Assessment of Drug Therapy Problems and Contributing Factors among Ambulatory Patient with Type 2 Diabetes mellitus in Dagmawi Menelik Hospital, Addis Ababa, Ethiopia

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A Thesis Submitted to the School of Pharmacy, Department of Pharmacology and Clinical Pharmacy in Partial Fulfillment of the Requirements for the Degree of Master's Degree in Pharmacy Practice (M- Pharm)

Addis Ababa University
Addis Ababa, Ethiopia
July 2021

Addis Ababa University

School of Graduate Studies

This is to certify that thesis prepared by Asmamaw Yenesew entitled “Assessment of Drug-Therapy Problems and Contributing Factors among Ambulatory Patient with Type 2 Diabetes mellitus visiting Menelik Hospital, Addis Ababa, Ethiopia” and submitted in partial fulfillment of the requirements for the degree of Master of Pharmacy in Pharmacy Practice comply with the regulations of the University and meets the accepted standards concerning originality and quality.

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Abstract

Assessment of drug therapy problems and Contributing Factors among Ambulatory Patient with Type 2 Diabetes mellitus in Menelik Hospital, Addis Ababa, Ethiopia

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Patients with diabetes are at high risk of drug therapy-associated problems (DTPs), as they are exposed to multiple medications. Studies conducted on DTPs in diabetic patients in Ethiopia are, however, limited. This study was, therefore, aimed to assess the magnitude, pattern, and factors associated with DTPs among patients with type 2 diabetes at Dagimawi Menelik Hospital (DMH). A cross-sectional study was conducted among 294 patients who fulfilled the inclusion criteria. Patients were interviewed using a structured data collection format, involving retrospective medical chart review. DTPs were assessed using Cipolle's classification system. Descriptive data were reported using tables and figures. A multivariate logistic regression analysis was performed to identify factors associated with DTPs. A total of 448 DTPs in 193 (65.6%) patients were identified. Most commonly identified DTPs were non-compliance, 118(26.3%), need additional drug, 110(24.6%), and dosage too low 89 (19.9%). On multivariate analysis, history of hospitalization (AOR= 4.34, 95% CI: 1.21, 15.54), poor glycaemic control (AOR= 59.5 95% CI: 18.9, 188.0)**,** presence of co-morbidity (AOR= 6.7, 95% CI: 2.4, 19.0) and diabetes complication (AOR= 4.1, 95% CI: 1.1, 15.2) were positively associated with occurrence of DTP On the other hand, physical activity (AOR= 0.2, 95% CI: 0.0, 0.7), absence of poly-pharmacy (≤3 drugs) (AOR= 0.1, 95% CI: 0.0, 0.6) were protective for the development of DTP. In conclusion, there was high prevalence of DTP particularly among patients with poor glycemic control, history of hospitalization, comorbidities, complications, inactivity and polypharmacy.. Further studies on the prevention and management of DTPs, therefore, need to be conducted.

Keywords**:** Diabetes mellitus, drug therapy problems, factors, Ethiopia

Acknowledgment

I extend my special thanks to the Almighty God and his mother St. Virgin Mary for everything of merit is due to his benevolence.

I would like to extend my deepest gratitude to my advisor Professor Eyasu Makonnen and my co-advisor Getachew Alemkere for their constructive advice, support, valuable comments, and suggestions during the process of this research thesis.

My acknowledgment also goes to my friends for their valuable comments and suggestions during this work. I am very grateful to the Addis Ababa health bureau for sponsoring me to attend the MSc program and I would like to thank Addis Ababa University School of pharmacy for giving me the chance to do my thesis. My acknowledgment goes also to Dagmawi Menelik Referral Hospital for permitting me to conduct the study. Finally, my deepest gratitude goes to my beloved wife Melkam Dagne.

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Abbreviations and Acronyms

ADA/EASD	American Diabetes Association/European Association for the Study of Diabetes
ADRs	Adverse Drug Reactions
CI	Confidence Interval
CVD	Cardiovascular Disease
DMH	Dagimawi Menelik Hospital
DM	Diabetes Mellitus
DTPs	Drug Therapy Problems
EHRIG	Ethiopian Hospital Reform Implementation Guidelines
HFSUH	Hiwot Fana Specialized University Hospital
IDF	International Diabetes Federation
JUSH	Jimma University specialized Hospital
PCNE	Pharmaceutical Care Network of Europe
PFSA	Pharmaceutical Fund and Supply Agency
SMBG	Self-Monitoring of Blood Glucose
SPSS	Statistical Package for Social Sciences
WHO	World Health Organization
TASH	Tikur Anbessa Specialized Hospital
T2DM	Type 2 Diabetes Mellitus

1. Introduction

1.1. Background

Diabetes Mellitus (DM) is a group of metabolic disorders characterized by persistent hyperglycemia due to deficiency in insulin secretion, insulin action, or both(ADA, 2019)). Globally, 415 million adults are estimated to have diabetes, and there are 318 million adults with impaired glucose tolerance which puts them at high risk of developing the disease gradually. Developing countries are suffering from the increasing burden of diabetes mellitus. In 2015, it was estimated that 9.5–29.3 million peoples live with diabetes in the Africa Region(Ayele *et al.*, 2018; Atlas, 2019).

DM is generally classified as type 1, type 2, gestational and other types of diabetes. In urban Ghana, type 2 DM (T2DM) affects at least 6% of adults (Danquah *et al.*, 2012) and it also accounts for 90–95% of the incidence of diabetes and is associated with a strong genetic predisposition, age, obesity, and lack of physical activity (Ayele *et al.*, 2018).

Review studies addressed a large economic burden caused by diabetes, most directly affecting patients in low-middle-income countries like Ethiopia (Teklay, Hussien and Tesfaye, 2013; Mesfin, Assegid and Beshir, 2017; Ayele *et al.*, 2018)). By 2025, it is estimated that more than 75% of people with diabetes will reside in low-income countries (Bagonza, Rutebemberwa, and Bazeyo, 2015)

A drug therapy problem (DTP) is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes. According to Cipolle, DTPs are classified into seven categories namely: patients with unmet conditions (need additional drug therapy), unnecessary drug therapy, and dose too low, dose too high, adverse drug reaction, ineffective drug therapy, and non-compliance(Ahmad, Mast and Hugtenburg, 2014; Cipolle, Strand and

Morley, 2021). Patients with T2DM receive a wide range of pharmacotherapeutic agents and are, therefore, at higher risk to experience DTPs associated with negative effects on patient outcomes and have the potential to increase the cost of care (Koyra, Tuka, and Tufa, 2017).

Diabetic patients are vulnerable to drug-related problems. Moreover, diabetes mellitus is often accompanied by various co-morbidities. The situation results in increasing the risk of drug-related problems (DTPs). (Zazuli, Rohaya, and Adnyana, 2017).

Medication adherence is defined as the extent to which a patient's medication-taking behavior coincides with the intention of the health advice he or she has been given. It is the most important factor that determines the therapeutic outcome, especially in a patient suffering from chronic illness like diabetes mellitus (Inamdar. *et al*., 2013). Adherence denotes the patient's self-initiated decision to closely adhere to treatment plans. Prescribers must monitor patients' adherence to medication and usage instructions for them to benefit from therapy (Inamdar, Kulkarni, Karajgi,Manvi,Ganachari, 2013). Many patients, especially patients with chronic illnesses, including, diabetes experience difficulties in following treatment recommendations. Even in developed countries, adherence to long-term therapy for chronic illnesses averages only 50%. non-compliance to medication results in getting less benefit from their drug therapy than expected (Mesfin, and Assegid, 2017).

1.2. Statement of the Problem

In recent years, diabetes has evolved to become one of the most serious health concerns in both the developed and developing world. The global increase in the prevalence of diabetes has been rapid and alarming. International Diabetic Federation (IDF) Atlas 9th edition 2019 estimated that 463 million adults aged 20–79 years are currently living with diabetes worldwide this represents 9.3% of the world's population in this age group. of which 80% live in low- and middle-income

countries(Atlas, 2019) If this tendency continues without rigorous action to prevent the disease, by 578 million (10.2%) by 2030 and to 700 million (10.9%) by 2045. one adult in 10, will have diabetes(Atlas, 2019). The largest increase will take place in the regions where developing economies are predominant. Since in low- and middle-income countries, 29% of diabetes deaths occurs among people under the age of 50, compared to 13% in high-income countries, it is a great burden for the quality of life of affected individuals, their families, and for the country's socioeconomic structure at large. Compared to the western world, the burden in the developing world, particularly in Africa, is even worse due to late diagnosis and poor access to diabetic care. The cost of management of diabetes mellitus is complex and multidisciplinary, i.e., expensive in poor resource countries where the majority of the population lives below a dollar per day. In most hospitals of Ethiopia, the cost of patient attendance rates and medical admissions are rising for diabetic management. Access to diabetes care in the country also does not meet the increments in the incidences and complications of the disease. Furthermore, studies show that blood glucose levels of diabetic patients remain high despite the treatment they receive indicating that there is a problem with the management of these patients (Koyra, Tuka, and Tufa, 2017).

Despite the vital roles which medicines play to prevent and control or treat different diseases, inappropriate use of medications may be dangerous and leads to problems related to medications. Drug therapy problems (DTPs) are significant public health issues 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, of which 50% are preventable (Zazuli, Rohaya, and Adnyana, 2017). Globally, more than half of all medicines are prescribed and dispensed inappropriately, overt that half of the patients fail to take them as prescribed. Numerous studies had recognized the type and pattern of DTPs in developed nations.

Conversely, there is a dearth of published data regarding the type and pattern of DTPs in under-resource donations (Ayele *et al.*, 2018).

Therefore, it is unequivocal that drug therapy problems (DTPs) may account for the lion's share of the problems in diabetes management in the country. Hence, early identification of types of DTPs and factors associated with them is essential for the optimization of diabetes management and also enable practitioner in collaboration with patients to construct a better care plan. Furthermore, resolving as well as preventing the occurrence of DTPs among T2DM patients has a tremendous positive impact on improving the clinical, humanistic, and economic outcomes of patients. Despite its serious negative impact on health outcomes, there are no sufficient studies conducted on this problem in the country.

Studies on the magnitude of DTPs and associated factors among patients with T2DM in Ethiopia could be helpful in the identification, prevention, and resolution of those problems in patients with diabetes. This is also helpful to show the gap in health care practice to empower the focus of healthcare providers and policymakers 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, the pattern of drug therapy problems, and factors associated with occurrence of DTPs among patients with T2DM.

1.3. Significance of the Study

Assessing the degree of drug therapy problems and their pattern among T2DM patients is crucial for taking action. Also identifying the most common factors associated with these drug therapy problems is a vital one to resolve problems. So, this study may serve as an input for the appropriateness of medications used in T2DM and to develop guidelines and protocols. This study mainly helps the Federal Ministry of Health, different health institutions, and health care

providers in this institution, and know about the prevalence and factors associated with drug-related problems in T2DM. It can also be used as baseline data to integrate programs working in this area. The data can also serve as a base for researchers and academic institutions to do similar studies in the country on medication use appropriateness in T2DM patients.

2. Literature review

2.1. Prevalence of Drug therapy problems and their pattern

Detecting DTPs is crucial in pharmaceutical care since they may interfere with optimal patient outcome, resulting in increased morbidity and mortality and thus incurring greater healthcare expenditures (Abunahlah et al., 2018)

The prospective, interventional study carried out for ten months in hospitalized patients with diabetes mellitus admitted under the general medicine department of Justice K S Hedge Charitable Hospital in India identified a total of 189 drug therapy problems from 151 patient case records. The number of drug-related problems was found to be more in males than females. Drug-related problems were commonly seen in patients aged between 61 and 70 years of age. The most common drug-related problems were found to be unnecessary drugs (17.98%) followed by ineffective drugs due to improper drug selection (16.40%) (Shareef, Fernandes, and Samaga, 2016).

The study done in Indonesia with T2DM patients identified 261 DTPs and Problems concerning drug choice were most common (55.2%) followed by needs additional (25.3%)in which problems per patient were, averaging 2.88 (SD=0.23) (Rohaya, and Adnyana, 2017).

A multi-center, cross-sectional study was conducted in T2DM outpatients in Jordan, out of 1494 patients, 81.2% of the patients had at least one DTP. Of these DTPs, 26.1% of the patients had unnecessary drugs and 19.6% needed additional drugs; whereas 16.7% of the patients had ineffective drugs and 10.6% of patients had a high dose.. (Alzoubi, and Scott, 2017).

A study in Malaysia showed that each diabetic patient experienced at least one DTP while a study in Denmark showed at least four DTPs per patient. However, studies conducted in Indonesia showed a lack of DTPs in diabetic patients, particularly in secondary health care facility settings (Zazuli, Rohaya, and Adnyana, 2017).

A total of 151 DTPs were found in a prospective study conducted in a Sri Lankan teaching hospital among 400 ambulatory diabetic patients using the Pharmaceutical Network Care of Europe (PCNE) classification. The most common identified DTP was the 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 patients use their medicines. Types of DTPs frequently identified were related to the selection of drugs (31.12%), inappropriate drug use (40.42%), drug required not given (23.4%), and 21.27% of drug duplications (Mamun et al, 2016).

A retrospective study in T2DM with hypertensive patients was conducted at a tertiary hospital in Malaysia. A total of 387 DTPs were identified from the total of 200 study patients using the PCNE tool. Among these, 90.5% of patients 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%). The most commonly involved drugs were aspirin, clopidogrel, simvastatin, amlodipine, and Metformin (Huri, and Wee, 2013).

Another retrospective study which involved 208 types 2 diabetes in-patients and out-patients with dyslipidemia were also conducted in the same study setting of Malaysia. A total of 406 DTPs were identified. Among these, 91.8% of patients had at least one DTP, averaging 1.94 ± 1.10 problems per patient. The most frequent types of DTPs were potential drug-drug interaction (18.0%), a drug not taken or administered (14.3%), and 11.8% of patients due to insufficient awareness of health and diseases (Huri and Ling, 2013).

A multi-center, cross-sectional study was conducted on 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 (Alzoubi and Scott, 2017).

A retrospective cohort study of DTPs in adult diabetic patients admitted to an Australian teaching hospital was conducted over two years. The common DTPs were medication errors (64.1%) associated with hypoglycemia and unintentional overdose (36). Likewise, in another study in Australia, 682 DTPs were identified using the PCNE classification, an average of 4.6 ± 1.7 per patient with T2DM (Van Roozendaal and Krass, 2009).

In an observational study conducted 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 were related to dosing (43.9%), followed by drug choice (17.3%) and adverse drug reactions (15.6%), respectively (Chung et al., 2017).

Patients discharged from academic and nonacademic hospitals were the subjects of an observational study performed in Amsterdam, Netherlands. A total of eight hospitals were involved in the project. In total, 992 potential DTPs were observed in the 340 patients (mean 2.9 ± 1.7). No drug was prescribed but clear indication, an unnecessarily long duration of treatment, dose too low, and incorrect drug selection were the DTPs most commonly observed. Ten percent of DTPs occur- ring in 71 patients were drug-drug interactions. DTP(Ahmad, Mast, and Hugtenburg, 2014).

According to findings from the retrospective study conducted among 300 participants from two hospitals in the United Kingdom (UK) and Saudi Arabia, the most common DTPs were lack of treatment effectiveness (45.2%) and ADR (45.2%), respectively (Al Hamid et al., 2016).

One study conducted in Nigeria on 399 T2DM patients in the hospital during the period and identified that non-compliance was the most common DTP occurring within the study patients at 26.1%, it was followed by the need for additional drugs respectively. Too low dosage problems were the least occurring DTP at 8% frequency (Ogbonna, 2015).

In one retrospective study conducted in 243 T2DM patients in Ethiopia, Woliata Sodo University, the prevalence of drug therapy problems was 83.1% out of which Need additional drug was the most common, 137(56.37%) followed by non-compliance 126(51.9%)(Koyra, Tuka, and Tufa, 2017).

One Institutional based retrospective cross-sectional study was conducted in HFSUH in Ethiopia identified 364 drug-related problems (DTPs) across the three categories of drug-related problems, giving an average of 1.8 DTPs per patient. The effect of drug treatment is not optimal 179 (49.2%), untreated indication and symptoms 77 (21.1%), unnecessary drug-treatment 39 (10.7%), and adverse drug reactions 69 (19%) were the most frequent categories of DTPs identified (Ayele et al., 2018).

A prospective cross-sectional study at JUSH in Ethiopia on 300 types 2 diabetic patients with hypertension assessed a total of 494 drug-related problems. The mean number of drug-related problems was 1.65 ± 1.05. The most common drug-related problems were the need for additional drug therapy (29.35%), ineffective drug (27.94%), and dose too low (15.8%) (Yimama, Jarso, and Desse, 2018).

A cross-sectional study was conducted on 418 patients at TASH in Ethiopia results in a total of 207 DTPs in 177 (42.3%) patients. Commonly identified DTPs were dosage too low (58, 28.0%), ineffective drug therapy (54, 26.1%), and need additional drug therapy (52, 25.1%). (Teklemariam, 2019).

Another cross-sectional study conducted in Debre Tabor Hospital, Ethiopia identified a total of 491 drug therapy problems with a mean of 1.86 ± 0.53 drug therapy problems per patient were identified, and 62.4% (264) of them experienced at least one drug therapy problem. Non-compliance (197, 40.1%), needs for additional drug therapy (119, 24.2%), and dosage too low (91, 18.5%) were the most frequently observed drug therapy problems in the study setting. Anti-diabetic drugs (88.4%), statins (44.5%), and aspirin (33.5%) were the most commonly involved drugs in drug therapy problems. (Kefale et al., 2020)

2.2. Factors associated with drug therapy problems

DTPs were found to be significantly associated with renal dysfunction, multiple drug use, CVDs, elderly age, and longer hospital stays in a study conducted in Malaysia with T2DM and hypertensive patients. (Huri and Wee, 2013).

In another study conducted in Malaysia with T2DM and dyslipidemia patients, drugs such as anti-hypertensive, lipid-modifying, and anti-diabetic agents were the drug classes that most likely 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 (Huri and Ling, 2013).

Another study in Jordan showed that the independent risk factors for DTPs identified were male gender, multiple medications use, gastrointestinal medication, and non-adherence to self-care(Scott, 2017).

A retrospective study conducted included 300 adult patients from two hospitals in the UK and Saudi, a total of 197 (65.7%) patients with diabetes and CVDs were hospitalized due to the incidence of DTPs. Moreover, the use of multiple medications and patients not taking medications appropriately were the main causes contributing to developing DTPs. The main drug

classes associated with DTPs were insulin and antihypertensive medicines (Al Hamid et al., 2016).

In a study done in India, factors significantly associated with DTPs were female gender, age of 18–50, being single marital status, mental problems, and presence of co-morbid conditions (Shareef, Fernandes and Samaga, 2016).

A retrospective study conducted with type-2 Diabetes in a Tertiary Hospital in Niger identified that Non-compliance was the most common DTP at 26.7%, while polypharmacy was identified as a major factor that contributed to DTP among the patients (Ogbonna, 2015).

A cross-sectional study conducted in Wolaita, Ethiopia indicated that Age ≥ 65, comorbidity, polypharmacy, and history of hospitalization had a significant association to cause drug therapy problems in T2DM patients (Koyra, Tuka, and Tufa, 2017).

Another prospective cross-sectional study at JUSH in Ethiopia identified predictors of Drug-related problems were age 41–60 years (AOR = 6.87, 95% CI 2.63–17.93), age > 60 years (AOR = 5.85, 95% CI 2.15–15.93), and the presence of co-morbidity (AOR = 3.0, 95% CI 1.11–8.16). (Yimama, Jarso, and Desse, 2018).

A cross sectional study done at TASH in Ethiopia with T2DM patients assessed the risk factors for DTP as Factors associated with DTPs were female gender ([AOR] = 2.31,95% CI:1.30–4.12); comorbidities (AOR = 3.61, 95% CI:1.19–10.96); married (AOR = 2.58,95% CI:1.23–5.48);; non-compliance (AOR = 5.26,95% CI:2.51–11.04) and residence out of Addis Ababa (AOR = 0.30, 95% CI:0.12–0.73). (Teklemariam, 2019).

In A cross sectional study done at Debre Tabor Hospital in Ethiopia with T2DM patients, the determinants of drug therapy problems were very low family income (adjusted odds ratio = 4.64, p = 0.010), age (45–65 years old) (adjusted odds ratio = 2.55, p = 0.008), presence of co-

morbidity (adjusted odds ratio = 9.19, $p < 0.001$), and taking ⩾5 medications (adjusted odds ratio = 2.84, $p = 0.001$) (Kefale et al., 2020).

2.3. Conceptual framework

Based on reviewed works in the literature, different factors affect development of DTPs. These factors are categorized as patient-related factors, drug-related factors, disease-related factors, and professional related factors (Whitley et al., 2006; Huri and Wee, 2013; Shareef, Fernandes, and Samaga, 2016; Ekoru et al., 2019) (**Figure 1**).

Figure 1 is constructed based on reviewed literature and shows their relationships

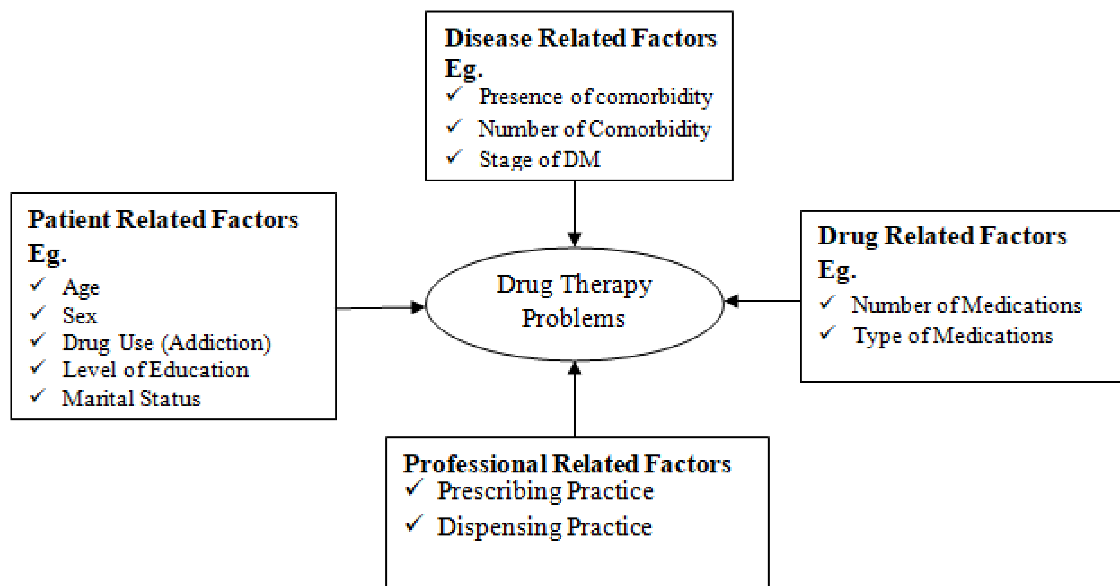

Figure 1: Conceptual framework of the study

3. Objective

3.1. General Objective

To assess drug therapy problems and contributing factors among ambulatory patients with T2DM in Dagmawi Menelik Hospital.

3.2. Specific Objectives

- ✓ To determine the prevalence of drug therapy problems among ambulatory patients with T2DM in DMH.
- ✓ To describe patterns of drug therapy problems among ambulatory patients with T2DM in DMH.
- ✓ To identify factors associated with occurrence of drug therapy problems among ambulatory patients with T2DM in DMH.

4. Methods

4.1. Study Setting

The study was conducted in Dagimawi Menelik Referral Hospital (DMH), which is located in the center of Addis Ababa, the capital of Ethiopia. DMH is one of the First Ethiopian hospitals under the Addis Ababa City Administration Health Bureau established in 1910 G.C. It serves the city community and other referral cases from different corners of Ethiopia. DMH provides various services, which include clinical, laboratory, diagnostic, forensic, pathology, and optometry. Among the clinics in DMH, a medical referral clinic is one of them where 292 diabetic cases were seen per month. Based on administrative sources data obtained prior to the data collection period, the hospital has 112 physicians, 34 pharmacists, 353 nurses, 125 other health professionals, and 354 administrative staff.

4.2. Study design and period

A facility-based cross-sectional study design was employed among ambulatory patient with T2DM who received care at DMH, Addis Ababa, Ethiopia from October 11, 2019, to January 11, and 2020.G.C

4.3. Source of population

All patients with T2DM attending the medical referral clinic of DMH.

4.4. Study population

The study population consisted of ambulatory adult patients with T2DM and undergoing treatment and had follow-up at DMH during the study period from October 11, 2019 to January 11, 20202.

4.4.1. Inclusion criteria

- ✓ Ambulatory patients diagnosed with type 2 diabetes
- ✓ Adult patients aged 20 years and above

- ✓ Patients taking antidiabetic drugs for at least 1 year
- ✓ Had regular follow up in the diabetes clinic for at least 1 year

4.4.2. Exclusion criteria

- ✓ Pregnant patients with preexisting (overt) type 2 diabetes were excluded as they are at high risk for gestational diabetes which will affect the DTP evaluation.
- ✓ Those with incomplete medical record chart
- ✓ Seriously ill patients to complete the interview

4.5. Sample size determination and sampling technique

The number of patients to be involved in the study was determined using the single Population proportion formula:

$$n = \frac{Z^2 a/2\ P\ (1-P)}{d^2}$$

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). (Note: even though other studies in other settings (tertiary hospital) in the country had reported DTP, we prefer to take the 50% prevalence as those findings are almost equivalent to the 50% prevalence and we will have an advantage of relatively high sample size with the 50% prevalence)

The calculated sample size using this formula is 384. The expected number of source population in the study period (N), based on the average number of patients coming to the DM clinic during the study period was 876.

Corrected sample size= N*n/**N+n ~267.** 10% contingency was considered, thus final sample size used in this study was **294.**

4.6. Study variables

4.6.1. 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)

4.6.2. Independent variables:

- ✓ Socio-demographic (age, sex, level of education, residence, and marital status),
- ✓ Social habits (physical activities, smoking, and alcohol use),
- ✓ Presence and number of co-morbid conditions and diabetes complications,
- ✓ Number of prescribed medications,
- ✓ Status of glycemic control
- ✓ self-monitoring of blood glucose,
- ✓ Duration of diabetes and drug treatment,
- ✓ History of diabetes-related hospitalization, and
- ✓ Source of medications and
- ✓ traditional medicine use.

4.7. Data collecting procedures

The data were collected between October 11, 2019 to January 11, 2020, for 3 months. An interviewer-administered questionnaire was used to gather patient demographic and clinical history. Additional data abstraction sheet was also used to take data form the medical records and treatment chart of each study participant after each clinical encounter.

Data was collected in steps. The first step, after consent received, was a patient interview using an interviewer administered structured questionnaire. The structured questionnaire addresses the baseline socio-demographic details such as age, sex, marital status, level of education, occupation, level of income, and patient status on cigarette smoking and alcohol intake. To complement the interviews, patient medical records were reviewed using a data abstraction

checklist. The abstraction included past medical history, medication history, and relevant physical examination as well as presentations of DTPs reported by the patient and other aspects of patient-related risk factors associated with DTPs as recorded in the medical charts.

The second step was medication chart review on the medical history, physical examination notes, laboratory tests, physician assessment and treatment.

Then, three clinical pharmacists had identified and classified potential and actual DTPs using evidence based clinical guidelines using all pertinent patient data. Primarily the IDF 2019 guideline was used. Drug-drug interactions were checked using Micromedex and Medscape and classified into two categories: a) serious drug-drug interactions requiring discontinuation of therapy or use of alternatives and b) drug-drug interactions requiring close monitoring and minor interactions.

4.8. Data processing and analysis

After collection, data were checked for completeness. Then entered, cleaned, and analyzed. The collected data were entered into Epi data software version 4.6.0.2 (Centers for Disease Control and Prevention, Atlanta, GA) and analyzed using IBM SPSS Statistics for Windows version 25 . Descriptive summary statistics were presented as means with standard deviation for normally distributed continuous variables. Categorical variables were summarized using frequencies and percent proportions. Bivariate logistic regression was used to analyze the associations between covariates with DTPs development. All covariates with $p<0.2$ in the univariable binary logistic regression were entered into the multiple variable binary logistic regression model using an enter method. Statistical significance was declared at $p<0.05$.

4.9. Data quality control and assurance

A pre-test was conducted among 10 patients before two days of the data collection period to check for the uniformity and understandability of the questionnaire. Besides, data collectors were

trained for two days. During data collection, regular supervision and follow-up were made. The principal investigator had cross-checked completeness and consistency of data every day. All materials used for data collection were arranged sequentially and data was stored in a safe and secure place.

4.10. Operational definition

Drug-therapy problem: Any undesirable event experienced by the patient that involves or is suspected to involve drug therapy and that actually or potentially interferes with desired health outcomes.

DTP counts: When a patient has more than one similar DTP's they were considered as one DTP. For instance, a patient with "low dose" will have a single DTP regardless of the number of drugs prescribed at low dose. Otherwise, different DTPs for a given patient, regardless of their frequency, were counted separately.

Alcohol use- Drinks any alcoholic beverage for women, more than one drink per day; for men, more than two drinks per day (one drink is equal to a 12-oz beer(350ml), 5-oz glass of wine(150ml), or 1.5-oz distilled spirits(45(ADA, 2019).

Exercise:

Non-regular: any exercise reported by a patient but not to the standard as defined under regular:

Regular: physical activity for at least 30 minutes per day for 5 days per week planned, structured, repetitive, and designed to improve or maintain physical fitness, physical performance, or health (WHO, 2018).

Poly-pharmacy: The daily consumption of more than 3 medications.

Good glycemic control: An individual who achieves the target level of fasting blood glucose (FBG) 70-130mg/dl.

Poor glycemic control: An individual who failed to achieve a glycemic goal, out of the normal range FBG >130mg/dl(Pathan *et al.*, 2017).

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(WHO, 2015).

4.11. Ethical Consideration

Before data collection, the proposal has been approved by the ethical review committee of the School of Pharmacy. A letter of support was obtained from Addis Ababa Regional Health Bureau. And finally, permission was settled from DMH management.

During data collection, the objective of the study was explained to the study patients and verbal consent was received. Besides, the confidentiality of the information was assured using anonymous coding for names and other personal identifiers.

5. Results

5.1. Socio-demographic characteristics

A total of 294 study patients involved in the study. More than half, (161, 54.8%), of the patients were females. The mean (±SD) age of the study patients was 55.17 ± 14.68 years and 125 (42.5%) were ≥60 years old. The majority of patients were married (185, 62.9%). Most patients, 249(84.7%) resided in Addis Ababa. One-third, 99 (33.7%), of the patients had at least a college and above level of education. One hundred seventy-one (58.2%) were employed. Only 4 (1.4%) and 29(9.9%) patients were active smokers and regular alcohol users, respectively. Even though, 234 (79.6%) patients responded that they do physical activity, only 97 (33%) adhered to regular physical activity (Table 1). patients

Table 1: Socio-demographic characteristics of ambulatory patients with type 2 diabetes on follow up at DMH, Addis Ababa, Ethiopia, 2021

Variables	Category		Study patients	
			Frequency	Percent
Sex	Male		133	45.2
	Female		161	54.8
Age	18 – 40		64	21.8
	41 – 60		105	35.7
	>60		125	42.5
	Mean ± SD			55.17 ± 14.68
Marital Status	Single		42	14.3
	Married		185	62.9
	Divorced		29	9.9
	Widowed		38	12.9
Religions	Orthodox		162	55.1
	Muslim		65	22.1
	Protestant		52	17.7
	Others*		15	5.1
Residence	Addis Ababa		249	84.7
	Out of Addis Ababa		45	15.3
Educational Status	No formal education		38	12.9
	Primary (1 - 8)		76	25.9
	Secondary (9 - 12)		81	27.6
	College and above		99	33.7
Employment status	Employed		171	58.2
	Unemployed		123	41.8
Smoking status	Smoker		4	1.4
	Non-smoker		290	98.6
Alcohol use	User		29	9.9
	Non user		265	90.1
Physical activity	Yes	Regular	97	33.0
		Non-regular	137	46.6
	No		60	20.4

Others: Catholics, Adventist*

5.2. Clinical characteristics

The mean duration of the diabetes disease since the first diagnosis was 2.12 ± 1.035 years. The most recent calculated mean (±SD) BMI of study patients was 24.28±2.7 kg/m2. Only 10 (3.4%) patients were obese (≥30kg/m2). Sixty-six (22.4%) patients had at least one hospitalization history related to diabetes, within the last year. More than half of study patients, 175 (59.5%), had access to self-monitoring of blood glucose (SMBG), and 152 (51.7%) patients got medications freely. The overall mean (±SD) value of FBG for the last four consecutive visits was 153.8±41.48. Only 139 (47.3%) patients met the intended glycemic target (FBG 70-130mg/dL). Of which only two (0.7%) patients had records below 70mg/dL (Table 2). patients

Table 2: Clinical characteristics of Ambulatory patients with type 2 diabetes on follow up at DMH, Addis Ababa, Ethiopia, 2020/21

		Study patients	
Variable	**Categories**	**frequency**	**Percentage**
Duration of diabetes (years)	1-5	97	33.0
	6-10	108	36.7
	11-15	45	15.3
	>15	44	15.0
	Mean ±SD		2.12±1.035
BMI (kg/m^2)	<18.5	3	1.0
	18.5-24.9	188	63.9
	25-29-9	93	31.6
	≥30	10	3.4
	Mean ±SD		24.28±2.7
Hospitalization due to diabetes	Yes	66	22.4
	No	228	77.6
Traditional medicine within 1 year	Yes	79	26.9
	No	215	73.1
Home SMBG use	Yes	175	59.5
	No	119	40.5
Medication source	Free	152	51.7
	Paid	142	48.3
Average FBG (mg/dl)	<70	2	.7
	70-130	139	47.3
	>130	153	52.0
	Mean ±SD	153.8±41.48	

BMI: Body mass index, FBS Fasting Blood Glucose, SD: standard deviation, SMBG: Self-Monitoring of Blood Glucose.

5.3. The pattern of comorbidities and complications in patients with type 2 diabetes

More than half of the study patients, 164 (55.8%) had co-morbid conditions with a mean ± SD of 1.44±0.497 co-morbidities. The most common co-morbid condition was hypertension, 120 (40.8%), followed by dyslipidemia 41(13.9%) and ischemic heart disease, 35(11.9%). Sixty-seven (22.8%) patients had also developed complications, among which the most common ones were diabetic neuropathy 41 (13.9%), diabetic retinopathy 32 (10.9%), and diabetic nephropathy 13(4.4%) (Table 3).

Table 3. The pattern of Co-morbidities and Complications on Ambulatory patients with type 2 diabetes on follow up at DMH, Addis Ababa, Ethiopia, 2020/21

Variables	Categories	Study patients(n=294)	
		Frequency	Percentage
Presence of co-morbidities	no	130	44.2
	yes	164	55.8
Co-morbidities	Hypertension	120	40.8
	Dyslipidaemia	41	13.9
	Heart Failure	35	11.9
	Others*	37	12.6
Number of co-morbidities per patient (n=164)	One	105	64.0
	Two	51	31.1
	Three and above	8	4.9
	Mean ±SD		1.41±.585
Presence of diabetic Complications	No	227	77.2
	Yes	67	22.8
Complications	Neuropathy	41	13.9
	Retinopathy	32	10.9
	Nephropathy	13	4.4
Number of complications per patient (n=67)	One	50	74.6
	Two	15	22.4
	Three	2	3.0
	Mean ±SD		1.28±.517

Others: Asthma, Gastritis, Urinary tract infections, Deep venous thrombosis, Foot Ulcer, and Cirrhosis*

5.4. The pattern of prescribed medications in patients with type 2 diabetes

Six hundred twenty-eight medications had been prescribed with the mean ± SD of 2.64±1.3 per patient. Patients on oral glucose-lowering drugs (OGLD) alone were 135 (21.5%), while those with metformin plus glibenclamide therapy were 104 (16.6%). One hundred and ten (17.5%) patients were on insulin alone of whom 87 (13.9%) were on Lente insulin therapy. Other medications were also prescribed for the co-morbidities and complications, of which, angiotensin-converting enzyme inhibitors (ACEIs) were frequently prescribed, 108 (17.2%),

followed by diuretics 50 (8.0%), satins 13 (2.8%), and aspirin, 25 (4.0%). Of all study patients, 40 (13.6%) took five and above medications per day**.** Patterns of medications prescribed are summarized in table 4.

Table 4: Prescribed medications among ambulatory patients with type 2 diabetes on follow up at DMH Addis Ababa, Ethiopia, 2020/21

Variables	Categories	Study patients (n=294)	
		Frequency	Percentage
Ant diabetic treatment regimen:	OGLD alone	135	21.5
	OGLD + Insulin	49	16.7
	Insulin alone	110	17.5
Specific antidiabetic medications	Metformin	32	5.1
	Metformin + Glibenclamide	104	16.6
	Metformin +Insulin	48	7.6
	Lente insulin (NPH)	87	13.9
	Mixtard	23	3.7
Other medications	ACEIs	108	17.2
	CCBs	39	6.2
	BBs	19	3.0
	Diuretics	50	8.0
	Antiplatelets	25	4.0
	Statins	33	5.3
	Others*	44	7.0
Number of medications per patient	One	69	23.5
	Two	72	24.5
	Three	88	29.9
	Four	25	8.5
	Five and above	40	13.6
	Mean ±SD	2.64±1.3	

*OGLD: Oral Glucose-Lowering Drugs, ACEIs: Angiotensin-Converting Enzyme Inhibitors, CCB: Calcium channel blockers BB: Beta blockers, Diuretics: (hydrochlorothiazide and furosemide)., Others *: omeprazole, amitriptyline, Ceftriaxone Spironolactone, Digoxin, tramadol, SD: standard deviation Neurobin, Salbutamol, Beclomethasone, Metronidazole, Warfarin, Ciprofloxacin, Norfloxacin, Paracetamol, Dorzolamide*

5.5. Drug therapy problems encountered and their causes

A total number of 448 DTPs were identified with a mean ± SD of 1.34±0.47 per patient. One hundred ninety-three (65.6%) patients had at least one DTP. The most commonly encountered DTPs were non-compliance, 118 (26.3%) commonly due to unavailability of drugs, 40 (8.9%), The second most common DTP was a need for additional drug therapy, 110 (24.55%), mostly 46 (10.2%) due to untreated conditions. Another commonly identified DTP was dosage too low 89(19.8%) because of sub-therapeutic dose (Table 5).

Table 5: Drug therapy problems and causes among ambulatory patients with type 2 diabetes on follow-up at DMH, Addis Ababa, Ethiopia.

Types of drug therapy Problems (n, %)	Specific causes	Study patients, N=294	
		Frequency	**Percent (%) ***
Unnecessary drug therapy (34, 7.6%)	No medical condition at that time	1	0.22
	No need for drug for that condition	15	3.3
	Duplicate therapy	15	3.3
	Non-drug therapy indicated	1	0.22
	Treating avoidable ADR	2	0.44
Needs additional drug (110, 24.55%)	Untreated condition	46	10.2
	Prophylaxis/prevention	43	9.5
	Synergistic	21	4.3
Ineffective drug (29, 6.5%)	Not effective for that condition	14	3.2
	Condition refractory to drug	10	2.2
	Inappropriate drug selection	5	1.1
Adverse drug reaction (61, 13.6%)	Unsafe drug	10	2.2
	Drug interaction	21	4.7
	Allergic reaction	18	4.0
	Contraindication	12	2.7
Low dose (89, 19.8%)	Sub therapeutic dose	89	19.9
	Over therapeutic dose	5	1.1
High dose (7, 1.65%)	Frequency inappropriate	2	0.55
	Forget the drug	20	4.5
	Not willing to take	5	1.1
Non-compliance (118, 26.3%)	Not understand instructions	13	2.8
	Cost of the drug	22	4.9
	Unavailability	40	8.9
	Can`t swallow/administer	11	2.5
	Regimen complexity	7	1.6
	Total number of patients with at least one DTP	193	65.6
	Total number of identified DTPs		448
	The average number of DTPs per patient		1.34±0.47

*****_Percentages are calculated per total number of DTPs identified (448). DTPs: drug therapy problems._

5.6. Number of drug therapy problems among the study patients

Out of 193 study patients with DTPs, the most frequently identified DTPs were two DTPs in 92 (47.7%), three DTPs in 38 (19.7%), and one DTP in 36 (18.7%) patients. Twenty-seven (14%) of patients had four and above DTPs. (**Figure 2**)

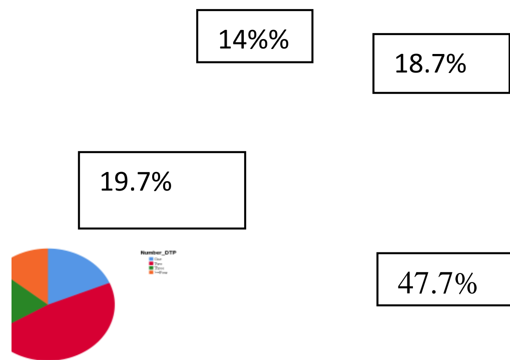

Figure 2: Number of drug therapy problems per patient among Type 2 diabetes mellitus patients attending at Diabetes clinic at DMH, Addis Ababa, Ethiopia

5.7. Drugs associated with drug-related problems

The most frequent classes of antidiabetic drugs associated with DTPs were Lente insulin (65) and metformin + glibenclamide (56). Metformin alone was the least anti-diabetic drug associated with DTP (9). Other than antidiabetic drugs, ACEIs (53), omeprazole (20) and other drugs (31) were the most commonly reported drugs for the occurrence of DTPs, followed by diuretics (49) and CCBs (35).

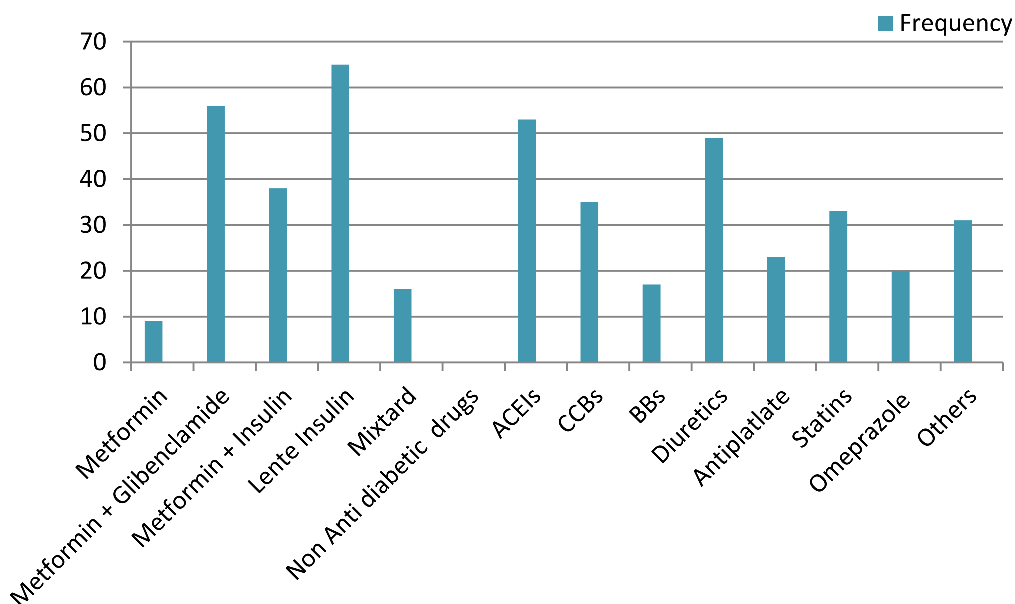

Figure 3: Drug classes associated with Drug-related problems among type 2 diabetes mellitus patients attending a Diabetes clinic at DMH, Addis Ababa, Ethiopia, 2019/20201. *ACEIs: Angiotensin-Converting Enzyme Inhibitors, CCBs: Calcium Channel Blockers, BBs: Beta Blockers; Others: Nonsteroidal Anti-Inflammatory Drugs, spironolactone, digoxin, warfarin, ceftriaxone, ciprofloxacin, Amitriptyline, neurobin, salbutamol, beclomethasone*

5.8. Factors associated with drug therapy problems

The variables that showed an association in univariate analysis (with a p-value of <0.2) were marital status, educational status, residence, medication source, employment status, glycemic control status, presence of co-morbidity, complication, physical activity and polypharmacy.

These variables were further analyzed by multivariable binary logistic regression with a P<0.05 cut of value. Therefore, in multivariate logistic regression analysis, it was found that those individuals who exercise were less likely to have DTPs (AOR= 0.18, 95% CI: 0.04, 0.74). On the other hand, patients who had a hospitalization history within one year were more than four times potential to develop DTP than patients who had no hospitalization history (AOR= 4.34, 95% CI: 1.21, 15.54). In this study, patients who had poor glycemic control status were independently associated with DTPs compared to patients who had good glycemic control status (AOR= 59.54, 95% CI: 18.85, 188.04). Patients that had co-morbidity were more than six times risky in developing DTPs (AOR= 6.70, 95% CI: 2.36, 19.00). On the other hand, study patients who had DM complication(s) were four times expected to develop DTPs than without complication (AOR= 4.06, 95% CI: 1.08, 15.24). Patients who took ≤3 drugs/day were less likely to develop DTPs compared to patients who took more than three drugs (AOR= 0.12, 95% CI: 0.02, 0.56).

Table 6: Bivariate and multivariate binary logistic regression analysis of factors associated with drug therapy problems among adult diabetic patients on follow up at Menelik Hospital, Addis Ababa, Ethiopia

Covariates	Categories (n, %)	Drug therapy problems		Odds ratio (95% C.I.)		
		Yes (n=193)	No(n=101)	Crude odds ratio	Adjusted odds ratio	p-value
Age (Years)	18-40	19 (29.7%)	45(70.3%	0.1 (0.1, 0.3)	0.7 (0.1, 3.5)	0.65
	41-60	80 (76.2%)	25(23.8%)	1.0 (0.6, 1.9)	1.6 (0.4, 5.8)	0.50
	>60	94 (75.2%)	31(24.8%)	[Reference]	[Reference]	0.36
Employment	Employed	96(56%)	75(44%)	0.3 (0.2, 0.6)	1.4 (0.4, 5.2)	0.66
	Unemployed	97(78.9%)	26(21.1%)	[Reference]	[Reference]	
Alcoholic	Yes	23(79.3%)	6(20.7%)	2.1 (0.8, 5.4)	0.410 (0.0, 5.7)	0.51
	No	170(64.1%)	95(35.9%)	[Reference]	[Reference]	
Physical activity	Yes	137 (58.5%)	97(41.5%)	0.1 (0.0, 0.3)	0.2(0.0, 0.7)	0.02
	No	56 (93.3%)	4(6.7%)	[Reference]	[Reference]	
DM duration (Years)	1 to 5	49 (50.5%)	48 (49.5%)	0.2 (0.1, 0.4)	1.1 (0.2, 5.1)	0.91
	6 to 10	70(64.8%)	38(35.2%)	0.4 (0.2, 0.8)	0.6 (0.1, 2.9)	0.56
	Above 10	74(83.1%)	15(16.9%)	[Reference]	[Reference]	0.56
Hospitalization history	Yes	53(80.3%)	13(19.7%)	2.6 (1.3, 5.0)	4.3 (1.2, 15.5)	0.02
	No	140 (61.4%)	88 (38.4%)	[Reference]	[Reference]	
Medication source	Free	97(63.8%)	55(36.2 %)	2.9(1.8, 4.8)	2 (0.8, 4.9)	0.15
	Paid	116(81.7%)	26(18.3%)	[Reference]	[Reference]	
Glycemic control	Poor	56(37%)	95(63%)	38.7 (16.0, 93.5)	59.5(18.8, 188.0)	0.000
	Good	137(95.8)	6(4.2%)	[Reference]	[Reference]	
Comorbidities	Yes	142(86.6%)	22(13.4%)	10.0(5.7, 17.7)	6.7 (2.4, 19.0)	0.000
	No	51(39.2%)	79(60.8%)	[Reference]	[Reference]	
Complication	Yes	59(88.1%)	8(11.9%)	5.1 (2.3, 11.2)	4.1 (1.1, 15.2)	0.038
	No	134(59.0%)	93(41.0%)	[Reference]	[Reference]	
Polypharmacy	No (≤3 drugs)	131(57.2%)	98(42.8%)	0.1 (0.0, 0.2)	0.1 (0.0, 0.6)	0.007
	Yes (>3 drugs)	62(95.4%)	3(4.6%)	[Reference]	[Reference]	

**Significance is for the adjusted odds ratio; C.I: confidence interval*

6. Discussion

This study aimed to assess the magnitude of DTPs in diabetic ambulatory patients and the associated factors. In this study, Cipolle`s DTPs classification system was used(Cipolle, Strand and Morley, 2021).

Drug therapy problems (DTPs) were identified based on IDF and in addition American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) guideline recommendations were used to identify DTPs (ADA, 2019)

According to the findings of this study, 65.6% of the patients had at least one DTP per patient. The main types of DTPs identified were non–compliance commonly due to unavailability of drugs, followed by needing additional drug therapy mostly due to untreated conditions. Nearly one-fifth of (19.8%) of the DTPs were sub-therapeutic-doses. Nearly half of the study patients (47.3%) were also within the intended glycemic control range (70-130 mg/dl).

The finding of the present study showed a slightly more prevalence of DTP than those of Sri Lanka studies (Mamunuwa .etal, 2016) and findings in TASH, Ethiopia (Teklemariam, 2019). The slight variation could be attributed to differences in study design (prospective), DTPs classification system (PCNE) employed, and study setup. In contrast, the findings of this study were considerably lower than those reported by two studies in Malaysia, in which more than 90% of patients had at least one DTP (Huri and Ling, 2013)(Huri and Wee, 2013). This discrepancy may be explained by differences in the type of diabetes study patients (our study patients were both type 2 diabetes only and type 2 diabetes with hypertension or dyslipidemia, while those of the Malaysian studies were only type 2 diabetes with hypertension or dyslipidemia). Thus, study patients with type 2 diabetes and hypertension and/or dyslipidemia could more likely experience DTPs.

The prevalence of DTPs in our study was also lower compared to that in a multi-center study conducted in Jordan (Alzoubi and Scott, 2017)which revealed 81.2%. This variation could be due to the difference in hospital settings where the study was conducted in five different teaching hospitals and due to the difference in sample size (1494). Similarly, this finding was also much lower than that of a study in Nigeria (Ogbonna, 2015). This difference might be due to a difference in the study setting (inpatient versus outpatient).

Moreover, the number of DTPs per patient (1.34±0.47)) was lower in the present study compared to that of other previous studies reported from Malaysia (Huri and Wee, 2013), Denmark (Haugbølle and Sørensen, 2006), Australia (Van Roozendaal and Krass, 2009), Nigeria (Ogbonna and Oparah, 2017), Ethiopia- Debre Tabor hospital (Kefale et al., 2020) and Wolaita Sodo (Koyra, Tuka, and Tufa, 2017), where the mean rate was more than 2 DTPs per patient. On the other hand, our study showed a slightly higher prevalence than the previous study done in China (Chung et al., 2017), which was 0.9±0.6 DTPs per patient, and a study done in Ethiopia (Teklemariam, 2019) which was 1.16 ±0.42 DTPs per patient. These discrepancies may be explained by differences in clinic setup and practitioners working in the field. In reality, healthcare systems vary with countries and healthcare facilities. The differences in the prevalence of DTPs observed across studies could also be explained by variation in inclusion criteria, population diversity, treatment guidelines, study period, study design, setting. and classification as well as an assessment method of DTPs. For instance, in our study, when a patient has more than one similar DTP's they were considered as one DTP; while in other studies they might have counted as more than one. This might explain why the overall magnitude of DTPs observed from the present study was lower compared to that of the previous studies.

Non-compliance (26.3%) was the most common type of DTP found in our study which was in agreement with the findings of other studies in Ethiopia (Kefale et al., 2020), India (Sajith. et al,

2014), and Nigeria (Ogbonna, 2015); while it was higher than that of other studies conducted in Uganda (Bagonza, Rutebemberwa, and Bazeyo, 2015) and Ethiopia. (Teklemariam, 2019). The difference in the rate of non-compliance might be explained by the difference in types of diabetes and co-morbid conditions, tools used (MMAS-4 versus 8 items), participant diversity, and sample size. Self-reported medication adherence might be different from facility-reported adherence as it could be overestimated or underestimated leading to bias. Another study conducted in the USA (Ettaro et al., 2004) identified a big economic burden associated with the non-compliance of patients.

Need additional drug therapy was the second most prevalent finding in the current study, which accounted for 24.55% of case problems mainly due to the presence of the untreated condition and lack of preventive drug therapy. This finding was in line with studies conducted in Sri Lanka (Mamunuwa. *et al*,2016) and in Ethiopia (Kefale *et al.*, 2020) (Teklemariam, 2019). The finding was, however, higher compared to those reported by other authors (Alzoubi and Scott, 2017)(Ogbonna, 2015). This discrepancy in prevalence might be due to differences in socioeconomic status, availability of medication in the country, and also this difference might be due to small sample size, and differences in health care practices.

Dosage too low was another prevalent DTPs (19.8%) among patients of this study. These data were similar to those of studies conducted in Ethiopia (Kefale *et al.*, 2020), which reported mainly due to too low a dose to produce the desired effect of 11.6%. In this study, the result for too low dose was more prevalent compared to those in other studies previously conducted in Nigeria 8.0% (Ogbonna, 2015), Ethiopia 15.8% (Yimama, Jarso, and Desse, 2018). This difference might be due to variation in sample size or lack of institutional guidelines and also patients might have resisted buying as they could not afford beyond. The prevalence in this study was, however, less compared to the one reported from china 23.3%(Chung *et al.*, 2017), and two

sites in Ethiopia at TASH 22.7% (Teklemariam, 2019) and woliata 26.7%(Koyra, Tuka, and Tufa, 2017). This variation could be because of the use of different DTPs classification systems, study design, and sample size.

Adverse drug reaction 13.6% was the fourth identified DTP in this study mainly due to drug interactions and allergic reactions. this result is in line with that of another study conducted in china 15.6% (Chung *et al.*, 2017). However, it was more prevalent than two of the studies conducted in Ethiopia 4.9% (Koyra, Tuka and Tufa, 2017;) and 5.8% (Teklemariam, 2019). This may be due to differences in study setup, study patients, and sample size; and the prevalence was less than that of a study done in the UK (45.2%) and Saudi Arabia (20.4%) (Al Hamid *et al.*, 2016). The variations in prevalence could be due to differences in study patients. Hospitalized patients with diabetes and CVDs are more susceptible to multiple drugs.

Unnecessary drug therapy 7.6**%**, Ineffective drug 6.5% and dose too high 1.65% were also identified in the current study, which was less prevalent compared to in other studies in Nigeria (Ogbonna, 2015; Shareef, Fernandes & Samaga, 2016) and in Ethiopia (Teklemariam, 2019); (Yimama, Jarso, and Desse, 2018) (Kefale and Degu, 2020). Apart from that, a study conducted in Ethiopia (Kefale and Degu, 2020) revealed that unnecessary drug therapy and dose too high were the most prevalent types of DTPs and another study in Malaysia (Huri and Ling, 2013); revealed that drug-drug interactions and unnecessary drug therapy were the most prevalent type of DTPs. This variation could be due to study patients and study setting differences. The way of assessing DTP might also have contributed to this gap. Thus, the current finding of unnecessary drug therapy, Ineffective drug, and dosage too high types of DTPs was lower in comparison to those in other previous studies reported in the literature.

The results obtained from multivariate logistic regression analysis indicated that differences between patients due to factors independently associated with the occurrence of DTPs. The

associated factors for certain groups of patients; not doing physical activity, patients with a history of hospitalization, patients with poor glycemic control, presence of co-morbidity, patients with diabetes complication(s), and polypharmacy (>3) increased the odds for developing DTPs.

These findings are in agreement with those of previous studies conducted in Malaysia which identified polypharmacy and comorbidity as risk factors for DTPs (Huri and Wee, 2013), and Nigeria which identified polypharmacy as a major factor that contributed to DTP (Ogbonna, 2015). And also in line with a study conducted in Ethiopia (Koyra, Tuka, and Tufa, 2017) and Turkey (Abunahlah et al., 2018) which identified comorbidity, polypharmacy, hospitalization history, and age as the most common factors for developing factors. even though age was not a factor in the current study.

Likewise, hospitalized patients had also the chance to get multiple drug therapies for their co-morbidities and complications that led them to be hospitalized (ADA, 2019)(Fowler, 2011).

A study done in the USA (Iglay et al., 2016) identified co-morbidities and diabetes complications as factors that make difficult patient management. A study conducted in sub-Saharan Africans (Ekoru et al., 2019) identified the burden of co-morbidities and diabetes complications as substantial highlighting the urgent need for innovative public health strategies that prioritize the promotion of healthy lifestyles for prevention and early detection of T2DM. A previous study reported that glycemic regulation was established as a major factor in the treatment of patients with type 2 diabetes and a cause of non-compliance (Inzucchi et al., 2015).

On the other hand, several co-morbidities per patient (≥3) was associated with a higher risk of developing at least one DTPs, which was similar to studies conducted in the UK and Saudi Arabia(Al Hamid et al., 2016) and Wolaita Sodo, Ethiopia (Koyra, Tuka, and Tufa, 2017). This could explain that patients with more co-morbidity are more likely to use multiple medications.

Thus, patients could be reluctant to take their medication appropriately due to the increasing non-compliance rate to their medications and linked with regimen complexity. In addition, the risk of ADR could be raised in patients with more co-morbidities.

6.1. Limitations of study

- The cross-sectional nature of the study did not allow follow-up.
- ADRs were considered based on patients' responses and/or from medical records without the establishment of a causal relationship.
- Studies with different designs, study populations, study settings and non-comparable sample sizes were used for comparison in the discussion section
- The result of the study may not be generalizable to all hospitals for this study was a single-centred study conducted in a referral hospital.
- Glycaemic control could be underestimated or overestimated, given that FBG measures were used. But the effort was made to minimize this issue by taking the mean average of the last four consecutive visits of FBG measurement values. But this might also be affected by extreme measurement values.
- Some variables which might have an interaction with the dependent variable might have affected the outcome. For instance, the high level of DTP risk among patients with poor glycaemic control status might be due to the co-relation of DTP and glycaemic control.

7. Conclusion

The magnitude of DTPs identified in patients with type 2 diabetes was considerably high. The most commonly identified DTPs were non-compliance, need additional drug therapy, and dosage too low. Nearly one-fourth of the patients of this study were non-compliant with their diabetic medications. The majority of DTPs occurred due to drug unavailability, presence of untreated conditions, and use of sub-therapeutic doses. The present study also found that more than half (52.0%) of the participants had unmet the intended glucose target and very significantly associated with developing DTPsFactors independently associated with developing DTPs were; physical inactivity, history of hospitalization, poor glycemic control, co-morbidities, diabetes complication(s), and polypharmacy (>3).

8. Recommendations

Based on the findings of this study, the following recommendations are given:

Federal Ministry of Health

- Strengthening the clinical Pharmacy service might help to optimize medication use in such settings.
- Developing/updating local treatment guidelines might help to decrease the high level of DTP among the T2DM patients in such settings.

Dagmawi Menelik Referral Hospital

- ➢ The hospital should better augment the multidisciplinary care system such as by employing clinical pharmacy staffs to decrease such high level of DTP in the hospital.
- ➢ Since medication non-adherence due to medication unavailability and cost are major contributes for the high DTP, maintaining the accessibility and availability of affordable medicines in a hospital may help.

Future studies should better focus on advanced study designs such as prospective or interventional studies might be considered to see better describe and understand the magnitude of the problem.

Clinical Pharmacists

- ✓ Early identification and resolution of DTPs may be vital in minimizing DTPs and maximizing the quality of the service given.

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Annexes

Questionnaire

Dear all

First of all, thank you for your willingness to answer this questionnaire. My name is Asmamaw Yenesew from the School of pharmacy, department of pharmacology, and clinical pharmacy. Currently, I am Doing MSc thesis entitled **Drug therapy problems and contributing factors 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 the diabetes clinic of Dagimawi Menelik hospital.

Signature-----------------------

Name of Principal Investigator **Asmamaw Yenesew** **Signature-------------------------**

For more Information Contact with the cell phone: **0920236931**

Part I: Patient's Socio-demographic information

<table>
<tr><th colspan="6">Socio-Demographic Characteristics:</th></tr>
<tr><td>1. Age(in a year):</td><td colspan="5">___________________________</td></tr>
<tr><td>2. Sex</td><td colspan="2">Male ☐</td><td colspan="2">Female ☐</td><td>Pregnant: Yes ☐ No ☐</td></tr>
<tr><td>3. Marital status:</td><td colspan="2">Single ☐</td><td colspan="2">Married ☐</td><td>Divorced ☐ Widowed ☐</td></tr>
<tr><td>4.Religion</td><td colspan="2">1. Orthodox ☐</td><td colspan="2">2. Muslim ☐</td><td>3. Protestant ☐ 4.Others___________</td></tr>
<tr><td>5. Educational status</td><td colspan="2">no formal education
Grade 1-8 ☐</td><td colspan="2">Grade 9-10 ☐
Grade 10-12 ☐</td><td>College diploma ☐
University degree and above ☐</td></tr>
<tr><td>6. Place of Residence</td><td colspan="5">Urban(AddisAbaba) Rural) our of AddisAbaba)</td></tr>
<tr><td>7. Occupation</td><td colspan="5">Government ☐ Retired ☐ Nojob(houswife) ☐
Privateoffice ☐ Self-Employed (farmer, dailylaborer) ☐</td></tr>
<tr><td>Monthly income</td><td colspan="5">________ETB</td></tr>
<tr><td colspan="3">Cigarette Smoker</td><td colspan="2">Yes ☐ No ☐</td><td>Ex-smoker/ former smoker ☐</td></tr>
<tr><td colspan="3">Alcohol user</td><td colspan="2">Yes ☐ No ☐</td><td>Ex-drinker/former drinker ☐</td></tr>
<tr><td rowspan="2">11.Physical Activity</td><td>Walk</td><td>Yes ☐</td><td colspan="2">No ☐ , if yes, for howlong?</td><td><30minutes/day >30minutes/day</td></tr>
<tr><td>Sport ☐</td><td>Yes ☐</td><td colspan="2">No ☐ if yes, for how long?</td><td>Daily ☐ 1-3d/week ☐ 4-6d /week ☐</td></tr>
<tr><th colspan="6">II. Clinical characteristics(supplementary to the information obtained from medical record chart):</th></tr>
<tr><td colspan="2">1.Duration of diabetes</td><td colspan="4">_________________Years. 2. Durationoftreatment_____________years.</td></tr>
<tr><td colspan="2">3.Hospitalization due to diabetes</td><td>Yes ☐</td><td>No ☐</td><td colspan="2">If, is yesduetoHypoglycemia ☐
others,specify_</td></tr>
<tr><td colspan="2">4.Traditional/herbal medicine use/OTC</td><td colspan="4">No ☐ Yes ☐, If yeslistthem______________________________
__________and for whatpurpose______________________________</td></tr>
<tr><td colspan="2">5.Use of Home SMBG</td><td colspan="4">No ☐ Yes ☐,</td></tr>
<tr><td colspan="2">6.Source of medication</td><td colspan="4">Forfree ☐ Paid ☐</td></tr>
</table>

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 last1year? ☐Yes☐ ☐No:☐

If yes, describe the manifestation of the events______________________________

2. If your answer is –yes‖forquestion number-1, answer the following questions:

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

□Yes □No □ Don‘tknow

2.2. Did the adverse reaction improve when the drug was discontinued or a specific antagonist/antidote was administered? □Yes □No □ Don‘tknow

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

□Yes □No □ Don‘tknow

2.4. Are there alternative causes (other than the drug) that could have on their own caused the reaction? □Yes: □No □ Don‘tknow

2.5. Was the reaction more severe when the dose was increased or less severe when the dose was decreased? □Yes: □ No □ Don‘tknow

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

□Yes: □ No: □ Don‘tknow

Part IV: DTPS (Non-compliance) reported by the patients

A. Do you have trouble in a swallow or administer your medicine? Yes No

B. Do you have trouble understanding or remembering how to take your medicine?

Yes No

C. Do you sometimes stop taking your medicine by yourself? Yes No

If yes, what is your reason lead to stop taking medicine?

____

______

D. Does the cost of medicine make it hard for you to take as prescribed?

Yes ☐ No ☐

E. Does the availability of a patient's medicine make it hard for you to take it as prescribed?

Yes ☐ No☐

F. Do you sometimes forget taking his/her medicine? Yes ☐ No ☐

G. Do you experience any undesirable effect when you taking your medication? Yes ☐ no ☐

If yes please select, Name of medicine-____________________

1. **Headache 2. Forgetfulness 3. Weight gain 4. Blurred vision**

5. Weakness 6. Hypersomnia 7. Confusion 8. Epigastric pain

11. Skin rash 12. Irritability, 13. Cough, 14. Falling, 15. Itching (skin rash) 16. Depression

17.Others._______________________________________

Part V:Dataabstraction format [Patients' medicalrecord chart review]

CardNumber________________UniqueID/Code:______Age(inyear)________________________

Weight(kg)_________________Height (cm)_________Body mass index(BMI)[kg/m2]__________

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

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/SGT					
	AST/SGPT					
	ALP					
	BUN					
	Srcr					
	eGFR					

Others:

1. 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	$Visit_3$	$Visit_2$	$Visit_1$	

2. Adverse DrugEvents(documented):

Drug Regimen	Adverse drug reaction /Drug allergies /Otheralerts	Event date

3. Past medical and medication history (hospitalizations, surgical procedures, injuries, pregnancies).___________________

Based on the most recent glucose level(FBS/RBS orA1c):

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

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 for drug for that condition Duplicate therapy Non-drug therapy indicated Treating avoidable ADR Addictive or Recreational drugs
	2. Needs additional drug therapy	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	□ The undesirable effect, not dose-related
		□ Unsafe drug for a 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
		□ The patient forgets to take the drug
		□ Direction is not understood
		□ The patient cannot swallow/administer

 Cost of medication too expensive
 Unavailability of medication
 Disbelieves in the drug effectiveness
 The patient felt better or worse
 Fear of adverse events
 Regimen complexity

ሀ. የታካሚዎች ማህበረሰባዊ ባህርያቶች መረጃ መሰብሰብያ ቅጽ
[በተዘጋጀሆት ሳጥን የ√ ምልክት ያድርጉ]   ካርድ
ቁ__________________________

በመጀመሪያ በምኒልክ ሆስፒታል ውስጥ የሁለተኛው ዓይነት የስኳር ታካሚ ሁነው መድኃኒት ከጀመሩ አንድ ዓመትና ከዚያ በላይ ወር በሊይ መሆናቸው ያረጋግጡ

1.እዴሜ፧ __________   2.ፆታ፧   ወንዶ☐   ሴት☐   እርጉዝ: አ☐ አይደ☐ም

3.የጋብቻ ሁኔታ፧   ያሊገባ/ች ☐   ያገባ/ች ☐   አግብቶ/ታ የፈታ☐   ሚስቱ/በሎ ☐   የሞተችበት/ባት

4. እምነት   ኦርቶድክስ☐   ሙስሊም☐   ፐሮቴስታንት☐   ሌሎች☐

5.የትምህርት ሁኔታ፧   መጻፍና ማንበብ ይችላል☐   ሁለተኛ ደረጃ (9ኛ-12ኛ)☐   አንደኛ ደረጃ (1ኛ-8ኛ) ☐   ኮላጅ ዲፕሎማና ከዛ በሊይ☐

6.አሁን የሚኖሩበት   ከተማ[አ . አ]☐   ገጠር [ከ አ . አ ውጭ) ☐

7. የሥራ ሁኔታ፧   ገቢ ያለው/ላት☐   ገቢ የሌለው/ሌላት ☐

8. ሲጋራ ያጨሳሉ?   አዎ አጨሳለሁ☐   አላጨስም☐

9. መጠጥ(አልኮል) ይጠጣሉ?   አዎ እጠጣለሁ   አልጠጣም☐

10 እንቅስቃሴ ያደርጋሉ   አዎ☐   አላደርግም☐

11. መልስዎ አዎ ከሆነ   በየጊዜው/በመደብኘነት ☐   መደበኛ ያልሆነ☐

12.ከስኳር ጋር የቆዩበት ዘመን--

13.በስኳር በሽታዎት ምክንያት ሆስፒታል ተኝተው ያውቃለ?   አዎ☐   አላውቅም☐

14.መልስዎት አዎ ከሆነ ምክንያትዎ   የደም ስኳር መጨመር☐   ማነስ ☐

15. የባህልመድኃኒት ይወስዲሉ   አዎ☐   አልወስድም ☐

16. የመድኃኒትዎ ምንጭ   በነፃ ☐   በገንዘብ☐

20. በቤትዎ የሱኳር (Glucometere) መሳርያ ይጠቀማለ?   አዎ ☐   አይደለም/የለኝም☐

መድሀኒት አወሳሰድን በተመለከተ

1.መድሀኒትዎን ለመዋጥ ወይም ለመጠቀም ተቸግረው ያውቃሉ ? አዎ ☐ የለም ☐

2.የመድሀኒትዎን አወሳሰድ ባለማስታወስዎ ምክንያት መድሀኒት ሳይወስዱ ቀርተው ያውቃሉ ?.

አዎ ☐ የለም ☐

3. የመድሀኒት ዋጋ ውድ በመሆኑ ምክንያት ሳይወስዱ ቀርተቀው ያውቃሉ? አዎ☐ የለም☐

4. መድሀኒት ገበያ ላይ ባለመገኘቱ ምክንያት አቋርጠው ያውቃሉ ? አዎ☐ የለም ☐

5. መድሀኒትዎን ረስተው ሳይወስዱ ቀርተው ያውቃሉ? አዎ ☐ የለም ☐

6. መድሀኒትዎን በራስዎ ምክንያት ሳይወስዱ ቀርተው ያውቃሉ? አዎ☐ የለም ☐

7.ለተራ ቁጥር 6 መልስዎ አዎ ከሆነ በምን ምክንያት---

8. መድሀኒትዎን በሚወስዱበት ጊዜ የጎንዮሽ ጉዳት አጋጥምዎት ያውቃሉ?. አዎ ☐ የለም ☐

9. ለተራ ቁጥር 8 መልስዎ አዎ ከሆነ ምን ------------------------------

ሀ. የራስ ምታት ለ. መርሳት ሳል ሐ. የቆዳ ሽፍታ መ. እንቅልፍ ማጣት

ሠ. የጨጓራ ማቃጠል ረ. ማሳከክ ሰ. በድብርት መውደቅ

ሸ. ክብደት መጨመር ቀ. ሌላም ካለ

10.በጎንዮሽ ምክንያት መድሀኒት አቋርጠው ያውቃሉ? አዎ ☐ የለም ☐

አዲስ አበባ ከተማ አስተዳደር ጤና ቢሮ
City Government of Addis Ababa Health Bureau

Ref.No. [handwritten, illegible]
Date 12/11/2017

TO:

- **Menilik II Referral Hospital**

Addis Ababa

Subject: Request to access Health Facilities to conduct approved research

The letter is to support **Asmamaw Yenesew** to conduct research, which is entitled as **"Assessment of Medication Related Problems and Contributing Factors Among Ambulatory Patients with Type 2 Diabetes Mellites Minilek Hospital, Addis Ababa, Ethiopia."** The study proposal was duly reviewed and approved by Addis Ababa Health Bureau IRB, and the principal investigator is informed with a copy of this letter to report any changes in the study procedures and submit an activity progress report to the Ethical Committee as required. Therefore we request the Health facility and staffs to provide support to the principal investigator.

With Regards

Dr. Yohannes W/kidan

Ethical Clearance Committee

Cc

- **Asmamaw Yenesew**
- **To Ethical Clearance Committee**

Addis Ababa