Drug Therapy Problems among Ambulatory Patients with Type 2 Diabetes at Endocrine and Metabolism Unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

By

Gebre Teklemariam Demoz (B.Pharm)

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This is to certify that the thesis prepared by Gebre Teklemariam Demoz, entitled: "Drug Therapy Problems among Ambulatory Patients with Type 2 Diabetes at Endocrine and Metabolism Unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia" and submitted in partial fulfillment of the requirements for 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.

Signed by the examining committee:

Internal examiner: Teshome Nedi (PhD) Signature_____ Date_____

External examiner: Legese Chelkeba (PhD) Signature_____ Date_____

Advisor: Workineh Shibeshi (PhD) Signature_____ Date_____

Advisor: Helen Yifter (MD) Signature_____ Date_____

Advisor: Minyahil Alebachew (PhD candidate) Signature_____ Date_____

_____

Head, Department or Graduate Program Coordinator

Abstract

Drug Therapy Problems among Ambulatory Patients with Type 2 Diabetes at Endocrine and Metabolism Unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

Gebre Teklemariam Demoz
Addis Ababa University, 2018

Patients with diabetes are at high risk of drug therapy problems (DTPs), as they are outstanding to multiple-medications. To date, studies regarding DTPs in patients with diabetes are limited in Ethiopia. Thus, this study was aimed to assess the magnitude, pattern and factors associated with DTPs among patients with type 2 diabetes at Tikur Anbessa Specialized Hospital. A cross sectional study was conducted among 357 participants who fulfilled the inclusion criteria. Participants were interviewed using structured data collection format, involving medical chart review retrospectively. Drug therapy problems (DTPs) were assessed using Cipolle's classification system. Data were reported by mean/percentage and multivariate logistic regression analysis was performed to identify factors associated with DTPs. A total of 193 DTPs in 164(45.9%) of participants were identified. Most commonly identified DTPs were ineffective drug therapy 54(26.1%), need additional drug 52(25.1%) and dosage too low 47(22.7%), Factors independently associated with DTPs were female gender (Adjusted Odds Ratio [AOR] =2.21, 95%CI; 1.32-3.72), number of comorbidities (≥3) (AOR=3.18, 95%CI;1.21-8.38), non-adherence (AOR=4.52,95%CI;2.34-8.73). One-fourth (24.9%) of the participants were non-adherent to their medications. Factors associated with non-adherence were diabetes complications (AOR=2.02, 95%CI; 1.02-3.22), being female gender (AOR=1.71, 95%CI; 1.01-2.76) and primary and above level of education (AOR=0.42, 95%CI; 0.18-0.96). Drug therapy problems were substantially high. Ineffective drug therapy, need additional drug therapy and dosage too low, were commonly identified DTPs. Nearly one-fourth of the study participants were non-adherent to their medications. In response to this finding, tailored future intervention that target in prevention and resolution of those problems could be vital.

***Key words*:** Diabetes mellitus, drug therapy problems, medication adherence, Ethiopia

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List of abbreviations

ADA/EASD	American Diabetes Association/European Association for the Study of Diabetes
ADEs	Adverse Drug Events
ADRs	Adverse Drug Reactions
AOR	Adjusted Odds Ratio
CI	Confidence Interval
CVD	Cardio Vascular Disease
DM	Diabetes Mellitus
DTPs	Drug Therapy Problems
eGFR	estimated Glomerular Filtration Rate
EHRIG	Ethiopian Hospital Reform implementation Guidelines
FBG	Fasting Blood Glucose
HbA_{1c}	Glycosylated Hemoglobin A_{1c}
IDF	International Diabetes Federation
LLAs	Lipid Lowering Agents
MTM	Medication Therapy Management
OGLD	Oral Glucose Lowering Drugs
OR	Odds Ratio
PCNE	Pharmaceutical Care Network of Europe
PFSA	Pharmaceutical Fund and Supply Agency
SMBG	Self-Monitoring of Blood Glucose
SPSS	Statistical Package for Social Sciences
TASH	Tikur Anbessa Specialized Hospital
WHO	World Health Organization

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1. Introduction

1.1. Background

Diabetes Mellitus (DM; diabetes) is a group of metabolic diseases characterized by the manifestation of persistent hyperglycemia due to deficiency in insulin secretion, insulin action or both. The types of DM generally classified as type 1, type 2, gestational and other types of diabetes (1-3). In the most recent World Health Organization (WHO) global report, a dramatic increase of diabetes is largely due to the rise in type 2 diabetes, accounted for 85-90% (4).

According to International Diabetes Federation (IDF), in 2017, about 425 million (8.8%) adults (20-79 years) are living with diabetes worldwide. By 2045 this figure projected to be raised-up to 629 million (9.9%), including about 108 million in Africa region(3). Diabetes prevalence has been rising more rapidly in middle and low income nations. In Ethiopia, about 1.8 million adults (20-79 years) were living with diabetes(4, 5). Moreover, the most recent WHO report showed that, the prevalence of people living with diabetes in Ethiopia is substantially increasing. Thus, the percentage was raised from (1980) 0.5% to (2014) 3.8%(5) and by 2017 reached to 5.2% (3).

Globally, diabetes was the third among the five leading global risks for mortality(6). In 2017, IDF reported that an estimated of 4.0 million deaths were due to diabetes(3). Every year, 5 million people die due to diabetes, one every 6 seconds(4). Continues upswing prevalence of diabetes worldwide, placing an increasing burden on healthcare systems. Global expenditure for the treatment of diabetes and its complications was estimated to be $727 billion in 2017 and is projected to increase to $776 billion by 2045(3). Although limited data were available in developing nations, the economic burden was greater in developing nations than developed nations (7). Thus, diabetes makes one of the leading worldwide health problems of this century(3).

Drug therapy problems (DTPs) are events or circumstance involving or suspected to be involved drug therapy that actually or potentially interfere with a desired health outcomes (8, 9). Drug therapy problems (DTPs) can occur at every step of the medication use process(9). To date there is no uniform systems of classification for DTPs as different literatures used various classification system. But according to Cipolle et al.(9), there are seven distinct categories of

DTPs. Such as unnecessary drug therapy, need additional drug therapy, ineffective drug therapy, dosage too low, adverse drug reaction, dosage too high and non-adherence.

An infinite number of DTPs were existing because of the rapid expanding range of drug products, the growing number of diseases and patients (9). Drug therapy problems (DTPs) are a significant public health issue in association with morbidity, mortality, and economic costs(10). One-third of the patients attending the emergency room of hospitals had at least one DTP(11). A study conducted in United State (US) indicated that the annual expenditures for antidiabetic drug therapies have been quadrupled to over $8.0 billion(12). The costs of hospital admissions due to drug therapy problems are also substantial (13). However, most of those problems that attributed to hospital admissions or visits are preventable(14).

According to Cipolle et al. (9), the scheme of how DTPs need to be assessed and identified is important. Assessments concerning an indication should be made first; then, effectiveness, followed by dosing and safety profile of the product. Finally, medication adherence problems, that represents the willingness and ability of the patient to take the medication as intended should be considered. Drug therapy problems and their causes should be categorized and clearly identified, unless and otherwise it could be difficult to resolve or prevent these problems. Thus, it is crucial to assess and identify, most likely need to design that rational care plan can be bring together (15).

1.2. Statement of the problem

In spite of medications have vital roles to prevent and control or treat different diseases, inappropriate use of medications may be insecure and lead to problems related to medications (16). Drug therapy problems (DTPs) are significant public health issue worldwide and have been significantly increased over the past few decades. It was estimated that about 5 to 10% of hospital admissions were due to the occurrence of DTPs, in which 50% of them are preventable (17). Globally, more than half of all medicines are prescribed and dispensed inappropriately, overt that half of the patients fail to take them as prescribed (18, 19). Numerous studies had recognized the type and pattern of DTPs in developed nations. Conversely, there is dearth of published data regarding the type and pattern of DTPs in under resourced nations(20).

Patients with diabetes are at high risk in experiencing a number of DTPs. Thus, the existences of DTPs are very frequent among ambulatory patients with diabetes (12, 21, 22). Studies reported that, more than 90% of patients with diabetes had at least one DTP (21, 23-25). Moreover, hospitalization due to DTPs in adult patients with diabetes and cardiovascular diseases (CVDs) accounts in 65% of the participants. This was mainly occurred due to lack of drug treatment effectiveness and adverse drug events (26).

Patients with diabetes are subject to receive multiple drug therapies for their multiple co-morbidities associated with their medical problem, as a result problems related to medications commonly encountered among them (12, 21). Antidiabetics, antihypertensives and lipid lowering agents were drug classes that mostly commonly involved in the event of DTPs (21). Majority of patients with diabetes had been experienced at least one episode of poor glycemic control. Multiple number of medications in use and medication non-adherence were commonly associated factors that attributed for the existence of DTPs among patients with diabetes (25).

As problems related to drugs are commonly encountered in patients with diabetes, they are highly exposed for significant morbidity, mortality, and cost expenditure (27). These problems are in charge for considerable costs, and about 6.5% of morbidity and mortality of hospital admission are related to medication errors (28). Drug therapy problems (DTPs) are a major safety issue for patients while treating their disease using medicines (29). Hence, such problems adversely affect patients' quality of life, increased hospitalization, overall health care

cost and risk of morbidity and mortality (30). Inappropriate use of drugs that leads to such problems need to be identified and resolved, since two-thirds of DTPs are preventable (28). Early detection of DTPs and associated factors can also enhance the prevention and resolution of such problems in patients with diabetes (23).

Drug therapy plays an important role in treating the disease and improving the health of patients with diabetes. However, its benefit may be compromised due to the occurrence of DTPs; as experiencing of DTPs is highly suspected among patients with diabetes. Therefore, in this era, diabetes is an alarming issue both for the community and for the government as well. As a result it needs a special attention on early identification, prevention and resolution of these problems that enhance appropriate use of drugs and in achieving the desired goal of therapies.

Still more studies are needed regarding the magnitude of DTPs and associated factors among patients with type 2 diabetes in Ethiopia, particularly in Tikur Anbessa Specialized Hospital (TASH). Thus, conducting of this study could be helpful in identification, prevention and resolving of those problems in patients with diabetes. This also helpful to show the gap in health care practice so as to empower the focus of healthcare providers and policy makers in designing strategies in preventing the occurrence of DTP, resolving and minimizing such problems.

Therefore, the primary aim of this study was to determine the magnitude of DTP, drugs involved in experiencing DTP and factors associated with DTPs among patients with type 2 diabetes.

1.3. Literature review

1.3.1. Drug therapy problems

Drug therapy problems are a major safety issue for patients with chronic illness (31). One study in United State (US) indicated that, 84% of participants (9,873) had at least one DTP. The most commonly experienced DTP in patients with diabetes was need additional drug therapy(33%,) followed by dosage too low(27%) and non-adherence(15%), respectively (12).

In India, a prospective study was conducted using Cipolle's classification. In the period of six months study duration, a total of 80 DTPs were identified in 190 patients with the incidence rate of 42%. Types of DTP were medication errors, non-compliance, untreated indications, drug interactions, and ADRs were the most commonly observed DTPs (32). Similarly, in Indian patients with diabetes, a total of 189 DTPs were identified from 151 patients. The most common problem found was drug use without indication (17.98%), followed by improper drug selection (16.40%) (33). Another finding in India, also showed that, inappropriate drug dosing (25.35%) and drug selection (23.94 %) were the most types of DTPs identified (30).

A prospective study done in Sri Lanka teaching hospital among 400 ambulatory patients with diabetes, a total of 151 DTPs were identified based on Pharmaceutical Network Care of Europe (PCNE) classification. The most common identified DTP was effect of drug treatment not optimal (39.73%), followed by unnecessary drug therapy (16.55%) and untreated indication (12.58%). Half (50.33%) of the DTPs identified were caused by the way of patients use their medicines. Types of DTPs frequently identified were related to selection of drugs (31.12%), inappropriate drug use (40.42%), drug required not given (23.4%) and 21.27% of drug duplications (22).

A retrospective study in type 2 diabetes with hypertension patients was conducted at a tertiary hospital of Malaysia. A total of 387 DTPs were identified from the total of 200 study participants using the PCNE tool. Among these, 90.5% of participants had at least one DTP, with an average of 1.9 ± 1.2 problems per patient. The most common DTPs experienced were insufficient awareness of health and diseases (26%), drug choice problems (23%), dosing problems (16%) and drug interactions (16%). Most commonly involved drugs were aspirin, clopidegrole, simvastatin, amlodipine and metformin (23).

Another retrospective study involved 208 type 2 diabetes in-patients and out-patients with dyslipidemia were also conducted at the same study setting of Malaysia. A total of 406 DTPs were identified. Among these, 91.8% of participants had at least one DTP, averaging 1.94 ± 1.10 problems per patient. The most frequent types of DTP were potential drug-drug interaction (18.0%), drug not taken or administered (14.3%) and 11.8% of participants due to insufficient awareness of health and diseases (21).

A multi-center, cross-sectional study was conducted in 1,494 patients with diabetes from outpatient diabetes clinics of five public hospitals in Jordan. Out of them, 81.2% had at least one DTP. The most prevalent identified types of DTPs were drug without indication (26.1%) and untreated conditions (19.6%), more effective drug is available (16.7%), need additional drug therapy or stepping up (19.6%), and 10.6% patient needed stepping down drug therapy (34).

In another study in Pakistan medical ward, a total of 33 DTPs were identified from 15 diabetes patients. Majority (60.06%) of the DTPs were resulted from drug-drug interactions (35). One study conducted in Denmark, also reported, a total of 635 DTPs were identified in 155 type 2 diabetes patients with an average of 4.1 DTPs per patient. Inappropriate use of drugs (171 cases) by the patient was the most common identified DTP, followed by inappropriate drug selection (57 cases) and 55 cases for side-effects (24).

A retrospective cohort study of DTPs in adult diabetes patients admitted to Australian teaching hospital was conducted over two-years. Drug therapy problems were associated with 686 (7.2%) admissions. The common DTPs were medication errors (64.1%) associated with hypoglycemia and unintentional overdose (36). Likewise, another study in Australia, 682 DTPs were identified using the PCNE classification, an average of 4.6 ± 1.7 per patient with type 2 diabetes (37).

In an observational study in China, a total of 522 elderly patients with diabetes were analyzed and 417 DTPs were identified using PCNE. The incidence of DTP was 62.8% (328/522) with a mean number of DTPs per patient 0.9±0.6. The most prevalent DTP categories was related to dosing (43.9%), followed by drug choice (17.3%) and adverse drug reactions (15.6%), respectively (38).

According to findings from the retrospective study conducted among 300 participants from two hospitals of United Kingdom (UK) and Saudi Arabia, a total of 197 (65.7%) adult patients with diabetes and CVDs were hospitalized due to the incidence of DTPs. Most common DTPs were lack of treatment effectiveness (45.2%) and ADR (45.2%), respectively (26).

A study done in Nigeria, showed that, a total number of 792 DTPs were identified from the total of 399 patients with type 2 diabetes, which indicates 94% of patients with an average of 2.1 problems per patient (25). Another prospective study conducted among 40 patients with diabetes was undertaken in the medical wards of Nigerian hospital. Findings from this study showed that, the mean rate of DTP was 4.05 ± 1.96 and the most encountered DTP was wrong drug 23.9%, followed by adverse drug reaction 16.4%, needs additional drug therapy 14.5% and dosage too high 14.47%. Other problems included were non-adherence 13.8%, dosage too low 11.3% and unnecessary drug therapy 5.6% (39).

In one cross sectional study conducted in Wolaita Sodo, Ethiopia among 243 patients with type 2 diabetes showed that, 83.1% of them had at least one DTP. Using Cipolle's DTP classification system, the most commonly identified type of DTP was need additional drug therapy (56.4%), followed by medication non-adherence (51.9%). Factors independently associated with developing DTPs were also reported; such as patients aged ≥ 65, presenting with number of comorbidities, multiple medications in use, and history of hospitalization (40).

1.3.2. Factors associated with drug therapy problems

In Malaysia, the occurrence of DTPs in patients with type 2 diabetes and hypertension significantly associated with renal impairment, multiple medication use, CVDs, elderly age, and longer hospital stay (23). In addition, drugs such as anti-hypertensive, lipid-modifying and anti-diabetic agents were the drug classes that most likely to be associated with DTPs in patients with diabetes and dyslipidemia. Male gender, renal impairment, multiple medication use and poor lipid control were factors that were significantly associated with DTP in patients with diabetes and dyslipidemia (21).

Another study in Jordan shows the independent risk factors for DTPs identified were male gender, multiple medications use, gastrointestinal medication, and non-adherence to self-care (34). A retrospective study conducted included 300 adult patients from two hospitals of UK and Saudi, a total of 197 (65.7%) patients with diabetes and CVDs were hospitalized due to the incidence of DTPs. Moreover, use of multiple medications and patient non-adherence were the main causes in contributing to develop DTPs. The main drug classes associated with DTPs were insulin and antihypertensive medicines (26).

Potentially non-adherent patients had a significantly higher HbA_{1c} than patients who adhered to therapy (37). From the study done by Claydon et al (36) factors significantly associated with DTPs are female gender, age of 18–50, being single marital status, mental problems, and presence of comorbid conditions (33).

1.3.3. Medication adherence and associated factors

A prospective study in 105 patients with diabetes in Indian hospital indicated that, adherence levels were 40.95%, 37.14% and 21.90% for high, medium and poor adherence, respectively. The correlation between patients' socio-demographic and adherence rate to antidiabetic therapy indicated that higher magnitude of adherence among men, the elderly, those with primary education and the unemployed patients. The most common reasons for non-adherence were inadequate knowledge about therapy, financial problem, patients feeling better, and feeling worse. Moreover, factors for non-adherence were identified as travel a lot and busy due to work load(41). In one study, only 41.8% of the patient had adequate glycemic control. The main external factors for non-adherence were lack of finance and perceived side effect of drug (42).

In a qualitative study of 45 American patients with diabetes found that poor pharmacy service quality and difficulty in coordinating multiple prescriptions were reported as key barriers for medication adherence (43). Conversely, in another cross sectional study in 423 patients with type 2 diabetes found that there was no association between adherence in patients with type 2 diabetes with socio-demographic and clinical variables(44). In Uganda, one cross sectional study was conducted in 521 patients with diabetes. The level of adherence to antidiabetic medication was found to be 83.3% and factors that were positively associated with adherence were; being on antidiabetic drugs for at least three years, adequate availability of diabetic drugs and provision of health education (45).

Based on the finding of Abebe et al (46) the self-reported adherence to antidiabetic medications was low for 25.4%, medium for 28.7% and high for 45.9% in 391 patients with diabetes. Poor wealth status, using traditional treatment, and service dissatisfaction were significantly associated with low adherence to the prescribed antidiabetic medications. A study done in Assela general hospital in 285 outpatients with diabetes reported that, 68.8% participants were adhered to their antidiabetic medications. Factors like, drug side effect, regimen complexity, failure to remember, low grade of education, low monthly income, and absence of glucometer at home are most commonly encountered for poor adherence to their medication (47).

Similarly, study was done in Hiwot Fana hospital, Ethiopia, using the Morisky's 4- item method of adherence demonstrated that, 70.4% of the study participants were adhered to the prescribed oral antidiabetic medications. Reasons for poor adherence given that, patients were not being

careful in taking their medication, patients forgot to take medications regularly, and few patients stopped medication when they felt better and worse. Educational status, residence and glycemic outcomes were reported as determinants for low adherence (48).

Another study in 270 patients with diabetes at Adama hospital found that, 21.8% of the participants recognized their non-adherence to forgetting to take their medications. Patients with duration of diabetes 5 years (82.07%) were more compliant to their medication than those with 5 years (60.8%), which was found to be statistically significant(49). In addition, in one study conducted at Jimma, 24.3% of patients with type 2 diabetes were non-adherent and this was significantly associated with presence of diabetes complication, poor glycemic control and diabetes related hospitalization(50).

Study done in TASH by Tessema et al. (51) (Master's thesis) reported that, adherence rate of patients with type 2 diabetes to their antidiabetic medications was found to be 66.8%. Younger age, increased number of prescribed medications and job type (being a farmer/daily laborer) were significantly associated with antidiabetic medication non-adherence. Most of the patients missed their medications because of forgetfulness. Number of medication was independently associated factors for poor adherence.

2. Objective

2.1. General objective

This study was aimed to assess drug therapy problems among ambulatory patients with type 2 diabetes at endocrine and metabolism unit of Tikur Anbessa Specialized Hospital.

2.2. Specific objectives

To determine the magnitude of drug therapy problems among patients with diabetes

To identify medications involved in drug therapy problems among patients with diabetes

To identify factors associated with drug therapy problems among patients with diabetes

3. Methodology

3.1. Study setting

The study was conducted at Addis Ababa University, Tikur Anbessa Specialized Hospital (TASH). This hospital is the largest public referral and teaching hospital in Ethiopia. This hospital is allied with College of Health Sciences, Addis Ababa University. It is the training center for postgraduates and undergraduate medical students, and other health sciences students. The hospital has about 800 beds and is in the provision of complicated diagnostic and treatment services for about approximately 370,000- 400,000 patients a year who come from different part of the country(52). This hospital has many follow up clinics for chronic illness. Diabetes clinic is one of them. There are 6 consultants/endocrinologists, one fellow and 6 internal medicine residents who were assigned for attachment in the clinic. This clinic had scheduled follow up for each type of patients with different metabolic disorders. Adult patients with type 2 diabetes are arranged to visit the clinic on every morning of Monday and Wednesday. About 180 patients with type 2 diabetes per a week were getting service in the diabetes clinic.

3.2. Study design and study period

A hospital based cross sectional study design was conducted. The data were collected for the period of three months (from April 1, 2017 to June 30, 2017) including data from patients' medical chart that recorded from July 1, 2016 to June 30, 2017.

3.3. Source and study of population

All patients with diabetes who visited the diabetes clinic of TASH were the source population of the study. All adult patients with type 2 diabetes who were on follow-up in the diabetes clinic of the hospital during the study period were a study population of the study.

5.1.1. Inclusion criteria

Patients diagnosed with type 2 diabetes aged 18 years and above

Ambulatory patients with type 2 diabetes who were taking antidiabetic drugs for at least 1 year

Patients with type 2 diabetes who had regular follow up in the diabetes clinic for at least 1 year

5.1.2. Exclusion criteria

Pregnant patients with preexisting (overt) type 2 diabetes

Ambulatory patients with type 2 diabetes with incomplete medical record chart

These patients with type 2 diabetes who were seriously ill to complete the interview

3.4. Sample size determination and sampling technique

The sample size required was calculated using single proportion sample size estimating formula.

$$n = \frac{\left(Z_{\alpha/2}\right)^2 P(1-P)}{d^2}$$

(Where n = required initial sample size, $Z\ \alpha/2$ = critical value for normal distribution at 95% confidence interval which equals 1.96 (Z value at alpha = 0.05), P = proportion of success; (p=0.5), q = proportion of patients with diabetes not having DTPs (q=0.5), and d = marginal error (5%=0.05): Therefore, substituting all the values in the above given formula, n =384. Considering 10% contingency (for non-response rate), the final sample size of the study be come to be 423 ambulatory patients with type 2 diabetes.

An approximate population of the study (based on appointment follow-up of the diabetes clinic registration) within the data collection period (three months), were 2160 (N), which was an average of 90 patients per day. The data collection period was extended and held for about three months based on their appointment to visit the clinic, which most of patients appointed for 3 to 6 months considering their disease conditions. The predetermined sample of participants per day was calculated by using total sample size (423) divided by the number of days scheduled per three months (24 days) of the study period and obtained about 18 patients. Hence, we decided to be sampled 18 participants per day. This was made for the purpose of participant distribution throughout the year for better representativeness.

A systematic sampling technique was used based on patients' sitting (two wings) for their regular follow-up, whereby participants were recruited until the predetermined sample size was achieved in the consecutive appointment days. The individual study participants were sampled by calculating sample interval using the formula, K=N/n, (where, ***N*** is the average number of patients with diabetes who estimated to visit the diabetes clinic based on their appointment, which was approximately 90 and ***n*** is the predetermined sample size per day, which is 18 and K is an interval in which each participant need to be approached):

$$K^{th}=90/18=5$$

Therefore, every 5th interval of participants was interviewed from the waiting area of the diabetes clinic before they entered to their doctors' room for their follow up. The first participant who took a seat in either of the wings was drawn first for the interview by using lottery method. However, inconsistency might be there due to the variation of the sitting wings and number of participants per day. A purposive sampling technique was also used for the physicians' opinion key informant data. This was included one senior consultant/ endocrinologist, one fellow and six residents, thus a total of 8 physicians were involved.

3.5. Study variables

Dependent variables:

Drug therapy problems (unnecessary drug therapy, need additional drug therapy, ineffective drug therapy, dosage too low, adverse drug reaction, dosage too high and non-adherence)

Independent variables:

Socio-demographic (age, gender, level of education, residence and marital status), social habits (physical activities, smoking and alcohol use), presence of co-morbid conditions and diabetes complications, number of prescribed medications, status of glycemic control and access for Self-monitoring of blood glucose, duration of the diabetes and drug treatment, diabetes related hospitalization, source of medications and traditional medicine use, and availability of medications.

3.6. Data collection instruments and procedures

Socio-demographics and medication adherence

Patients' primary and secondary data were collected using structured data collection tools which include questionnaire and data abstraction format, respectively. This was complemented by self-administered key informant questionnaire. The primary data, such as patients' socio-demographics, clinical data (including noticed drug adverse events), medication adherence and reasons for poor adherence were collected by using interviewer administered questionnaire. Modified Morisky's Adherence Scale (MMAS-8) (53) was used to measure patients' adherence to their medication. MMAS-8 is an 8-item self-report measure of adherence. Items 1 through 7 have response choices "yes" or "no" whereas item 8 has a 5-point likert response choices. Each 'no' response is rated as '1' and each 'yes' is rated as '0' except for item 5(reversed), in which each response 'yes' is rated as '1' and 'no' is rated as '0'. Item 8

concerning the difficulty to remember taking medications is scored "Never/Rarely = 0, Once in a while = 1, sometimes = 2, usually = 3 and all the time = 4. The higher scores the higher adherence. The total scores range from 0 to 8 and grouped into three levels: high adherence (score = 8), medium adherence (score of 6 to < 8), and low adherence, score< 6 (annex III).

Data collection procedure

A total of 423 patients with diabetes who have been followed up the diabetes clinic of TASH for at least 1 year were invited to participate in the study. For the purpose of this study, the questionnaire was translated into an official Ethiopian language, Amharic (Annex III). The translation process was followed a stepwise process. Before using the Amharic version, back translation to the original language (English) was made to check the consistency. Patients were interviewed face to face to be filled out their socio-demographic and relevant clinical profiles and completed the MMAS-8. Interviewers were approached the individual participants by asking them the duration of antidiabetic drug therapy and follow up, to make sure an individual was on antidiabetic drug therapy for at least 1 year and had regular follow up for a minimum of 1 year at this diabetes clinic. Then, a full explanation on the purpose of the study was provided for each participant, after which they asked their consent. The interview was held in the waiting area of the diabetes clinic before they entered into the physician's room for regular follow up.

Medical Chart Review

The patients' secondary data was collected via medical chart review using a long-established by Ethiopian Hospital Reform implementation Guidelines (EHRIG), Ethiopia Ministry of Health (MOH) and Pharmaceuticals Fund and Supply Agency (PFSA) data abstraction format(54, 55) [Annex III] which were endorsed by experts from the diabetes center and clinical pharmacists. After the interview was completed, the patients' medical chart were reviewed retrospectively starting one year back (01 July, 2016) up to the end of data collection period (30 June, 2017). Patients' medical chart was reviewed on a daily basis following the patient interview. The data that were collected from patients' charts included: medical conditions, prescribed medications with their indication, safety profile, drug duplication, dosage regimen , past medication and medical history, and pertinent laboratory values, like Fasting Blood Glucose (FBG), lipid profiles, blood pressure (BP) values, estimated glomerular filtration rate (eGFR). Two pharmacists (one as supervisor) and two nurses were

recurited to review patients' medical chart and patient intrview, respectively. Inorder to minimize bias, data collectors were recurited from othre centers of the TASH other than diabetes clinic.

Classification and identification of drug therapy problems

For every study participant, who was interviewed, a comprehensive medication chart review was conducted. To examine the magnitude of DTPs in patients with diabetes, these problems were broadly classified in to seven distinct groups based on Cipolle et al.(9) classification system. This classification system is widely accepted patient centered text book, which standardized guideline for clinicians while practicing pharmaceutical care service and authorized by EHRIG and PFSA to be implemented the provision of pharmaceutical care service in Ethiopian hospitals (54, 55). These DTPs were identified with respect to the participant's age, comorbid conditions and diabetes complications, glycemic control, drug safety profile and the proper drug selection, dosage titration, indication for therapy, and untreated indication. Adverse drug reactions were identified by considering patients' data for any possible adverse event related to medications.

Patients' clinical characteristics and organ functions were also taken into account when deciding about the appropriateness of drug therapy. Renal function was assessed by calculating eGFR using the Chronic Kidney Disease Epidemiology collaboration equations(56). Total number of medications per patient per day also calculated from the medical record, only the patients' ongoing medications were involved.

A single of most recent HbA1c measurement value of patients were also recorded. In addition, for those who had no recorded HbA_{1c}, an average of FBG values of the last 3 consecutive follow up measures was taken to estimate the glycemic control and to see drug regimen. According to IDF and American Diabetes Association-European Association for the Study of Diabetes (ADA-EASD) guidelines(57, 58), an average FBG level of above 130 mg/dl for patients between 18 and 60 years old with no comorbid and values above 150 mg/dl for those above 60 years of age and patients with multiple comorbid, were taken as indicator of poor glycemic control.

The existence of DTPs was recognized by experts from the diabetes center and clinical pharmacists who had longe experience in management of patients with diabetes and provision of pharmaceutical care practice, respectively. Thus, the identification was performed based on each clinical condition of the individual patients using international guidelines for clinical practice such as ADA-EASD and IDF as most physicians in the clinic were using these guidelines(57, 58). Deviations that were based on the patient's individual treatment goal and risk factors were not considered to be DTPs. Thus, while identifying DTPs not solely sticky to the guideline, glycemic target that confirmed with the recent physicians' assessment for participants' glycemic control status was also considered.

Up on completion of the DTP identification, a self-administered key informant questionnaire was given to the physicians. Thus, the data obtained from physicians included: (1) the presence and implementation of guideline and possible factors for DTPs (i) Patient related factors like patient preference, adherence issue, affordability to pay for medications and laboratory services. (ii) Drug related factors like safety profile, adequate and continuous availability of medications with their alternative/options and laboratory service and local cost of the medications. (iii) Health facility/administrative related factors like presence of institutional clinical guidelines and protocols, clinic set up (accessibility and expansion of services like laboratory service). (2) Barriers that can hinder the pharmacological management services of patients with diabetes.

While identifying DTPs, those mentioned factors were not considered, since the intention of the current study was aimed to determine the magnitude and the possible factors for DTPs in patients with diabetes at the clinic. However, concerning pertinent DTPs were discussed with some residents (physicians) as well as obtained their suggestions. For ethical purpose, recommendation was proposed for some DTPs. The recommendation was not documented whether applied or not.

3.7. Data quality management

Pre-test was performed on 5% of the sample at the diabetes clinic of TASH (as information contamination between ambulatory patients with diabetes was found to be minimal) for completeness of variables one week before the actual data collection started. Based on the results obtained from pre-test, amendment was made on the assessment tools and way of

assessment. Training was given for one day to the data collectors. Orientation was also given by the principal investigator (PI) and the supervisor as needed. The principal investigator and the supervisor were closely supervising the data collection on a daily bases. Besides, the PI wisely entered the data into EpiData Entry Client and carefully cleaned the data before starting analysis. Over all, data analysis was performed under the supervision of biostatistician.

3.8. Data entry, analysis and presentation

Variables were coded, and database was set and entered using EpiData Manager Version 4.0.2.00, EpiData Entry Client, respectively(59). Then, data were cleaned and exported in to SPSS version 22.0 for analysis. Descriptive statistics included mean and standard deviation for continuous variables and frequency and percentage for categorical data were used to summarize socio-demographic and relevant clinical characteristics of the study participants.

Multi-collinearity among variables was checked by using linear regression (variance inflation factor) for continuous variables and bivariate correlation (Pearson correlation) for categorical variables. All of the variables were not strongly correlated, indicating the assumption of multi-collinearity was no longer violated. Bivariate and multivariate logistic regression analysis was performed to investigate associations and factors associated with the occurrence of DTPs, respectively. After checking the absence of collinearity among variables, variables in bivariate analysis with *p*-value ≤ 0.20 were further analyzed in multivariate logistic regression to control the effect of confounders (60, 61). Statistical significance was considered at p value ≤ 0.05.

The final results for the factors associated with DTPs were presented using Odds Ratios (ORs) with its 95% confidence intervals (CIs) in correspondences to the p value of the multivariate logistic regression analysis set by ≤ 0.05. On top of performing an association for each type of DTPs and status of glycemic control, column based cross-tabulation was also made to determine the association between DTPs and glycemic control and presented with sensitivity (true positive) and specificity (true negative). From this analysis, sensitivity measured how the presences of DTP negatively affect in achieving the desired glycemic goal accurately and the specificity also tell us the correct test for identification of DTPs in achieving glycemic target in the absence of DTPs. The higher percentage of true positive and true negative compared to the false positive and false negative, respectively, the more accurate the test.

Flow chart of participants involved for analysis

During the three months' study period, the diabetes clinic was served for about 2160 outpatients who were objectively diagnosed with type 2 diabetes. We approached for 423 participants, and 357 (with 84.4% response rate) of them were included in the final analysis. Sixty six (66) participants were excluded from the final analysis. Of whom, 61 participants were found to be diagnosed with type 2 diabetes, 4 participants were because of incomplete/ inaccessible medical chart and 1 was not on antidiabetic medication(**Fig 1**).

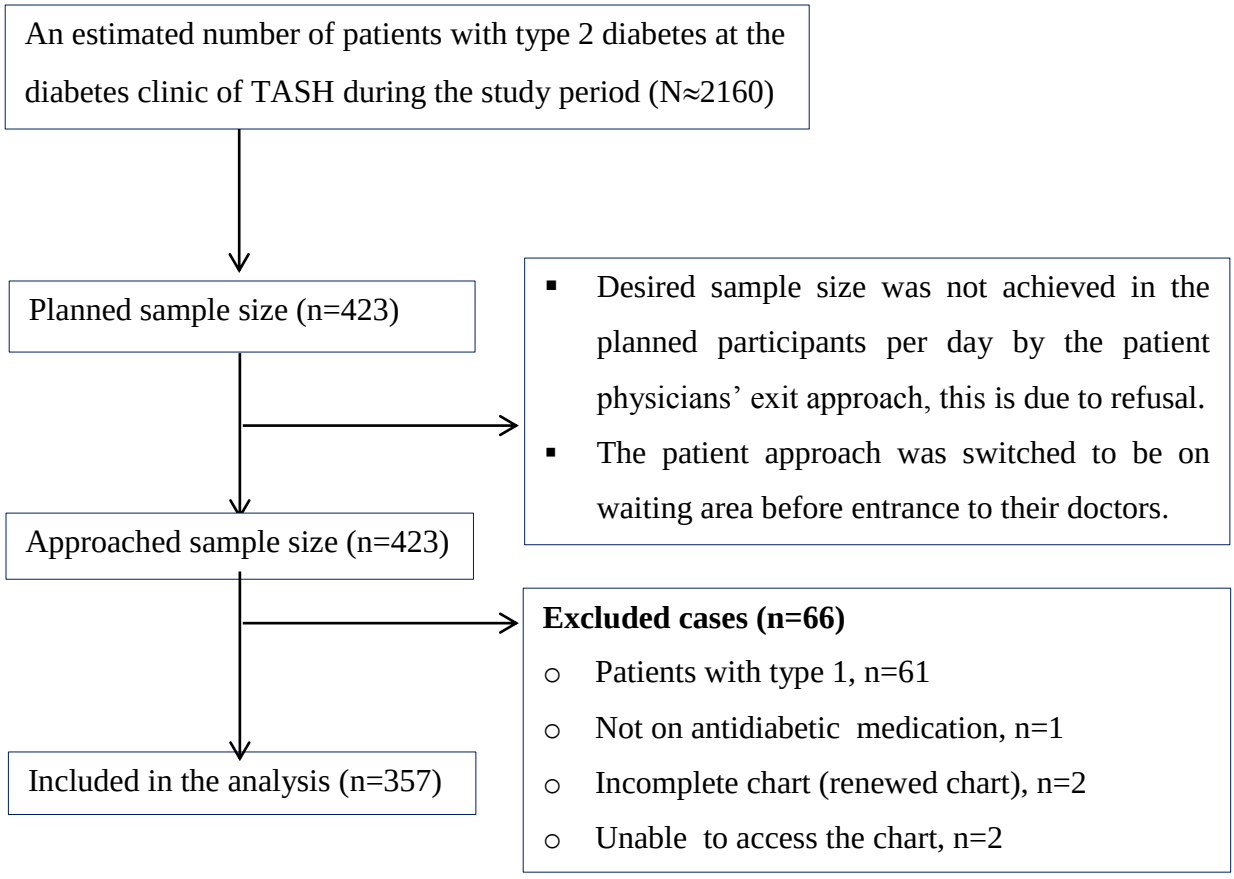

Figure 1: Flow chart of participants' sample size involved in the analysis

3.9. Ethical considerations

For ethical clearance prior to data collection, the study proposal approval was obtained from the Ethical Review Board of School of Pharmacy as well as subsequent permission was obtained from the head of the endocrine and metabolism unit of TASH. During data collection, name of the participants were not included and record card numbers was used. Data analysis was performed using a code number that have been given to each participant's data collection tool. Confidentiality and privacy of all information accessed from the patient's medical record was kept and restricted from any disclosure other than allowed to access them. The right of participants to withdraw from the interview at any time or not to participate in the study was respected. Before conducting the interview, purpose of the study was explained for each participant. After full understanding, consent (Annex II) was obtained from each participant.

3.10. Operational definition of terms that were used in this study

Adverse Drug Event (ADE): Any untoward occurrence that may present during treatment temporally associated with the use of pharmaceutical product but that does not necessarily have a causal relation to the treatment(62).

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(62).

Drug Therapy Problem (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(8, 9). (Further breakdown of the categories and their details, see at annex II).

Non-Adherence: is the extent of deviation of drug taking behaviour of a patient from the agreed recommendations by health care provider which was measured with Morisky's 8- item scale in which when the MMAS-8 score <6, he/she is considered as non-adherent

Good glycemic control: an individual who achieve the target level of FBG 70-130mg/dl(57).

Poor glycemic control: an individual who failed to achieve glycemic goal, out of the normal range FBG 70-130mg/dl(57).

Younger adult age group: Patients with the age of 20 to 40 years

Middle adult age group: Patients with the age of 41 to 60 years

Elderly age group: Patients with the age >60 years, this is WHO age classification (63).

Employed: governmental, private (non/profitable, self-employed, laborers and farmer)

No formal education- a person not certified with any grade level of education.

Alcohol use- drinks any alcoholic beverage regularly for more than 1 and 2 units (1unit = 300ml of 4-5% of alcoholic concentration) of drink per day for female and male, respectively (57, 64).

Physical activity: doing exercise for at least 30 minutes per day for 5 days per week (57)

Unemployed: participants who had no their own known income.

Sensitivity: Participants who presented with DTP and poor glycemic control

Specificity: Participants who presented without DTP and good glycemic control

4. Results

4.1. Socio-demographic characteristics

In this study, a total of 357 study participants were included. More than half, 189(52.9%) of the participants were females. The mean (±SD) age of the study participants was 56.1 ± 11.6 years and more than half, 188(52.7%) of them were in the middle age (41-60 years). Majority, 308(86.2%) of the participants were ever married. Most, 304(85.2%) of the study participants resided in Addis Ababa. Nearly two-fifth (39.5% of the participants were at least College/University level of education holders and 201(56.3%) of the participants were employed. Only 2(0.6%) and 40(11.2%) of the participants were current smokers and regular alcohol user, respectively. However, more than 70% of the participants have been conveyed as they are adherent to regular physical activity (Table 1)**.**

Table 1: Socio-demographic characteristics of ambulatory patients with type 2 diabetes on follow up at TASH, Addis Ababa, Ethiopia, 2017

Variables	Categories	Study participants (N=357)	
		Frequency	Percentage
Sex	Male	168	47.1
	Female	189	52.9
Age (years)	Mean ± SD		56.1±11.6
	20-40	22	6.2
	41-60	188	52.7
	>60	147	41.1
Marital status	Single	13	3.6
	Married	308	86.2
	Divorced	20	5.6
	Widowed	16	4.5
Religious	Orthodox	288	80.7
	Muslim	36	10.1
	Protestant	27	7.6
	Others*	6	9.8
Place of residence	Addis Ababa	304	85.2
	Out of Addis Ababa	53	14.8
Educational status	No formal education	50	14.0
	Primary(1-8)	63	17.6
	Secondary(9-12)	103	28.9
	College/University	141	39.5
Employment status	Employed	201	56.3
	Unemployed	156	43.7
Smoking status	Current smoker	2	0.6
Alcohol use	Regular user	40	11.2
Physical activity	Regular activity	252	70.6

Others*: Catholic and Seventh day church followers. SD: standard deviation. Percentages are calculated per column.

4.2. Clinical characteristics

The clinical characteristics of patients with diabetes are described in Table 2.The mean duration of the diabetes disease since diagnosis was 11.64 ± 6.95 years. Weight control is also an important non-pharmacological therapy in reducing risks for patients with diabetes. Their most recent calculated mean (±SD) BMI for 71 participants was 27.15±4.46 kg/m^2. Of these, majority (76%) of the obese (≥30kg/m^2) participants were seen in female gender. Hospitalization events related to diabetes, 82(23.0%) at least once within the last year were also reported. The events were due to acute diabetes complications, thus hyperglycemic (18%) and hypoglycemic episodes (5%). The overall mean (±SD) average value of FBG for the last three consecutive visits was 172.60±44.0. Only 62(17.4%) of the participants were meeting the intended glycemic target (FBG 70-130mg/dL). Out of those, 2(0.6%) of participants were recorded below 70mg/dL.

Of the total study participants, 278(77.9%) had comorbid conditions with a mean (±SD) of 1.66±0.66 comorbidities per patient. The most common comorbid diseases was hypertension, 188(52.7%), followed by dyslipidemia 171(47.9%) and ischemic heart disease 37(10.4%). Moreover, 115(32.2%) participants had developed chronic diabetes complications. The most commonly encountered diabetes complication was diabetic neuropathy 87(24.4%), followed by diabetic retinopathy 25(7.0%) and diabetic nephropathy 18(5.0%).

Table 2: Clinical characteristics of ambulatory patients with type 2 diabetes on follow up at TASH, Addis Ababa, Ethiopia, 2017

Variables	Categories	Study participants (N=357)	
		Frequency	Percentage
Duration of diabetes(years)	Mean ± SD		11.64±6.95
	1-5	67	18.8
	5-10	105	18.4
	11-15	95	26.6
	>15	90	25.2
BMI(kg/m^2), (n=71)	Mean±SD		27.15±4.46
Hospitalization events within the last year (n,%, yes)		82	23.0
Accesses for SMBG(n,% yes)	Regular use	274	76.8
Average FBG(mg/dL)	Mean ± SD		172.60±44.
	<70	2	0.6
	70-130	62	17.4
	>130	293	82.1
Presence of comorbid conditions (n,%, yes)		278	77.9
	Hypertension	188	52.7
	Dyslipidemia	171	47.9
	IHD	37	10.4
	Others*	50	14.0
Number of comorbidities per patient	Mean± SD		1.66± 0.66
	1-2	252	70.6
	≥3	26	7.3
Presence of diabetes complications(n,%, yes)		115	32.2
	Neuropathy	87	24.4
	Retinopathy	25	7.0
	Nephropathy	18	5.0
Number of complications per patient	Mean ± SD		1.22±0.53
	1-2	108	30.3
	≥3	5	1.4

Others*: Asthma and Thyroid disorders. FBG: Fasting Blood Glucose, IHD: Ischemic heart disease, SMBG: Self-Monitoring of Blood Glucose.

4.3. Pattern of prescribed medications in patients with type 2 diabetes

In our study, the participants had on a mean (±SD) of 4.18±1.8 current medications in use. Patients with type 2 diabetes who were on OGLD alone 167(46.8%), followed by OGLD plus insulin 101(30.8%) and insulin alone 80(22.4%). In addition, antihypertensives, 191(45.7%), statins, 196(46.9%), and aspirin, 166(39.7%) were most frequently prescribed drugs (Table 3).

Table 3: Prescribed medications among ambulatory patients with type 2 diabetes on follow up at TASH, Addis Ababa, Ethiopia, 2017

Treatment Categories		Study participants (N=357)	
		Frequency	Percentage
Antidiabetic treatment regimen:	OGLD alone	167	46.8
	OGLD + Insulin	110	30.8
	Insulin alone	80	22.4
Specific antidiabetic medications	Metformin	46	12.9
	Glibenclamide	11	3.1
	Metformin + Glibenclamide	101	30.8
	Metformin +Insulin	110	28.4
	Metformin + Glimepiride	9	2.4
Other medications			
	ACEIs/ARBs	166	39.7
	Calcium channel blockers	71	17.0
	Beta blockers	44	10.5
	Diuretics	63	15.1
	Antiplatelets(Aspirin)	166	39.7
	Lipid lowering agents(Statins)	196	46.9
	Antiasthmatics	9	2.2
	Others*	113	26.1
Number of medication per patient	Mean ± SD		4.18±1.8
	<5	201	48.2
	≥5	156	34.0
Source of medication (n,%, for free)	For free	220	61.6
Traditional medicine Use (n,%, yes)	Occasional	11	3.1

*Proton pump inhibitors (omeprazole, pantoprazole), amitriptyline, carbamazepine, gabapentin, tramadol and proplythiouracil. ACEIs: Angiotension Converting Enzyme Inhibitors (enalapril and lisnopril), ARBs: Angiotension II receptor blockers (losartan), Calcium channel blockers (Nifedipin and amlodipine), Beta blockers (propranolol, atenolol and metoprolol), Diuretics (hydrochlorothiazide and furosemide). SD: standard deviation, OGLD: Oral Glucose Lowering Drugs

4.4. Experienced drug therapy problems and causes

A total of 193 DTPs were identified with a mean (±SD) of 1.2±0.61 DTPs per patient. One or more DTP were identified in 164(45.9%) of the study participants. The most commonly encountered type of DTP was ineffective drug therapy 54 (26.1%), followed by need additional drug therapy 52 (25.1%) and dosage too low 44(22.7%) [Table 4].

Table 4: Drug therapy problems and causes among ambulatory patients with type 2 diabetes on follow up at TASH, Addis Ababa, Ethiopia, 2017 (n=193)

Types of drug therapy problems	Causes	Study participants (N=357)	
		Frequency	Percentage
Ineffective drug therapy		54	26.1
	Inappropriate drug selection	54	26.1
Need additional drug therapy		52	25.1
	Synergistic drug therapy	30	14.5
	Prophylaxis drug therapy	16	7.7
	Untreated medical condition	6	2.9
Dosage too low		47	22.7
	Dose too low(sub-therapeutic dose)	47	22.7
Unnecessary drug therapy		20	9.7
	Duplication drug therapy	20	9.7
Adverse drug reaction		16	5.8
	Undesirable drug effect	12	5.8
	Unsafe for the patient/contraindication	4	1.9
Dosage too high		4	1.9
	Dose too high (Over therapeutic dose)	4	1.9
Total number of participants with at least one DTP		164	45.9
Total number of identified DTPs			193
Average number of DTPs per patient			1.2±0.61

Percentages are calculated per row, which was per 193 problems. DTPs: drug therapy problems.

According to the Cipolle's DTP classification system, medication non-adherence was also categorized as 7th type of DTPs. However, for better emphasize it depicted separately in **Fig. 5.**

4.4.1. Number of drug therapy problems among the study participants

Although 45.9% of the study participants had one or more DTPs, majority (80%) of them had a single DTP and only 4% of them had more than two DTPs per patient were identified (**Fig 2**).

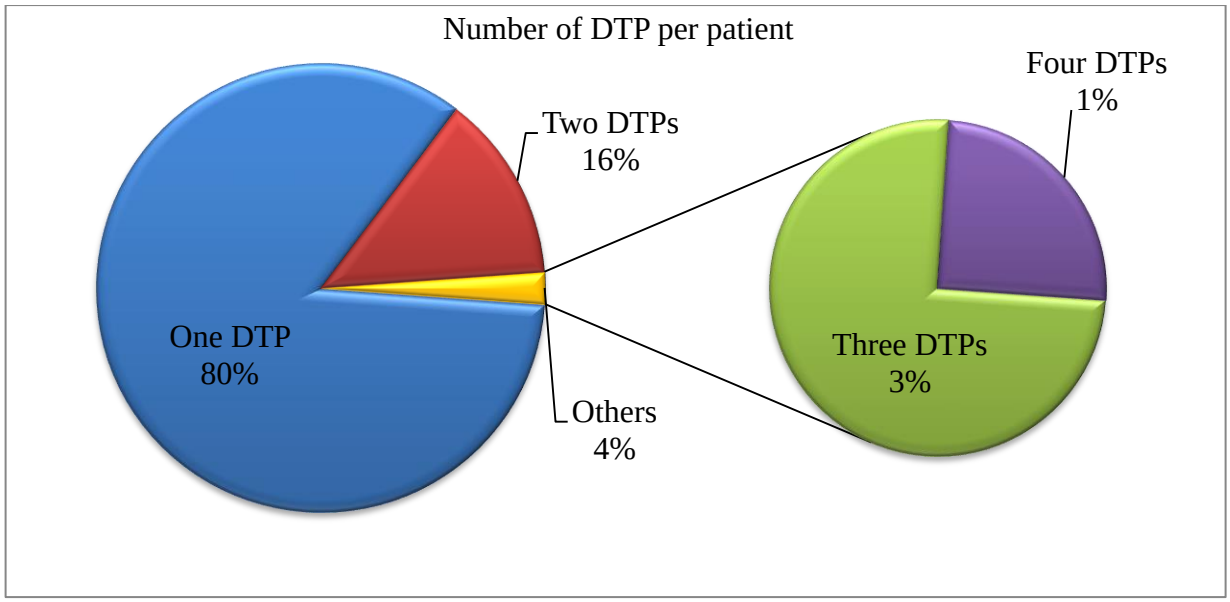

Figure 2: Number of drug therapy problems among ambulatory patients with type 2 diabetes on follow up at TASH, Addis Ababa, Ethiopia, 2017

DTP: drug therapy problems

4.4.2. Medications involved in experiencing drug therapy problems

The most commonly involved medication in experiencing DTPs was metformin plus insulin 56(29.0), followed by metformin plus glibenclamide 38(19.7%) and insulin 32(16.6%). In addition, lipid lowering agents 29(15.0%) and aspirin 23(12.0%), were also attributed in experiencing drug therapy problems (**Fig 3**).

Need additional drug therapy category of DTP was mainly (39 cases) encountered in those patients who were on oral glucose lowering drug (OGLD) alone regimen. Participants (21 and 20 cases) who were on combination of oral and insulin GLDs were also susceptible for ineffective drug therapy and sub-optimal dose, respectively.

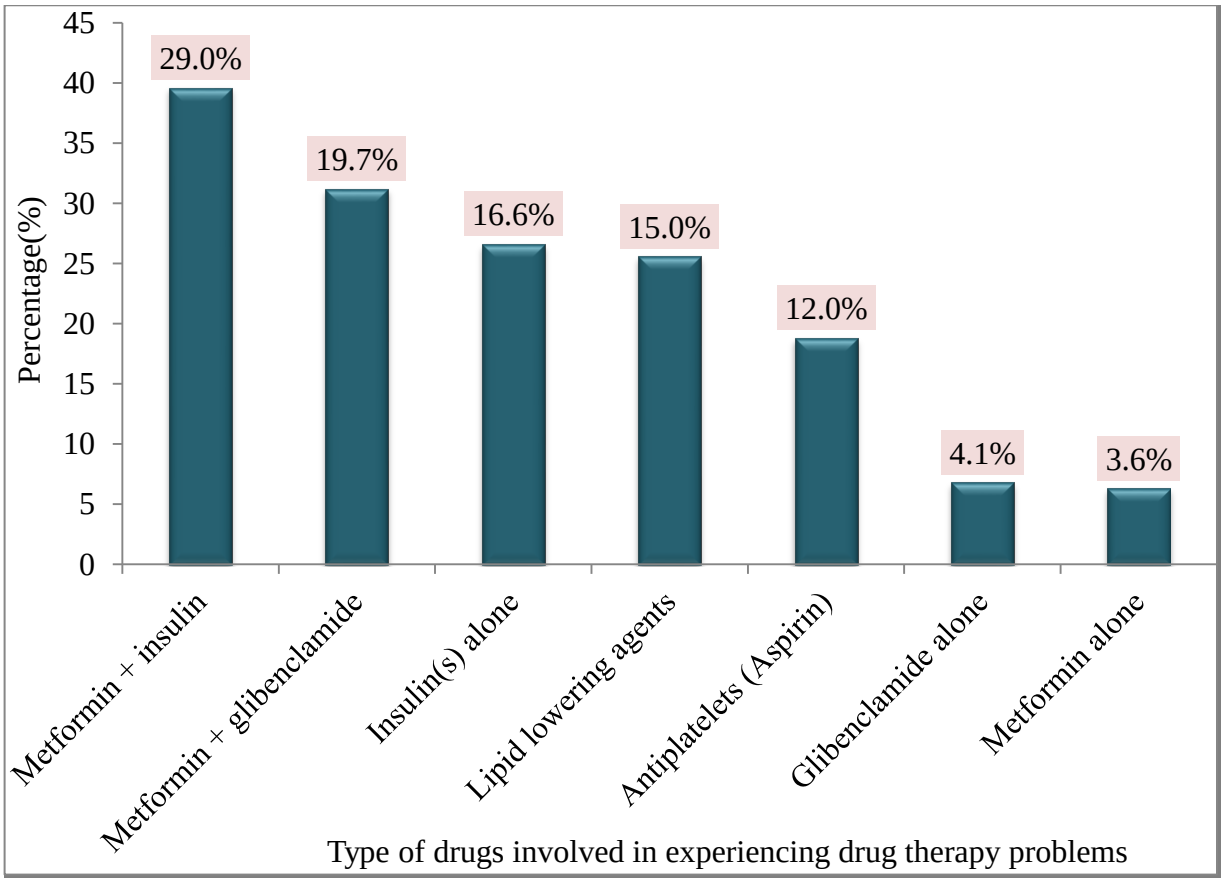

Figure 3: Medications involved in the occurrence of drug therapy problems among ambulatory patients with type 2 diabetes on follow up at TASH, Addis Ababa, Ethiopia, 2017

4.4.3. Identified drug therapy problems in patients with type 2 diabetes

Dosage too low drug therapy problem was commonly observed in patients with type 2 diabetes. Twenty seven cases were on low dose of single oral glycemic lowering agent for repeated follow-up who need to titrate up to the maximum recommended dose of the drug until the desired goal is achieved.

In the case of ineffective drug therapy problem, the choice of drug product was inconsistent with the evidence based guideline recommendations(57, 58). For example, 8 cases were taking glibenclamide with no clear contraindication or intolerance of metformin. Similarly, 7 cases were started glibenclamide (20mg/day) and then added metformin (500mg/day) as add on therapy. Likewise, 40 and 28 cases were on low dose of metformin (500mg/day) plus insulin and insulin alone with no clear contraindication for oral antidiabetic drugs, respectively.

On the other hand, there were also patients on a single/double oral antidiabetic therapy who needed to be added other oral agent or to initiate insulin drug therapy to achieve the desired goals of therapy. Four (4) and 27 cases were taking only a maximum dose of single OGLD and maximum dose of two oral glucose lowering agents, respectively.

In patients with diabetes other than antidiabetic drugs were also assessed for DTPs. Those drugs mainly included lipid lowering agents (statins) and antiplatelet (aspirin). Fourteen (14) cases with the comorbid hypertension and/ or ischemic heart disease were on neither any of antiplatelets nor any of lipid lowering agents. Majority of those problems were involved in patients at high risk of CVDs or established CVDs who required aspirin or statins as preventive medications, specifically to prevent myocardial infarction and/or stroke in patients with post myocardial infarction, ischemic heart disease or hypertension. Few examples of DTPs identified among these participants are listed in Table 5.

Table 5: Examples of identified drug therapy problems experienced among ambulatory patients with type 2 diabetes on follow up at TASH, Addis Ababa, Ethiopia, 2017

Patient presentation	Prescribed medications	Examples of identified DTPs in patients with type 2 diabetes (comments)
Age=40, Sex= Female Dx: Type 2 DM FBG=137,135,130 SrCr=0.6	NPH 30/14(for a long period of time) Metformin 500mg daily eGFR=132ml/min/1.73m^2	○ Unnecessary Drug therapy(duplication)=NPH versus her recent FBG value ○ Ineffective drug therapy(selection problem)=NPH is punishment therapy ○ Dosage too low(low dose)=Metformin need to titrate first to the maximum of its recommended tolerable dose (maximum of 2gm per day)
Age=62, Sex= Male Dx= Type 2 DM FBG=245,76,99,56 SrCr=1.0	NPH 10 daily Glibenclamide 10 mg bid Metformin 500 mg bid eGFR=70ml/min/1.73m^2	• Unnecessary drug therapy (inappropriate duplication)=Glibenclamide • Dosage too low(dose too low)= need to maximize dose of Metformin first • Adverse drug reaction (unsafe for the patient)=Glibenclamide + NPH, Glibenclamide is high risk of hypoglycemia, especially for this age group. • Ineffective drug therapy (drug selection/inappropriate drug combination) =Glibenclamide + NPH (he was at risk of hypoglycemia, not preferred)
Age=69, Sex= Male Dx: Type 2 DM + HTN Peripheral Neuropathy Hx of Ischemic stroke FBG=118,BP=150/70	Metformin 500mg bid Enalapril 10mg bid Amitriptyline25mg daily Aspirin 81mg daily No recorded SrCr	• Need additional drug therapy(secondary prevention for his CVDs)= Lipid lowering agents (statins, high intensive therapy with atorvastatin or rosuvastatin), since the patient had established CVD(ischemic stroke) and he had also comorbid of HTN, the leading cause for CVDs and age between 40 and 75 years old with type 2 DM are at high risk of CVDs.
Age=47,Sex= Female Dx: type 2 DM FBG=145,131,151 SrCr=1.1	Glibenclamide 5mg bid (before metformin) Metformin 500mg Qd(2nd) eGFR=69ml/min/1.73m^2	○ Ineffective drug therapy(selection problem)=Glibenclamide We have safer drug(Glimepiride instead of glibenclamide) ○ Unnecessary drug therapy(inappropriate duplication)=Glibenclamide ○ Dosage too low(dose too low)=Metformin(as justified above)

(Continue)

Table 5: Examples of identified drug therapy problems experienced among ambulatory patients with type 2 diabetes……*(Continued)*

Age=48,Sex=Female Dx: type 2 DM + IHD + Hyperthyroidism FBG=274,HbA1c=9.6% 289,276: SrCr=0.59 LDL=46,HDL=43, TG=82, TC=100	NPH 62/52 + RI 10/10 Metformin 1gm bid PTU 50 tid Metoprolol 50 Qd Atorvastatin 40 Qd eGFR=126ml/min/1.73m^2	○ Dosage too low(dose too low)= NPH/ RI need to titrate up to monitor her glucose level as she was taking (refilled) same dose of those mentioned medications for the last three consecutive visits ○ Need additional drug therapy (for synergistic effect)= need to add other oral antidiabetic drug as add on therapy
Age=40,Sex=Female Dx: Type 2 DM FBG=137,135,120 SrCr=0.60	NPH 30/14(long period) Metformin 500mg Qd(2nd) eGFR=132ml/min/1.73m^2	▪ Ineffective drug therapy (drug selection problem)=NPH, for longer time Insulin should be used as a punishment therapy for type 2 diabetic patients ▪ Adverse drug reaction (undesired drug effect) = NPH, as she had a multiple history of hypoglycemic episodes (reported and documented in chart). ▪ Unnecessary drug therapy (inappropriate duplication)=NPH ▪ Dosage too low(dose too low)= Metformin , titrate metformin first
Age=78, Sex=Male Dx=Type 2 DM+HTN FBG=49,136,70 SrCr=1.3, BP=150/90 LDL=142,HDL=39, TG=90, TC=190	NPH 76/58 Enalapril 10mg daily Amlodipine 5mg daily Aspirin 81 mg daily eGFR=61ml/min/1.73m^2	○ Dosage too high=NPH, need to adjust the dose(hypoglycemia) ○ Adverse drug reaction(undesirable drug effect)=NPH, hypoglycemia ○ Need additional drug therapy (untreated medical condition)= Lipid lowering agents. Though he is an elder patients (not recommended using statin in this age), his lipid profile revealed elevated /decreased from the normal range.

Dx: Diagnosis, Hx: History, LDL: Low density of lipoprotein, HDL High density of lipoprotein, TG: Triglycerides, TC: Total Cholesterol, LLA: Lipid Lowering Agent, HTN: hypertension, Qd: every day (daily), NPH: Neutral Protamine Hagedorn, RI: Regular Insulin, CVD: Cardiovascular Disease, FBG: Fasting Blood Glucose, SrCr: Serum Creatine. PTU: Propylthiouracil

4.4.4. Reasons for the occurrence of drug therapy problems (physicians' suggestion)

The possible reasons for the occurrence of DTPs (if any) quantitatively obtained from physicians are presented in Table 6. Virtually all (100%) of the physicians suggested that, the possible reason for the occurrence of DTPs (if any) in patients with diabetes could be the availability and local cost issue of alternative medications and inconsistency of using guidelines (as no institutional guideline). The other reasons could be patient related issues; affordability (88%), and adherence issue (75%) and drug related safety profile; side effect (25%) of medications.

Table 6: Reasons for the occurrence of drug therapy problems among ambulatory patients with type 2 diabetes on follow up at TASH, Addis Ababa, Ethiopia, 2017(N=8)

Variables	Categories	n, %	Comments(examples)
Patient related	Adherence	6(75)	Patient preference(E.g; resistant to initiate insulin)
	Affordability	7(88)	Patients cannot afford (E.g; private pharmacies)
Drug related	Side effect	2(25)	Side effect of drugs(E.g; GI intolerance of metformin, or allergic for insulin initiation)
	Availability	8(100)	Medication availability issue(E.g prescribing of glibenclamide instead of other as add on therapy
	Local cost	8(100)	Cost issue (E.g; using of glibenclamide to metformin instead of glimepiride or other OGLDs)
Institution related	Accessibility	8(100)	Inadequate and inconsistency of medication accessibility with the guidelines recommendations
	Guideline	8(100)	No specific institutional guideline in the clinic
	Clinic Setup	6(75)	Limitation lab for monitoring, (no A1c in the clinic) Patient load (number of patient versus physician, may hinder for provision of patient counseling)
Guideline in use	IDF	6(75)	
	ADA-EASD	5(63)	
	ADA	4(50)	
	Mixed	3(38)	

IDF: International Diabetes Federation, ADA-EASD: American Diabetes Association-European Association for the Study of Diabetes. Mixed: including national guideline/protocol and clinical experience.

4.4.5. Factors associated with the occurrence of drug therapy problems

According to the multivariate logistic regression analysis (Table 7), seven variables were significantly associated with the occurrence of DTPs. From the Adjusted odds ratio (AOR) for sex (AOR=2.21, 95% CI:1.32 - 3.72, p=0.003) which indicated that being female genders were more than two times more likely than male genders to develop DTPs. Meanwhile, medication adherence (AOR=4.52, 95% CI: 2.34-8.73, p<0.001) indicated that patients with poor adherence (below 8 summative score) to their medication had a strong positive relation in developing DTPs. In addition there were also an association related to number of comorbidities (AOR=3.18, 95%CI: 1.21-8.38, p=0.019) patients with ≥3 comorbid conditions were 4 times more likely than participants with lesser number of comorbidities in experiencing DTP.

However, number of medications per patient, presence of comorbid conditions, duration of diabetes, age group, level of education, employment status, physical activity, accesses for SMBG and source of medication had no statistically significant association with developing of DTPs. In addition, other variables like smoking, alcohol use, residence, marital status, BMI and use of traditional medicine were not included in this analysis because of fewer respondents which subjected in shifting to one side.

Table 7: Bivariate and multivariate analysis of factors associated with drug therapy problems among patients with type 2 diabetes on follow up at TASH, Addis Ababa, Ethiopia, 2017

Covariates	Categories (n, %)	Drug Therapy Problem		Odds Ratios (95% CI)		P-value
		No (n=193)	Yes(n=164)	Crude	Adjusted	
Age	Mean(±SD)	56.1±11.6		1.12(0.95-1.21)		
	20-60	126(53.2)	111(41.8)	1.00		
	60+	67(55.8)	53(44.2)	1.11(0.79-1.71)		
Sex	Male	104(61.9)	64(38.1)	1.00		
	Female	89(47.1)	100(52.9)	1.77(1.18-2.63)**	2.21(1.32-3.72)	**0.003**
Educational status	No formal education	26(52.0)	24(48.0)	1.20(0.69-2.42)		
	Primary(1-8)	38(60.3)	25(39.7)	0.86(0.51-1.71)		
	Secondary(9-12)	55(53.4)	48(46.6)	1.17(0.75-1.81)		
	College/University	74(52.5)	67(47.5)	1.00		
Employment status	Employed	113(56.2)	88(43.8)	1.00		
	Unemployed	80(51.3)	76(48.7)	1.14(0.77-1.69)		
Physical exercise	No	51(48.6)	54(41.4)	1.36(0.88-2.09)*	1.26(0.74.0-2.17)	0.401
	Yes	142(56.3)	110(43.7)	1.00		
Access for SMBG	No	41(49.4)	42(50.6)	1.07(0.68-1.68)		
	Yes	152(55.5)	122(44.5)	1.00		
Duration of diabetes	1-5	40(59.7)	27(40.3)	1.00		
	6-10	55(52.4)	50(47.6)	1.42(0.80-2.53)		
	>10	98(53.0)	87(47.0)	1.29(0.76-2.19)		

(Continue)

(Continued)

Table 7: Bivariate and multivariate analysis of factors associated with drug therapy problems among ambulatory patients with type 2 diabetes on follow up at TASH, Addis Ababa, Ethiopia, 2017

Covariates	Categories (n, %)	Drug Therapy Problem		Odds Ratios (95% CI)		P-value
		No (n=193)	Yes(n=164)	Crude	Adjusted	
Comorbidities	No	45(57.0)	34(43.0)	1.00		
	Yes	148(53.2)	130(46.8)	1.40(0.91-2.16)*	1.04(0.56*1.91)	0.91
Complication	No	136(56.2)	106(43.8)	1.00		
	Yes	57(49.6)	58(50.4)	1.51(0.98-2.31)		
Number of Comorbidities	1-2	140(55.1)	114(44.9)	1.00		
	≥3	9(36.0)	16(64.0)	2.11(0.92-4.81)**	3.18(1.21-8.38)	**0.019**
Number complication	1-2	57(50.0)	57(50.0)	1.00		
	≥3	3(60.0)	2(40.0)	0.69(0.11-4.28)		
No of medications	<5	114(56.7)	87(43.3)	1.00		
	≥5	79(50.6)	77(49.4)	1.43(0.96-2.13)*	1.19(0.71.0-1.99)	0.521
Adherence status	High(=8)	109(69.4)	48(30.6)	1.00		
	Medium(6-<8)	52(46.8)	59(53.2)	2.74(1.71-4.39)**	3.04(1.66-5.54)	**<0.001**
	Low(<6)	32(36.0)	57(64.0)	3.98(2.39-6.64)**	4.52(2.34-8.73)	**<0.001**

Percentages are calculated per row. Variables in bivariate analysis with p≤0.20 and ≤0.05 indicated by * and **, respectively. Statistically significant in multivariate analysis set at: p≤0.05, set in **bold** typeface. CI: Confidence interval at 95 %, OGLD: Oral Glucose Lowering Drugs.

4.4.6. Association between drug therapy problems and glycemic control

To determine the association between participants who had experienced DTPs and their glycemic control status, an overall of cross tabulation for DTP was performed. The result indicated that, the sensitivity (events predicted to be events) versus specificity (nonevents predicted to be nonevents) were given by 57.8% and 79.6.0%, with the p value <0.001, respectively. From this, sensitivity(true positive) measured how the presence of DTP negatively affect in achieving the desired glycemic goal accurately and the specificity(true negative) also tell us the accuracy of the correlation in achieving glycemic target in the absence of DTPs (Table 8).

Table 8: Association between types of drug therapy problems and glycemic control among ambulatory patients with type 2 diabetes on follow up at TASH, Addis Ababa, Ethiopia, 2017

Types of drug therapy problems (n=193)	Status of glycemic control (n, %)		P value
	Poor	Good	
Unnecessary drug therapy	9(45.0)	11(55.0)	0.021
Needs additional drug therapy	47(90.4)	5(9.6)	0.001
Ineffective drug product	50(92.6)	4(7.4)	<0.001
Dose too low	44(93.6)	3(6.4)	<0.001
Adverse drug reaction	11(68.8)	5(31.2)	0.972
Dose too high	4(100.0)	0(0.0)	0.171

The overall presence of DTP		Status of glycemic control (n, %)		
		Poor	Good	P value
Drug therapy problems	Yes	**141(57.8)[a]**	23(20.4)[c]	<0.001
	No	103(42.2)[b]	**90(79.6)[d]**	

Pearson Chi-Square=43.61 and linear by linear association=43.20 with COR=4.92

aSensitivity (true positive) and **d**specificity (true negative), [b]false positive and [c]false negative

4.5. Medication adherence

According to the Morisky's 8 items assessment scale, the cut off for adherence, high adherent 191(45.7%), medium adherent 127(30.40%), and low adherent 100(23.90%) participants were who scored 8, <8-6 and <6, respectively. Forgetfulness 127(35.6%) of taking their pills was the most prevalent item, followed by difficulty in remembering [sometimes] to take their pills 88(24.6%) and treatment plan inconvenience 87(24.6%) [Table].

Table 9: The 8-items Morisky medication adherence scale among ambulatory patients with type 2 diabetes on follow up at TASH, Addis Ababa, Ethiopia, 2017 (N=357)

Items		Number of participants who responded	
		Yes =0(n, %)	No=1(n, %)
1. Do you sometimes forget to take your medicines?		127(35.6)	230(64.4)
2. Did you missing your medications other than forgetting?		50(14.0)	307(86.0)
3. Did you stop taking your medicine when you felt worse?		35(9.8)	322(90.2)
4. Did you forget your medicine when travel or leave home?		27(7.6)	330(92.4)
5. Did you take all your medicine yesterday? [Reverted].		341(95.5)	16(4.5)
6. When you feel well, did you stop taking your medicine?		26(7.3)	331(92.7)
7. Do you ever feel hassled taking medicine inconvenience?		87(24.4)	270(75.6)
8. Did you get difficulty remembering to take your medicine?			
	Never/Rarely	217(60.8)	140(39.2)
	Once in a while	46(12.9)	311(87.1)
	Sometimes	88(24.6)	269(75.4)
	Usually	5(1.4)	352(98.6)
	All the time	1(0.3)	356(99.7)

Participants who answered " **Yes** " to:		Distribution of Scores	Total score, n (%)
0 items	High	8	157(44.0)
1 item	Medium	7	51(14.28)
2 items	Medium	6	60(16.80)
3 items	Low	5	54(12.90)
4 items	Low	4	18(5.04)
5 items	Low	3	14(3.92)
6 items	Low	2	2(0.560)
7 items	Low	1	1(0.28)
8 items	Low	0	0(0.00)

Cut off point	Score, n (%)	Category
8	157(44.00)	High
(6-<8)	111(31.10)	Medium
<6	89(24.90)	Low

4.5.1. Medication adherence scale category by type of diabetes

This study was intended to measure the level of non-adherence; thus, medication adherence was grouped as non-adherent (low adherence) and adherent (medium+high) level. Therefore, according to the MMAS-8 with the cut-off point (summated scores of <6) of patients with diabetes were reported as adherent 268(75.1%) and non-adherent 89(24.9%) to their medication. The mean (±SD) score of the MMAS-8 in this study was also 6.13±1.52 **(Fig 4)**.

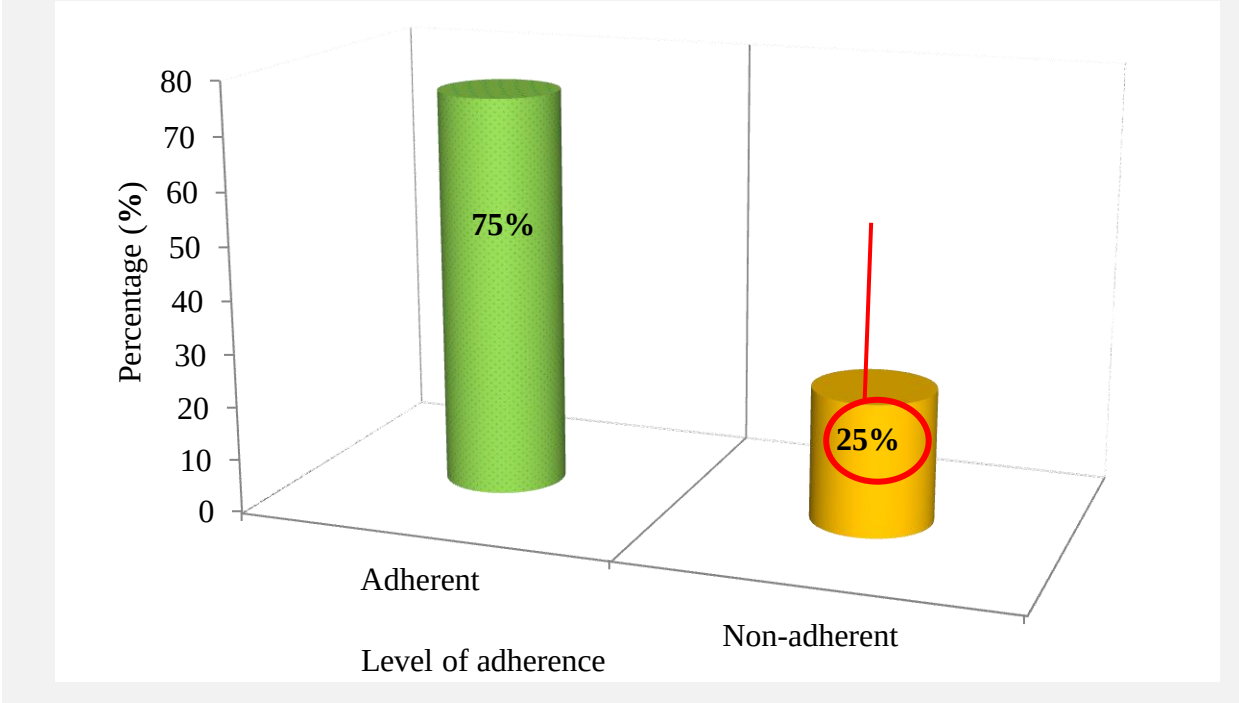

Figure 4: Proportion of medication adherence among ambulatory patients with type 2 diabetes on follow up at TASH, Addis Ababa, Ethiopia, 2017(N=357)

4.5.2. Reasons for poor medication adherence

The most common reason for poor adherence reported by participants was simply forgetting (unintentionally) 131(36.7%) taking of their medicine, followed by inadequate availability of medications 102(28.6%) and affordability problem due to cost of medication too expensive 45(12.6%) [Table10].

Table 10: Possible reasons for poor adherence among ambulatory patients with type 2 diabetes on follow up at TASH, Addis Ababa, Ethiopia, 2017

	Study participants (N=357)	
Reasons	Frequency	Percentage
Forgetting to take their medicine	131	36.7
Inadequate availability of medication	102	28.6
Cost of medication too expensive	45	12.6
Fear of medication adverse events	35	9.8
Difficulty of administration/time schedule	28	7.8
Inadequate instruction/counseling/education	26	7.3
When feeling better or worsen	23	6.4
Busy due to workload	13	3.6
During fasting period	21	5.9
Regimen Complexity	21	3.6
Patient prefers not to take	15	2.8
Disbelief in drug effectiveness	13	3.6

Percentages are calculated per column.

4.5.3. Factors associated with the occurrence of poor medication adherence

As illustrated in Table 11, the only associated factors statistically significant with poor medication adherence in the multivariable analysis were gender, level of education and diabetes complication. From the AOR, being female gender (AOR=1.71, 95%CI: 1.01-2.76, p=0.047) was positively associated with non-adherence to their antidiabetic medication. Surprisingly, gender difference did not reach statistically significant level in the bivariate analysis, thus, the p value was >0.05. In addition participants who had completed primary, secondary and college /university grade level of education (AOR=0.38, 95%CI: 0.21-0.92, p=0.043, AOR=0.42, 95%CI: 0.19-0.90, p=0.023), and AOR=0.39, 95%CI: 0.29-0.95, p=0.041), respectively were a protective factor against the occurrence of non-adherence to their medication. The presence of diabetes complication (AOR=2.02, 95%CI: 1.01-3.22, p=0.008) also has a positive effect for the occurrence of poor medication adherence.

Table 11: Bivariate and multivariate analysis of factors associated with medication non-adherence among ambulatory patients with type 2 diabetes on follow up at TASH, Addis Ababa, Ethiopia, 2017

Covariates	Categories	Non-adherence		Odds Ratio (95% CI)		P-value
		No (n=318)	Yes (n=100)	Crude	Adjusted	
Sex	Male	134(79.8)	34(20.2)	1.00		
	Female	134(70.9)	55(29.1)	1.71(0.97-2.41)	1.57(1.01-2.76)	**0.047**
Age	20-60	184(77.6)	53(22.4)	1.00		
	60+	84(70.0)	36(30.0)	1.61(1.04-2.41)*	1.22(0.70-2.04)	0.210
Education	No formal education	30(60.0.)	20(40.0)	1.00		
	Primary (grade 1-8)	49(77.8)	14(22.2)	0.43(0.20-0.94)*	0.38(0.21-0.92)	**0.043**
	Secondary (grade 9-12)	83(80.6)	20(19.4)	0.40(0.17-0.78)*	0.42(0.19-0.90)	**0.023**
	College/University	106(75.2)	35(24.8)	0.39(0.19-0.80)*	0.39(0.29-0.95)	**0.041**
Employment	Employed	156(77.6)	45(22.4)	1.00		
	Unemployed	112(71.8)	44(28.2)	0.69(0.43-1.03)	0.82(0.61-1.80)	0.610
Complication	No	191(78.9)	51(21.1)	1.00		
	Yes	77(67.0)	38(33.0)	1.07(0.21-0.88)*	2.02(1.00-3.22)	**0.008**
Source of drug	Free	159 (72.3)	61(27.7)	1.00		
	Paid	109(79.6)	28(20.4)	0.59(0.39-1.01)	1.34(0.81-2.19)	0.11
ADR	No	259(76.0)	82(24.0)	1.00		
	Yes	9(56.3)	7(43.7)	2.82(0.90-8.03)*	3.51(0.91-7.21)	0.141

Percentages are calculated per row. *****Variables in bivariate analysis ≤0.05, statistically significant set at: p≤0.05. ADRs: Adverse Drug Reaction.

5. Discussion

The current study was aimed to determine the magnitude and factors associated with developing DTPs among ambulatory patients with diabetes. Cipolle's et al.(9) DTPs classification system was used. Drug therapy problems (DTPs) were identified based on IDF and ADA-EASD guideline recommendations (57, 58). Findings of this study revealed that more than two-fifth (45.9%) of the study participants had at least one DTP per patient. The main types of DTPs identified were related to use of ineffective drug therapy, need additional drug therapy and dosage too low,. These problems were mainly caused due to inappropriate drug selection, need of additional drug therapy and use of sub-therapeutic dose for prevention and/or for synergistic effect. Nearly one-fourth (24.9%) of the study participants were non-adherent to their medications. Below one-fifth (17.4%) of participants were also to be found in the intended glycemic target (70-130mg/dL).

Results of the present study was slightly more prevalent than findings in Sri Lanka(22, 32). This slight variation could be due to difference in study design (prospective) and DTPs classification system (PCNE) used. In contrast, findings of this study was considerably lower than that reported by two studies in Malaysia, in which more than 90% of patients had at least one DTP (21, 23). This discrepancy might be explained by variation in the study participants; whereby this study included both patients with type 2 diabetes regardless of their comorbid conditions; while those two previous studies included only type 2 diabetes with hypertension or dyslipidemia. Thus, the later studies' participants with type 2 diabetes and hypertension and/or dyslipidemia could be more likelihood in experiencing DTPs.

Compared to a multi-central study conducted in Jordan (34) which revealed 81.2%, the current finding was also lower. This variation could be due to the difference in setting in which the study was conducted in five different teaching hospitals and sample size (1494) recruited. Similarly, this finding was also much lower than the two different studies in Nigeria (25, 39). This difference might be due to difference in study setting (inpatient versus outpatient). Thus, the odds of experiencing DTPs was more in inpatients with type 2 diabetes as data collectors had the opportunity of close monitoring for each problems experienced by their patient. Likewise, hospitalized patients had also the chance to use different or multiple drug therapies

for their multiple comorbidities and complications that lead them to be hospitalized (2, 12, 57, 65).

Moreover, in this study the number of DTPs per patient (mean ±SD,1.2±0.61) was lower than many of other previous studies reported from Pakistan(35), Malaysia(21, 23), Denmark(24), Australia(37), Nigeria(25, 39), and Ethiopia-Wolaita Sodo(40), which showed that, the mean rate was more than 2 DTPs per patient. However, this result was slightly higher than a study done by Wong et al.(38) in China, which was 0.9±0.6 DTPs per patient. Such discrepancies might be explained due to dissimilarity in clinic set up and professionals working in the area. In fact, countries and health facilities may use different health care systems.

Taken together, in previously conducted studies both the proportion of participants with DTPs and the average number of DTPs per patient were lower or higher than the findings revealed in this study. These wide discrepancies across studies could be explained in part by variation in participant selection criteria, population diversity, use of different guideline recommendations and variation in study period, study design and setting whereby the study conducted. Methods how DTPs were classified and assessed could also be one aspect need to consider; for example, in this study, when a patient needed to add two different types of medications for different condition, it was still counted as one DTP. In addition, we recorded only as DTP for these participants who needed treatment modification but not did at the most their recent visit. Thus, the overall magnitude of DTPs observed from this study was lower compared to numerous studies' findings. Furthermore, non-adherence in this study was calculated separately as we assessed it from patient interview using different (other than Cipolle DTP assessment tool) validated tool.

The use of ineffective drug therapy (26.1%) was the most common problem of this study. This finding was consistent with two studies in India (30, 33) and one study in China (38), that reported it as the second most commonly experienced type of DTP in patients with diabetes. However; numerically results in this study was higher than other previous findings in the literature (12, 23, 25, 30, 33, 34, 38) and lower than two studies in Sri Lanka(22) and UK and Saudi (26). The most likely explanation is that, this deviation could be due to use of different reference, absence of institutional guideline in our set up, unavailability of alternative drugs and difference in participants' socio-economics, poor capacity to afford better options.

Furthermore, in case of problems related to the use of ineffective drug therapy, the choice of drug product was inconsistent with the guidelines (57, 58). Eight (8) cases were taking glibenclamide from the very beginning with no clear contraindication for metformin. Similarly, 7 cases were started glibenclamide and then added low dose of metformin as add on therapy. Particularly, because of its long half-life and increased risk of hypoglycemia, the most recent IDF guideline (57, 66) does not recommend to use glibenclamide. It is not only prohibitive to use as first line but also as add on therapy next to metformin, thus the guideline recommends to use sulfonylureas (except glibenclamide) as add on therapy if not achieved the intended glycemic target with the maximum tolerable dose of metformin therapy.

Likewise, 40 and 28 cases were found to be on low dose of metformin plus insulin and insulin alone with no clear contraindication for oral antidiabetic agents, respectively. This phenomenon was associated with the absence of institutional guideline in our set up and unavailability of alternative antidiabetic medications greatly attributed for the occurrence of such type of DTPs. Indeed, this could be explained by the reasons suggested from physicians, such as gastric intolerance of patients for metformin, unavailability (100%) of better alternative OGLD in the clinic other than glibenclamide and inability of patients to afford (88%) for better alternatives due to participants' socio-economic problem. In fact, in Africa and many of other middle income nations, patients with diabetes are suffering from unavailability and unaffordability of their drugs resulting to remain the leading barrier in diabetes care (66, 67). Therefore, this pronounced incidence of drug selection problems in our study may highlight a need for the prescribers and responsible body to pay more emphasize in selecting drugs to patients with diabetes.

Need additional drug therapy was the second most prevalent finding in the current study, which accounted for 25.1% of case problems. This finding was in line with one study in Sri Lanka(22) whereas it was more predominant compared to studies reported by other authors' (25, 34, 39). In this study, there were patients on oral antidiabetic therapy who needed other oral agent or insulin to be added to their therapy to achieve the desired goals of therapy. Four (4) and 27 cases were taking only a maximum dose of single oral glycemic lowering agent and maximum dose of two oral glucose lowering agents, respectively. Most likely, this could be explained due to patient resistant (poor adherence) to add other oral glucose lowering agent or to initiate

insulin. In part, this was justified by the prescribers (75%) as a reason. Indicating that, effort is needed to promote patient adherence to their medication by generating their receptiveness in recognizing the benefit of each antidiabetic drug therapy.

Moreover, there were also patients who needed to add medications other than antidiabetic drugs for the prevention and/or reduction of different diabetes complications. Majority of these problems also experienced in patients who required statins and/or aspirin as primary or secondary preventive medications, specifically to prevent myocardial infarction and/or stroke in patients with post myocardial infarction, ischemic heart disease or hypertension. For example, 14 cases with the comorbid hypertension and/ or post ischemic heart disease were on neither any of antiplatelet nor any of lipid lowering agents. In addition, 12 and 8 cases were on statin alone and aspirin alone, respectively. Patients with type 2 diabetes with risk of cardiovascular events were not prescribed antiplatelet and/or lipid lowering agents considered as DTPs(37) and need additional drug therapy as a primary prevention. This indicated that, statins and/or aspirin were underutilized in patients with type 2 diabetes. Certainly, only nearly two- fifth (39.5%) of participants of this study had recorded lipid profile. Thus, need to emphasize periodic monitoring of their lipid in optimizing the utilization of statins and/or and antiplatelets in response to the CVDs risks factors among patients with diabetes, especially in type 2 diabetes.

Dosage too low was another prevalent DTPs 47(22.7%) among participants of this study. This data were closer with the studies conducted in India(30) and US (12), which reported the most commonly encountered type of DTP in patients with diabetes was drug dosing problem, accounted for 25.35% and 27%, respectively. This problem indicate that the dose of the drug where the patient was taking being insufficient to produce the desired glycemic target. Hence, there was a need to titrate/step up the dosage regimen of the medication in response to the recorded glucose level.

Twenty seven (27) cases were on low dose of single oral glucose lowering agent for repeated follow-up versus poor glycemic control who needed to titrate-up to the maximum recommended dose of the drug until the desired goal is achieved (57, 58). In this case, the physician prescribed the drug and appropriately selected that indicated for the medical problem.

However, the drug therapy was not being sufficient for the patient because the dose being taken could not achieve the desired goals of therapy.

In this study, the result for dosage too low was more prevalent compared to other five studies previously conducted (23, 25, 39).This discrepancy might be due to variation in sample size or lack of institutional guideline. This might also be associated with the suggestions explained by prescribers in the clinic given that, escalating the dose of specific drug has a direct effect on increasing its cost, in which patient resist to buy as they cannot afford beyond. Whereas, this finding was less prevalent than one study reported from Sri Lanka (22), which conducted in almost same sample size. This variation could be because of use of different DTPs classification system and study design.

On the other hand, unnecessary drug therapy, adverse drug reaction and dose too high types of DTPs identified in the current study were less prevalent compared to other studies (22, 25, 33, 34, 39). But one from those studies (39) reported less prevalent than the present study for those problems related to use of unnecessary drug therapy. However, the present study was in line with one study in US by Cipolle et al.(12). Apart from that, a study conducted in Pakistan(35) and Malaysia(21); revealed that drug-drug interaction and unnecessary drug therapy were the most prevalent type of DTPs. This variation could be due to study participants and studies setting difference. The way of assessing DTP was also attributed to this disagreement.

One study done in two nations, UK and Saudi (26), reported for ADRs and ineffective drug therapy were the most commonly identified DTPs in patients with diabetes and CVDs. Reasonably, this variation could be due to difference in study participants, thereby, hospitalized patients with diabetes and CVDs are more susceptible for multiple drugs. This was probably due to the lack of periodic assessment of patients' renal and hepatic functions in the current study. Thus, the current finding of unnecessary drug therapy, adverse drug reaction and dosage too high types of DTPs were lower in comparison to other previous studies reported in the literature. In fact, only 209 (58.5%) participants of this study had recorded eGFR, with a mean (±SD) of 52.3±14.23 (mL/minute/1.73m^2), calculated from their serum creatine. Hence, periodic assessment and monitoring of patients' organ function could have a positive impact in case of dosage adjustment/regimen change of drug therapies in patients with impaired their organ functions may preclude or minimize undesired effects of medications.

A similar manner was observed with the causes for DTPs. In this study, all of the identified problems associated with ineffective drug therapies were caused due to inappropriate drug selection which was failure to prescribe the first line antidiabetic drug therapy as recommended by the guidelines(57, 58). This result was comparable with the finding reported from Malaysia (23). In contrary, in another study done in two nations (UK and Saudi) (26), reported for ADRs (45.2%) and drug selection problem (45.2%) were the most commonly identified causes for the occurrence DTP in patients with diabetes and cardiovascular diseases. Obviously, this variation could be due to difference study population, thereby, hospitalized patients with diabetes and CVDs are more susceptible for multiple drug therapies, resulting to be experienced more DTPs.

In this study, the most reported causes for ADRs were hypoglycemia, dyspepsia and weight gain. In these cases, patients might be needed dose adjustment or change in regimen. Therefore, out of these patients who were on glibenclamide or insulin, about 5 cases were reported as experienced more of hypoglycemic episodes in the previous one year period prior to enrollment in the study. This was similar to the finding reported by Huri et al.(23). In addition, 11, 6 and 3 cases were found from GI problem (dyspepsia), weight gain and other undesirable drug effects, respectively. These all participants who had those undesirable drug effects were on metformin, glibenclamide or insulin drug therapies. These effects were consistent with other previous study, which indicated undesirable drug effects were often encountered in causing DTPs (26).

However, findings in our study were lower than the study reported from Australian patients with diabetes (37). In addition, the present result was not in line with study done by Claydon et al (36), which reported medication error and unintentional overdose use of drugs were the most common causes for DTPs. Most likely, this disagreement might be due to poor documentation system and patients' knowledge difference in noticing these drug effects. Apart from that, the variation across studies might be explained by the differences in prescribing patterns and practice in different health care settings and use of different methods to assess DTPs. For example, in this study the undesirable drug effects identified were mainly based on patient report, from their chart and established guidelines. Therefore, in clinical practice, patients with diabetes could be used drugs which are unsafe for the particular patient, yet close monitoring is needed and any undesirable drug effect should be identified and corrected. Indeed that, efforts is required to minimize these problems related to undesired drug effects in patients with

diabetes and educating them about noticing and managing of such effects associated with their medications. Thus, they require emphasis on creating awareness of insulin dose adjustment in response to their measured glucose values in minimizing the occurrence of hypoglycemic episodes.

Furthermore, in our study, commonly encountered drug classes associated with DTPs were antidiabetics (oral and insulin), antiplatelets and lipid lowering agents (statins). This finding was in line with findings reported from two studies conducted in Malaysia (21, 23). Most commonly, insulin treatment regimen was more likely associated with dosage too low, as it is a cornerstone of drug therapy for patients with type 2, who had poorly responded for OGLDs. Likewise, stains and aspirin were more likely attendant for the occurrence of need additional drug therapy for preventive or untreated medical condition.

The results obtained from multivariate logistic regression analysis indicated that differences between participants due to factors independently associated with the occurrence of DTPs. The associated factors for certain groups of participants; being female gender, participants with poor adherence to their medication and presence of multiple (≥3) comorbidities were increased the odds for developing DTPs.

In the present study, there was no statistical association observed in patients with multiple drug regimens in experiencing DTP. Conversely, it was well recognized that multiple drug use of patients with diabetes come to be more prevalent, thereby increasing the tendency in developing DTPs. In light of this event, previously conducted studies (21, 23, 26, 30, 35, 40) that assessed DTPs in patients with diabetes reported that multiple drug regimen was associated factor for the occurrence of DTPs. This might be related with nearly half (48.2%) of the study participants were on less than 5 medications, with a mean (±SD) of 4.18±1.8 medications per patient. This was lesser compared to other studies (21, 23, 33). Therefore, this variation might be indicated that, there was a lesser number of drugs utilization in Ethiopian patients with diabetes in outpatient setting. Thus, many of participants were failed to be adhered to their prescribed additional drug therapy while needed (physicians' justification). Indeed that, these differences explained due to factors associated with local cost of drugs in private and limited access to desired medications.

On the other hand, number of comorbidities per patient (≥3) were associated with a higher risk of developing at least one DTPs, which was similar to studies conducted in UK and Saudi Arabia (36) and Wolaita Sodo, Ethiopia(40). This could be explained that participants with more comorbidity are more likely to own multiple medications. Thus, participants could be reluctant to take their medication appropriately due to increasing non-adherence rate to their medications and linked with regimen complexity. In addition, the risk of ADR could be raised in patients with more number of comorbidities. Unfortunately, nearly four in fifth (77.9%) of participants in our study had different comorbid conditions and those may be needed to add drug therapy. Thus, this signals that, patients with diabetes also needed to be considered their multiple comorbid conditions.

Similarly, the current finding was consistent with the study conducted by Claydon et al (36), as shown, being female gender was significantly associated with developing of DTPs. However, in three studies, male gender was reported as an associated factor for DTPs in patients with diabetes (21, 33, 34). In present study, the reason could be due to: (1) Ethiopian female might not attend their follow up therapy as needed as male due to additional work load in home and thus be less likely to follow their drug therapy attentively (2) less adherent to the life style modification therapies, like regular physical activity. In fact, this could be related with obesity, 60% of participants with ≥30 kg/m^2 BMI were found among female participants of this study.

A good explanation for such issues was supported by WHO(5) and Lester (68), which reported more physical inactivity, obesity and overweight were observed in Ethiopian females than males. Moreover, this association might also be related with the poor glycemic control, which was relatively more seen in females (59%) and had a strong association with the occurrence of DTPs. This is in agreement with three different studies, implies fewer women were achieved their glycemic target compared to men (69-71). Biological and psychosocial factors could be responsible for gender differences in glycemic control (72, 73). Gender difference influence the liability to diabetes therapies; negatively affect in accessing health services and health seeking behaviour for women, and amplify the impact of diabetes on them. Thus, many of women in the world had inadequate accesses to treatment, care and education (74).

Furthermore, in this study dosage too low that need to be titrated their dose was higher in female participants than male participants (71.3% versus 28.7 %, p= 0.002). This is agreed with

the study found that, women had needed a higher insulin dose per their weight than men (69). Thus, prescribers need to be aware of the need to titrate insulin dosing, principally in women with diabetes, to achieve the intended glycemic target in participants with poor glycemic control.

In our study, poor medication adherence was also found as an important factor for the occurrence of DTP. This finding was supported by another three studies (26, 35, 37). This could be an indicator, in which patients might have poor knowledge/ignorance about their illness, medications and/or poor provision of counseling/education service. These outlooks are questionable, whether health care providers are not doing what was needed to support their patients in creating awareness and understanding their illness and prescribed medications or patients' related factors. This study was highlighted that non-adherence is an important factor for DTPs which was supplemented by almost all the physicians' opinion.

Besides, prescribers advocated that, they failed to step up drug therapy when they suspect that poor glycemic control or elevation of their FBG levels might be linked with poor medication adherence. However, medication adherence should not be supposed as the patient's problem alone. It might be come from frustration to agree the prescription entirely with the patient and/or failure to provide continuous support that the patient need once the drug has been dispensed. Hence, need to establish patients' perspective in ensuring and inspiring to discuss about the aim of their drug therapy to resolve such problems related to medication adherence.

Previous **s**tudies also extensively have been reported that the increased age, in which being elderly (>60 years old) was found that an associated factors for DTPs (23, 30, 33), but no statistical significance association was seen in the present study. This could be due to the difference in study participants' average age (56.1 ± 11.6), which was less than in other studies participants' average age. This could also be explained by similar age group of the study participants, more than half of them were to be found between 40 and 60 ages. Though, three in ten of participants had a history of hospitalization events due to hypoglycemic and/or hyperglycemic episodes, failed to be associated with DTPs. This was not agreed with the study conducted by Hailu et al.(40), which reported history of diabetes related hospital admission was independently associated with developing DTPs. This disagreement might be due to difference

in participants' awareness to their drug therapies and in early management of acute diabetes complications.

In this study, though more than three-fourth (76.8%) of participants had an access to SMBG, only 17.4% of participants were to be found in the intended glucose target (70-130mg/dL). The sensitivity and specificity values for this study were 57.8% and 79.6%, respectively, indicating that more than half of the participants who had DTPs were accurately identified in line with participants who were not meeting the intended glycemic target. Almost four in five (79.6%) of the study participants who did not experience DTPs properly classified as being with a good glycemic control. Thus, good fitting in association with the events predicted to be events and nonevents predicted to be nonevents. In part, this findings were comparable to one study conducted in Jordan (34) showed a sensitivity (65.4%) and specificity (63.0%) in patients with diabetes who were correctly classified their glycemic control status who experienced DTP.

This implies, ultimately the prediction capability of poor glycemic control had a strong association with the occurrence of DTPs. Thus, it seems to suggest that some level of clinical inertia, where physicians might be slowly in responding to the clinical parameters. The treatment practice showed that, there was a need to intensify drug therapy. Indeed, a lack of achieving glycemic control might also be explained by missing of the right drug therapy, although 26.1% of participants were receiving two or more antidiabetic agents in their recent visit.

In the present study, 24.9% of participants were non-adherent to their medications. This percentage was closer with one study conducted in India(41), and three studies in Ethiopia(46, 49, 50). Whereas, lower compared to five studies conducted in different health facilities of Ethiopia(47, 48, 51, 75) and higher than study conducted in Uganda(45). Unfortunately, this variation might be explained by difference in study participants' types of diabetes and comorbid conditions, tools used (MMAS-4 versus 8 items), participant diversity and sample size. Thus, being self-reported medication adherence and being conducted at health facility might also be overestimated/ underestimated and therefore lead to bias.

Moreover, in this study, factors independently associated with non-adherence were identified. Presences of diabetes complication, being female gender, participants who completed at least

primary levels of education were factors associated with medication non-adherence. Participants who developed complications reduced the odds of participants' adherence to their medications. Accordingly, participants who developed complications were non-adherent to their medication twice (AOR=2.02) of participants who didn't develop diabetes complications. Indicating that, complications could be deteriorated the patients' adherence rate to their medications by 100%. This might be explained by the presence of diabetes complications; in which it was prevalent as more than three in tenths (32.2%) of the participants had been developed diabetes complications, as developing diabetes complication was prevalent in Ethiopia(76). This could also be due to delayed diagnosing and poor screening for DM in Ethiopia(77). The current finding was consistent with else finding reported from Jimma(50), which indicated presence of diabetes complication was associated factor for poor medication adherence in patients with diabetes.

In case of educational status, having primary or secondary level of education decreased the odds of participants' being non-adherence to their medication by 58%. This result was consistent with three studies conducted in Ethiopia by Kassahun et al.(47), Jemal et al.(48), and Ali et al.(75) and one study in India by Sajith et al.(41). In addition, the present finding revealed that, being female gender were more likely non-adherent to their medication than male participants. This result also in agreement with the study of Sajith et al.(41). Poor self-care were also reported more in female patients with diabetes (78).

Unlike to the study reported by Wabe et al.(42) and Kassahun et al.(47), in this study age, drug adverse events and diuretic medications were not statistically significant in association with medication adherence rate. Irrespective of their percentages, studies extensively reported that, the most common reasons responded by participants were forgetting taking of their pills, unavailability and cost of drugs, fear of drug side effects, regimen complexity, inconvenience of time schedule and inadequate provision of instruction(41, 42, 46-48, 51, 79). In this study, there was no significant association with participants on multiple medications regimen, drug related adverse effects and presence of comorbid conditions. This was in contrary of reports from Teklay et al.(50), that indicated they had been associated with medication non-adherence.

Moreover, findings of the present study markedly point out that poor medication adherence poses an extensive challenge to attend their needed drug therapies or to achieve the desired goal

of therapy among patients with diabetes. Consequently, this work signals a need for continuous comprehensive adherence monitoring and provision of counseling/education service for patients with diabetes particularly for those developed chronic diabetes complications, participants who had no level of education and female gender.

6. Limitations of the study

This study was conducted in the well-organized national referral clinic for diabetes patients staffed with 6 senior consultants/endocrinologists. Despite of this certain limitations of this study should be considered.

- Being conducted in a single center public hospital
- Being used health facility based cross sectional study design
- Retrospective nature of study design may limit relevant information sources
- Glycemic control could be underestimated or overestimated, given that the glucose monitoring parameter used was more of the values from their FBG measures. But effort was made to minimize this issue by taking the mean average of the last three consecutive visits of FBG measurement values. But this might also be affected by extreme measurement values.

7. Conclusion

The magnitude of DTPs identified in patients with diabetes was considerably high. The most commonly identified DTPs were ineffective drug therapy, need additional drug therapy and dosage too low. Majority of those DTPs were caused due to inappropriate drug selection, lack of adding synergistic or preventive drug therapy and use of sub-therapeutic dose. Factors independently associated with developing DTPs were being female gender, three and above number of comorbidities, and poor medication adherence. It can be concluded that, nearly one-fourth participants of this study were non adherent to their medications. The present study also found that, below one- fifth of participants had met the intended glucose target.

8. Recommendations

Based on our findings from the current study, the following recommendations are put forward.

- ✓ The clinic need to prepare its own guideline for better management as referral clinic
- ✓ Prescribers should stick with evidence based guidelines when they prescribe medications
- ✓ Health care providers should pay more attention to patients at high risk of DTPs like patients with female gender, greater number of comorbid, poor medication adherence.
- ✓ Moreover, health care providers shall emphasize the negative impact of DTPs and associated factors in achieving the desired goal of therapies.
- ✓ Early identification, prevention and resolution may be vital in minimizing those problems.
- ✓ Making drugs available in affordable and effective/safer with lower possible price as needed
- ✓ Establish policies and strategies to ensure rightful access to essential antidiabetic medicines and monitoring parameters
- ✓ Conducting further studies like an interventional study is also recommended.

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Annexes

Annex I: Participants' information sheet

Name of principal investigator: **Gebre Teklemariam Demoz**

Name of study area: Endocrine and Metabolism unit of Tikur Anbessa Specialized Hospital

Research budget covered by: Addis Ababa University

Research objective: To assess the magnitude and factors associated with drug therapy problems among ambulatory patients with type 2 diabetes at Tikur Anbessa Specialized Hospital.

Significance of the study: Drug therapy problems lead to poor clinical outcomes, increased healthcare costs and decreased quality of life; thus, they should be identified, resolved and prevented in a manner of the situation as much as possible.

Risks: The risk could be the lowest to the patient during the study. The only threat for the interviewee could be spending time (may be a maximum of 30 minutes was spent).

Participant right: The right of interviewees to withdraw at any time from the interview or not to participate and to escape questions which are not confortable for them was reserved.

Beneficial: The study could be beneficial for patient's quality service delivery system to come across and to promote an intervention for the future perspective.

Confidentialities: The study result did not include patient's name and address. Hence confidentiality was kept as data was accessed only by ethically conducted, well trained and experienced health professionals of the study as well as interviewed and analyzed by the principal investigator.

Agreement: participants were fully voluntary to participate in the study.

Whom to contact: If participants have any kind of difficulties about the study, fell-free to contact the PI: Gebre Teklemariam: Cell Phone: **0914031986/gebretd2006@gmail.com.**

Annex II: Informed consent

Name of the investigator: Gebre Teklemariam Demoz

Research title: Drug Therapy Problems among Ambulatory Patients with Type 2 Diabetes at Endocrine and metabolism Unit of Tikur Anbessa Specialized Hospital, Ethiopia

Card number:_____ Code number_____

1. I confirm that I understand the information sheet for the above study and have had the opportunity to ask questions.

2. I understand that my participation is completely voluntary and that I am free to withdraw at any time, without giving any reason, without legal rights being affected.

3. I understand that my response will be looked and secured and necessary information will be extracted. I give you a permission to have an access to all my response.

4. I agree to take part in the above study. I would like to confirm my agreement by signing.

Participant's name _____ Signature:_____date_____

Data collector's name: _____ Signature:_____date_____

I thank you very much for your willingness to participate honestly and cooperatively!

Annex III: Data collection tools

Addis Ababa University

College of Health Sciences

School of Pharmacy

This tool was used to assess **"Drug Therapy Problems among Ambulatory Patients with Type 2 Diabetes at Endocrine and Metabolism Unit of Tikur Anbessa Specialized Hospital"**

Dear data collector(s),

First of all I would like to thank you for your willingness to accept my request and to participate as a data collector in this study which will surely be of great significance in contributing to determine the magnitude and factors associated with drug therapy problems among ambulatory patients with type 2 diabetes on follow up at TASH. This data will then enable the concerned bodies to emphasize on the identified problems and the associated factors to formulate and implement Medication Therapy Management (MTM) services as a part of pharmaceutical care services in turn to identify, resolve and prevent them for the future. Finally, I would like to greatly acknowledge, in advance, your indispensible roles in maintaining the quality of this data honestly and effective output of the present study. I promise you to be timely respond whenever you face challenges during the data collection period.

The principal investigator!

English version

Part I: Patient's Socio-demographic information

Socio-Demographic Characteristics:			
1. Age(in year):	_____		
2. Sex	Male ☐	Female ☐	Pregnant: Yes ☐ No ☐
3. Marital status:	Single ☐	Married ☐	Divorced ☐ Widowed ☐
4. Religion	1. Orthodox	2. Muslim	3. Protestant 4. Others_____
5. Educational status	no formal education ☐ Grade 1-8 ☐	Grade 9-10 ☐ Grade 10-12 ☐	College diploma ☐ University degree and above ☐
6. Place of Residence	Urban(Addis Ababa) ☐ ☐ Rural) our of Addis Ababa)		
7. Occupation	☐ Government ☐ Retired ☐ No job(houswife) ☐ Private office ☐ Self-Employed (farmer, daily laborer)		
Monthly income	_____ETB		

Cigarette Smoker			Yes ☐ No ☐	Ex-smoker/ former smoker ☐
Alcohol user			Yes ☐ No ☐	Ex-drinker/former drinker ☐
11.Physical Activity	Walk ☐	Yes ☐	No ☐, if yes, for how long?	<30minutes /day ☐ >30minutes/day ☐
	Sport ☐	Yes ☐	No ☐ if yes, for how long?	Daily ☐ 1-3d/week ☐ 4-6d /week ☐

II. Clinical characteristics(supplementary to the information obtained from medical record chart):			
1.Duration of diabetes	_____ Years. 2. Duration of treatment_____years.		
3.Hospitalization due to diabetes	Yes ☐	No ☐	If, yes due to Hyperglycemia ☐ Hypoglycemia ☐ ☐ others, specify _____
4.Traditional/herbal medicine use/OTC	☐ No ☐ Yes , If yes list them_____ and for what purpose_____		
5.Use of Home SMBG	☐ No ☐ Yes ,		
6.Source of medication	☐ For free ☐ Paid		

Part-II: 8-Items Morisky Medication Adherence Scale- (MMAS-8)

No	Items				No	Yes
1	Do you sometimes forget to take your pills?				+1	0
2	People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?				+1	0
3	Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?				+1	0
4	When you travel or leave home, do you sometimes forget to bring along your medicine?				+1	0
5	Did you take all your medicine yesterday?[reverted]				0	+1
6	When you feel like your symptoms are under control, do you sometimes stop taking your medicine?				+1	0
7	Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?				+1	0
8	How often do you have difficulty remembering to take all your medicine?					
		A. Never/Rarely	A=4	**The item result ÷ 4=**	+	
		B. Once in a while	B=3	1.00		
		C. Sometimes	C=2	0.75		
		D. Usually	D=1	0.50		
		E. All the time	E=0	0.25 0.00, respectively		
	Total score					

Scoring scale:

Each 'no' response rated as 1 and each 'yes' response rated as 0 for items 1 to 7, except for item 5 reversed. For item 8, the code (0-4) has standardized by dividing the result by 4 to calculate the summated score. The MMAS-8 range from 0 to 8 with the total score of **<6= poor adherence, 6-<8= medium adherence, 8= high adherence).**

Possible reasons/determinants for poor medication Adherence:

Mark [×] No [√] Yes

- ☐ Cost of medication too expensive
- ☐ Inadequate availability of medication
- ☐ Fear of medication adverse events
- ☐ Regimen complexity
- ☐ Difficulty of administration
- ☐ Inadequate instruction
- ☐ Simply Forgetfulness
- ☐ Disbelief in drug effectiveness
- ☐ Patient prefers not to take
- ☐ Feeling better or worse
- ☐ Due to work load/busy
- ☐ During fasting
- ☐ Others_____

Part III: Assessment of adverse drug reaction/allergic reaction

1. Have you experienced any undesirable, unusual adverse drug events /allergic reaction to the prescribed medicines for you since the last 1 year? ☐Yes ☐No:

If yes, describe the manifestation of the events_____

2. If your answer is "yes" for question number-1, answer the following questions:

2.1. Did the adverse event occur after the suspected drug was administered?

☐ Yes ☐ No ☐ Don't know

2.2. Did the adverse reaction improve when the drug was discontinued or a specific antagonist/antidote was administered? ☐Yes ☐ No ☐ Don't know

2.3. Did the adverse reaction reappear when the drug was re-administered?

☐ Yes ☐ No ☐ Don't know

2.4. Are there alternative causes (other than the drug) that could have on their own caused the reaction? ☐ Yes: ☐ No ☐ Don't know

2.5. Was the reaction more severe when the dose was increased or less severe when the dose was decreased? ☐ Yes: ☐ No ☐ Don't know

2.6. Did you have a similar reaction to the same or similar drugs in *any* previous exposure?

☐ Yes: ☐ No: ☐ Don't know

Part IV: Key informant questionnaire (Self-administered)

Dear all!

First of all, thank you for your willingness to answer this questionnaire. My name is Gebre Teklemariam from School of pharmacy, department of pharmacology and clinical pharmacy. Currently, I am doing MSc thesis entitled by "drug therapy problems among ambulatory patients with type 2 diabetes" regarding physicians' experience and existing practice while managing adult ambulatory diabetic patients. The purpose of this study is to assess the magnitude, pattern of drug therapy problems and to identify associated factors which aimed to empower the management practice of patients in diabetes clinic of Tikur Anbessa Specialized Hospital.

1. Current level of education (position)?
    1. Sub-specialist/senior(Internist, Endocrinologist, Diabetelogist)
    2. Fellows
    3. Resident(R1, R2 or R3)
    4. Other, specify_____
2. Which type of guideline(s) you are using for pharmacological management of your patient?
    1. Institutional based 3. National based/STG
    2. International based 4. Mixed 5. Not using any of the above
3. Specifically, what international guideline(s) you are using?
    1. IDF 2. ADA 3. ADA-EASD 4. Others, Specify;_____
4. Do you follow the guideline strictly? (keeping individualizing patients) 1. Yes 2. No
5. What could be the possible reasons (justifications/obstacles) for the development of DTPs (if any)? Or that can hinder to follow the guideline?
    1. Patient preference(Eg. resistant to initiate insulin or to add dual therapy)
    2. Adherence issue (Eg. falling the patient not to take medication as prescribed)
    3. Medication availability issue(Eg prescribing Glibenclamide instead of metformin)
    4. Side effect of drugs (Eg. GI intolerance of Metformin, or Injection site pain/insulin)
    5. Cost issue (Eg. adding of Glibenclamide to metformin instead of glimepiride or other)
    6. Poor accessibility of the guidelines (Eg. using hardcopy as a desk-reference)
    7. Patient load (number of patient vs physician, this may hinder provision of counseling)
    8. Health facility/administration issue (Eg. Limitation of rooms for examination)
    9. Others, specify_____
7. Generally, what could be the possible barriers for diabetes treatment within this center?
    1. Patient related (specify if any) _____
    2. Professionals related (specify if any) _____
    3. Institution related (specify if any) _____
    4. Others (specify if any) _____

I thank you very much for your time and willingness to be filled this data honestly!

Part V: Data abstraction format [Patients' medical record chart review]

Card Number_____ Unique ID/Code: _____Age (in year) _____

Weight (kg) _____Height (cm) _____Body mass index (BMI)[kg/m2] _____

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

Parameters	Time of sequence	Most Recent	$Visit_3$	$Visit_2$	$Visit_1$	Average
Blood glucose level and BP	FBS(mg/dL):					
	HbA1c (%):					
	BP, mmHg					
Lipid profiles	LDL: mg/dl					
	HDL: mg/dl					
	TG: mg/dl					
	Total Cholesterol					
OFTs	ALT/SGOPT					
	AST/SGPT					
	ALP					
	BUN					
	SrCr					
	eGFR					

2. Current medical conditions and medications (including Comorbid and complications) (in sequence)

Medical Problem lists	Product name (Generic Name)	Regimens (dose, route, frequency, duration)				Response
		Current	$Visit_3$	$Visit_2$	$Visit_1$	

3. Adverse Drug Events(documented):

Drug Regimen	Adverse drug reaction /Drug allergies /Other alerts	Event date

4. Past medical and medication history (hospitalizations, surgical procedures, injuries, pregnancies)._____

- Based on the most recent glucose level(FBS/RBS or A1c):

1. Poorly /Sub-optimal controlled 2. Good/Well /optimal controlled 3. Not state

Cipolle's drug therapy problems classification system

Domains	Drug Therapy Problems	Common Causes
i. Indication	1. Unnecessary drug therapy	No medical condition at that time No need of drug for that condition Duplicate therapy Non-drug therapy indicated Treating avoidable ADR
	2. Needs additional drug therapy	Addictive or Recreational drugs Untreated indication Preventive or prophylactic Synergistic or potentiating
ii. Ineffectiveness	3. Needs different drug product	Inappropriate drug selection Condition refractory to drugs Dosage form inappropriate Not effective for the condition
	4. Dosage too low	Wrong dose(sub-therapeutic dose) Frequency inappropriate Drug interaction Duration inappropriate
iii. Safety	5. Adverse drug reaction	Undesirable effect not dose related Unsafe drug for patient Drug interaction not dose related Allergic reactions Contraindication present
	6. Dosage too high	Wrong dose(over therapeutic dose) Frequency inappropriate Duration inappropriate Drug interaction Incorrect administration
iv. Adherence	7. Non-adherence	No willingness to take the drug Patient forget to take the drug Direction is not understood Patient cannot swallow/administer Cost of medication too expensive Unavailability of medication Disbelieves on the drug effectiveness Patient felt better or worse Fear of adverse events Regimen complexity

Total number of identified DTPs =_____ Total number of identified Causes_____

Logical questions to identify whether or not the patient is experiencing drug therapy problem

1. Is the medication (indication) appropriate?
   a. Is there a clinical indication for each medication being taken?
   b. Are all of the patient's medical conditions that can benefit from drug therapy being treated?
2. Is the drug therapy effective for the disease condition?
   a. Is the most effective drug product being used?
   b. Is the dosage of the medication sufficient to achieve the goals of therapy?
   c. Is the dosage form appropriate?
3. Is the drug therapy as safe as possible?
   a. Is there any adverse drug reaction being experienced?
   b. Is there any sign of toxicity (based on clinical parameters (signs and symptoms) or lab. values)?
4. Is the patient adherent to his/her medication?
   a. Is the patient willing and able to take the medications as intended?
   b. Adherence assessment

   ✓ About how many days of the month have you missed taking prescribed medications?
   ✓ Have you ever stopped or started taking any of the prescribed medications on your own?
   ✓ Have you had difficulty taking your medications as prescribed? If so, why?
      ❖ Is it because;(Reasons):

      i. You do not understand the instructions?
      ii. You prefer not to take the medication?
      iii. You forget to take the medication?
      iv. The drug product is too expensive for you?
      v. You experienced side effects while taking the medications?
      vi. You cannot swallow or self-administer the drug product appropriately?
      vii. The drug product is not available for you?
      viii. Others, please specify._____

Amharic version

በጥናቱ ለሚሳተፉ የፍቃደኝነት ማረጋገጫ

እኔ ለዚህ ጥናት ሙሉ በሙሉ ተነግሮኝ ተረድቻለሁ ። አላማውም በተመላላሽ የስኳር ህመምተኞች ህክምና ላይ ያሉ ከመድኃኒት የተያያዙ ችግሮች መገምገም እና መለየት ነው። ይህ ተሳትፎ በፈቃደኝነት ላይ የተመሰረተ መሆኑን ተረድቻለሁ። በተጨማሪም የተረዳሁት በዚህ ተሳትፎ የአገኟኛለሁ የምለው ምንም ዓይነት የተለየ አገልግሎት፤ክፍያ ወይም ስጦታ እንደማይኖር ተረድቻለሁ። ይህ ውል የሚያገለግለው ለዚህ ጥናት ብቻ ነው። ከዚህ በታች ስሜ የተገለፀው በዚህ ጥናት ለመሳተፍ ተስማምቼለሁ።

	ስም	ፊርማ	ቀን
1.	ተሳታፊ፤_____	_____	_____
2.	መረጃ ሰብሳቢ ፤ _____	_____	_____
3.	የጥናቱ ተመራማሪ ፤ ገብረ ተክለማርያም	_____	_____

ለተሳትፎዎት አመሰግናለሁ!

ስሜ:_____

እኔ የገብረ ተክለማያም የሚባል በአሁን ሰዓት በክሊኒካል ፋርማሲ ማስተርስ ለምረቃ የሚሰራ መረጃ ሰብሳቢ ነኝ።

የጥናቱ ዋና አላማ በተመላላሽ የስኳር በሽቶኞች ህክምና ላይ ያሉ ከመድሀኒት የተያያዙ ችግሮች መገምገም እና መንስኤዎቻቸው መለየት ነው። ጥናቱ ምስጢር ጠባቂ መሆኑን ላረጋግልጥዎት እወዳለሁኝ፤ ቃለመጠይቁን በፈለጋችሁት ሰዓት ማቋረጥ ይችላሉ፤ በዚህጥናት ምላሽ በመስጠት ስለትብብርዎ በድጋሜ አመሰግናለሁኝ።

የቃለ መጠይቁ ውጤት፤

☐ ሙሉ ለሙሉ ተጠናቅቀዋል ☐ በከፊል ተጠናቅቀዋል

☐ ተነፍገዋል ☐ ሌላ_____

ሀ. የታካሚዎች ማህበረሰባዊ ባህርያቶች መረጃ መሰብሰቢያ ቅጽ

- [በተዘጋጀለት ሳጥን የ√ ምልክት ያድርጉ] ካርድ ቁ_____
- በመጀመርያ በጥቁር አንበሳ የስኳር ህመምተኛ ሁኖ መድኃኒት ከጀመሩ ከ 3 ወር በላይ መሆናቸው ያረጋግጡ

1.እድሜ፤_____	2.ፆታ፤	☐ ወንድ ☐ ሴት	እርጉዝ: ☐ አዎ ☐ አይደለም
3.የጋብቻ ሁኔታ፤	☐ ያላገባ/ች	☐ ያገባ/ች	☐ አግብቶ/ታ የፈታ/ች ☐ ሚስቱ/በሏ የሞተች/ባት
4. እምነት	☐ኦርቶዶክስ	☐ ሙስሊም ☐ ፕሮቴስታንት	☐ ካቶሊክ ☐ ሌሎች
5.የትምህርት ሁኔታ፤	☐ መጻፍና ማንብብ አይችሉም ☐ መጻፍና ማንብብ ይችላሉ ☐ አንደኛ ደረጃ (1ኛ-8ኛ)		☐ ሁለተኛ ደረጃ (9ኛ-12ኛ) ☐ ኮሌጅ ዲፕሎማ ☐ ዩኒቨርስቲ ዲግሪ እና ከዛ በላይ
6.አሁን የሚኖሩበት	☐ ከተማ[አ . አ]	☐ገጠር [ከ አ . አ ውጭ/ከፍለ ሀገር]_____	
7. የሥራ ሁኔታ፤	☐ቋሚ የመንግስት መስርያ ቤት ሰራተኛ ☐ ቋሚ የግል መስርያ ቤት ሰራተኛ	☐ ጥሮታ ☐ የግል ስራ ያለው/ያላት	☐ ሥራ የሌለው/የሌላት
8. በወር ሚያገኙት ገቢ_____(የኢትዮጵያ ብር)			☐ ገቢ የሌለው/የሌላት
10. ሲጋራ ያጨሳሉ?	☐ አላጭስም ☐ አዎ	☐ ድሮ አጭስ ነበር አሁን ግን አቁሜለሁ	
መልስዎ አዎ ከሆነ ፤ መጠኑ በቀን_____ፓኬት		ለስንት ዓመት_____	
11. መጠጥ(አልኮል) ይጠጣሉ?	☐ አልጠጣም ☐ አዎ	☐ ድሮ እጠጣ ነበር አሁን ግን አቁሜለሁ	
መልስዎ አዎ ከሆነ ፤መጠኑ በቀን_____		ለስንት ዓመት_____	
12. ቡና ይጠጣሉ? ☐ አልጠጣም ☐ አዎ መልስዎ አዎ ከሆነ ፤ መጠኑ በቀን_____ሲኒ		☐ በሱኳር ☐ ያለሱኳር	
14. የአካል እንቅስቃሴ	የእግር ጉዞ ያዘወትራሉ ?	☐አላደርግም ☐ አዎ	መልስዎ አዎ ከሆነ በቀን ለምን ያህል ግዜ ይጓዛሉ? ☐ ከ30 ደቂቃ በላይ ☐ ከ 30 ደቂቃ በታች
	የአካል ብቃት/ስፖርት ያዘወትራሉ?	☐ አላደርግም ☐ አዎ	መልስዎ አዎ ከሆነ በሳምንት ለምን ያህል ግዜ ይሰራሉ? ☐ በየቀኑ / ሣምነት ሙሉ ☐ 3-6ቀናት ☐ 1-2ቀናት
15.በስኳር በሽታዎት ምክንያት ሆስፒታል ተኝቶ ያውቃሉ?		☐አላውቅም	☐ አዎ
መልስዎት አዎ ከሆነ ምክንያትዎ	☐ የደም ስኳር መጨመር = በዓመት ስንት ግዜ?_____ ☐ የደም ስኳር ማነስ = በዓመት ሰንት ግዜ?_____		
16. የባህል እና ያለሓኪም ትእዛዝ መድኃኒት ይወስዳሉ?		☐ በፍጹም	☐ አዎ፤ አዎ ከሆነ ይገለፅ_____
19. የመድኃኒትዎ ምንጭ	☐ሁሉ ግዜ በነፃ	☐ አልፎ አልፎ በነፃ ☐ ሁሉ ግዜ በገንዘብ	☐ አልፎ አልፎ በገንዘብ
17.በሽታዎት ተመርምሮ ካወቁ ስንት ግዜ ሆኖቷል ?_____		የስኳር መድኃኒት መውሰድ ከጀመሩ ስንት ግዜ ሆኖቷል ?_____	
20. በቤትዎ የሱኳር (Glucometere) መሳርያ ይጠቀማሉ?		☐ አዎ ☐ አይደለም/የለኝም	

ለ. የስኳር በሽታ ታካሚዎች በመድኃኒት አወሳሰድ/አጠቃቀም ዙርያ ግምገማ በተመለከተ(ሞሪስኪ ስምንት)

ተ ቁ	ጥያቄዎች		አይደለም	አዎ
1	አንድ አንዴ መድኃኒት መውሰድ ረስተው ያውቃሉ?		+1	0
2	አንድ አንድ ሰዎች ከመርሳት ውጭ መድኃኒትዎ ያለመውሰድ ችግር አለ፤ ባለፈው ሳምንት ውስጥ መድኃኒትዎ ያልወሰዱበት ቀን አለ?		+1	0
3	ሃኪምዎትን ሳያማክሩ በበሽታዎ ብሶት ምክንያት መድኃኒትዎ መውሰድ አቋርጠው ያወቃሉ?		+1	0
4	ወደ ሌላ ቦታ ሲጓዙ ወይንም ከቤት ወጥተው ሲሄዱ መድኃኒትዎ ይዘው ከመሄድ ረስተውት ያውቃሉ ?		+1	0
5	በትላንትናው ዕለት ሁሉንም መድኃኒትዎ በትክክል ወስደዋል?		0	1
6	የበሽታዎ ምልክቶች አልቀነሰም ብለው አንድ አንዴ መድኃኒት መውሰድ አቋርጠው ያውቃሉ?		+1	0
7	መድኃኒት በትክክል አለመውሰድ የአንድ አንድ ሰዎች ዋነኛ ችግር ነው፤ የህክምና መርሃ ግብርዎ በትክክል መከታተል ችግር ሆኖበት ያቃል?		+1	0
8	ሁሉኑም መድኃኒት መውሰድዎን ማስታወስ የከበድዎት ስንት ግዜ ነው? ፈጽሞ ☐ በሆነ ግዜ አንድ ግዜ ☐ አንድ አንድ ግዜ☐ አብዛኛው ግዜ☐ ሁሉ ግዜ☐	4 3 2 1 0 የመልስ ውጤት በ 4 ሲካፈል የሆናል=		
		ድምር		

ለመድኃኒትዎ በአግባብ አለመውሰድ ምክንያት ሊሆኑ የሚችሉ(ከታች ከተዘረዘሩት ከአንድ በላይ መምረጥ ይቻላል)

1. የመድኃኒት ዋጋ ውድነት ----------□አዎ □አይደለም
2. የመድኃኒት በቂ አቅርቦት አለመኖር----------□አዎ □አይደለም
3. የመድኃኒቱ የጎንዮሽ ጉዳት ፍርሀት----------□አዎ □አይደለም
4. የመድኃኒቱ አወሳሰድ ዘዴ ከባድነት እና ብዙ ዓይነት መድኃኒት በመሆኑ----------□አዎ □አይደለም
5. የመድኃኒቱ አወሳሰድ የግዜ ሰሌዳ አለመመቻቸት----------□አዎ □አይደለም
6. ስለ በሽታው እና መድኃኒቱ በቂ የሆነ የምክር አልግሎት አለማግኘት----------□አዎ □አይደለም
7. ያለምንም ምክንያት በመርሳት ብቻ ----------□አዎ □አይደለም
8. የመድኃኒት ፈዋሽነት አለመተማመን/አለማመን ----------□አዎ □አይደለም
9. መድኃኒት ላለመውሰድ መምረጥ----------□አዎ □አይደለም
10. ህመሙ ሲሻሎት ወይም ሲብስቦት----------□አዎ □አይደለም
11. በስራ ጫና ምክንያት የሚወሰድበት ሰዓት ማሳለፍ እና መተው----------□አዎ □አይደለም
12. በፆም ምክንያት ሰዓቱን ጠብቆ አለመውሰድ----------□አዎ □አይደለም
13. ሌሎች_____

መ. ከመድኃኒት የተያያዙ የጎንዮሽ ጉዳት ወይም የሰውነት ቁጣ ግምገማ በተመለከተ

1. ከባለፈው ዓመት ወዲህ ያለው ግዜ ከሚወስዱባቸው መድኃኒት በተያየዘ ያልተለመደ/ያልተፈለገ ሁኔታ/የጎንዮሽ ጉዳት/ የሰውነት መቆጣት አጋጥሞት ያውቃል? □አዎ □አይደለም ፤ መልስዎ አዎ ከሆነ የመድኃኒቱ ዓይነት እና የሁኔታው ምልክት ይግለጽ፡-

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2. የጥያቄ ቁጥር 1 መልስዎ አዎ ከሆነ፤ ለሚከተሉትን ጥያቄዎች መልስ ይስጡ

2.1. ጉዳቱ/ቁጣው መድሐኒቱን ከወሰዱ በኋላ ነው የተከሰተው?----------□አዎ □አይደለም □አይታወቅም

2.2. መድኃኒቱ ካቋረጡት በኋላ ጉዳቱ አሻሽሏል/ቁሟል? ----------□አዎ □አይደለም □አይታወቅም

2.3. መድኃኒቱ እንደገና ሲወስዱት ምልክቱ/ጉዳቱ እንደገና ተከስቷል? ----------□አዎ □አይደለም □አይታወቅም

2.4. ከመድኃኒቱ ውጭ ሌላ እንደዚህ ዓይነት ጉዳት/ቁጣ ሊያመጣ የሚችል አለ?----------□አዎ □አይደለም □አይታወቅም

2.5. ጉዳቱ የመድኃኒቱ መጠን ሲጨምር ብሷል ወይም መጠኑ ሲቀንስ ቀንሷል? ----------□አዎ □አይደለም □አይታወቅ

2.6. ከዚህ በፊት እንደዚህ ዓይነት ተመሳሳይ ጉዳት ለተመሳሳይ መድኃኒት አጋጥሞት ነበር?-□አዎ □አይደለም □አይታወቅም