____

Family History (FH): _____

Functional History (if relevant- i.e. geriatrics, stroke patient, homeless, etc.): _____

Physical Examination (PE)/**vital** signs:

Parameters	**Date(dd/mm/yy**									
BP										
PR										
RR										
T^0										
Others:										

Current Medical Conditions *(List medical conditions in numbered spaces with relevant information/parameters)*

1.	2.	3.	4.
5.	6.	7.	8.
Head to toe Assessment regarding other complaints/concerns/bothersome symptoms: Complaints/Concerns: Bothersome symptoms: Do any ever require self-treatment?			

Relevant **laboratory** series results (Lab Findings of at least for three consecutive results).

Parameters	Date(dd/mm/yy									
HbA1c (%):										
FBS(mg/dL):										
RBS(mg/dL):										
Lipid profiles	LDL: mg/dl									
	TG: mg/dl									
	HDL: mg/dl									
	Total C									
OFTs	ALT/SGOPT									
	AST/SGPT									
	ALP									
	GFR									
	SrCr									
Others										

Medications (Prescription, Non-Prescription, Herbal Products)

Medication Name, strength	How taken Dose, route, frequency, time of day, special instruction	Purpose for use	Starting date	Stopped date	Who stopped it? Reason for stopping	Issues identified		Additional comments
						Yes: proceed to DTPs identified	No: verify to continue as per	
						◯	◯	
						◯	◯	

Drug Therapy Problems Identified and Addressed by MTM Pharmacists

Drug therapy problems identified

No drug therapy problems were identified

Priority Number Drug Therapy Problem (DTP)

_____

_____

_____

_____

For those drug therapy problems above which can be corrected with *immediate action* and *no further research or consultation*, document your plan below:

DTP	Proposed solution	Discussed with patient	Follow-up plan

Pharmacy Care Plan

Data: Subjective information provided by the patient and/or objective data that you have collected.

Assessment: State the drug therapy problem.

Plan: For each alternative, consider treatment efficacy, safety, drug interactions,

adherence, cost, drug cover age and non-pharmacological interventions.

Alternative#1:

Alternative#2:

Monitoring:

Planned date of follow-up:_____

Pharmacist signature_____ Date of Review_____

Patient action plan

Date of comprehensive medication review:_____

As a result of comprehensive medication review, I will do the following:

1.
2.
3.

Patient follow record

Date follow up	Reason for follow-up	Results	Pharmacist comments &plan
		Any new concerns?	Intervention complete? ☐ Yes ☐ No
		Any new concerns?	Intervention complete? Yes No
		Any new concerns?	Intervention complete? Yes No

Annex II

Drug Therapy Problems Identified and Addressed by MTM Pharmacists

DTP type	Categories of DTP	Drug therapy problem cause
Indication	1. Unnecessary drug therapy	☐ Duplicate therapy ☐ No medical indication at this time ☐ Nondrug therapy more appropriate ☐ Addiction/recreational drug use ☐ Treating avoidable adverse reaction
	2. Needs additional drug therapy	☐ Preventive therapy ☐ Untreated condition ☐ Synergistic therapy
Effectiveness	3. Ineffective drug	☐ More effective drug available ☐ Condition refractory to drug ☐ Dosage form inappropriate ☐ Contraindication present ☐ Drug not indicated for condition
	4. Dosage too low	☐ Ineffective dose ☐ Needs additional monitoring ☐ Frequency inappropriate ☐ Incorrect administration ☐ Drug interaction ☐ Incorrect storage ☐ Duration inappropriate
Safety	5. Adverse drug reaction	☐ Undesirable effect ☐ Unsafe drug for the patient ☐ Drug interaction ☐ Incorrect administration ☐ Allergic reaction ☐ Dosage increase/decrease too fast

	6. Dosage too high	☐ Dose too high ☐ Needs additional monitoring ☐ Frequency too short ☐ Duration too long ☐ Drug interaction
Compliance	7. None adherent	☐ Does not understand instructions ☐ Cannot afford drug product ☐ Patient prefers not to take ☐ Patient forgets to take ☐ Drug product not available ☐ Cannot swallow/administer drug

Annex III

Morisky 8-Item Medication Adherence Questionnaire
Scores: >2 = low adherence
1 or 2 = medium adherence
0 = high adherence

Questions	Patient Answer Score (Yes=1; No=0)
Do you sometimes forget to take your medicine?	
People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medicine?	
Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?	
When you travel or leave home, do you sometimes forget to bring along your medicine?	
Did you take all your medicines yesterday?	
When you feel like your symptoms are under control, do you sometimes stop taking your medicine?	
Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	
How often do you have difficulty remembering to take all your medicine? A. Never/rarely____ B. Once in a while____ C. Sometimes_____ D. Usually____ E. All the time____	A = 0; B-E = 1
Total score____	

Annex IV

SATMED-Q® Questionnaire

We want to ask you about your satisfaction with the medicine you are taking. You may be taking medicines to treat more than one medical condition. For each question, put a cross through the number that best reflects your opinion. There are no right or wrong answers. If you are not sure of any of the answers, mark the one you consider most appropriate.

	Not at all	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
▪ **Undesirable side effects**					
1. The side effects of the medicine interfere with my physical activity (e.g. lifting, walking, jogging, etc.).	⓪	①	②	③	④
2. The side effects of the medicine interfere with my leisure and free time activities (e.g. gardening, reading, dancing, visiting friends, etc.)	⓪	①	②	③	④
3. The side effects of the medicine interfere with my daily activities (e.g. shopping, working, housekeeping, etc.).	⓪	①	②	③	④
▪ **Efficacy of the medicine**					
4. The medicine I am taking reduces my symptoms.	⓪	①	②	③	④
5. I am satisfied with the time it takes for the medicine to start to have an effect.	⓪	①	②	③	④
6. I feel better now than I did before starting the treatment.	⓪	①	②	③	④
▪ **Convenience and ease of use** of the medicine.					
7. I find my medicine convenient to take.	⓪	①	②	③	④
8. I find it easy to use/take the medicine in its present form (taste, size, etc).	⓪	①	②	③	④
9. The timetable for taking the medicine suits me.	⓪	①	②	③	④

▪ **Impact of the medicine** on your everyday life.					
10. Thanks to the medicine I am taking I can undertake my leisure and free time activities.	⓪	①	②	③	④
11. Thanks to my medicine I can more easily look after my personal hygiene (e.g. shaving, brushing my hair, bathing, etc.)	⓪	①	②	③	④
12. Thanks to my medicine I can perform my everyday chores better.	⓪	①	②	③	④
▪ **Medical follow-up/review** of your condition					
13. My doctor has informed me in detail about my medical condition.	⓪	①	②	③	④
14. My doctor has informed me about the right way to treat my medical condition.	⓪	①	②	③	④
▪ **Overall opinion** of the medicine and your health					
15. I intend to continue using this treatment.	⓪	①	②	③	④
16. I feel happy with my treatment.	⓪	①	②	③	④
17. In general, I feel satisfied with the treatment.	⓪	①	②	③	④