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Patients Misunderstanding of Dosage Instructions among Patients Attending Kenema Pharmacy: Do Pharmacists Ask 'Tell me so I know you understand?'

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Abstract
Background: Despite the advance in drug development and availability of dozens of drugs in the healthcare system today, knowledge of patients about dispensed medicines is poor to the extent suppositories are being swallowed by patients. The size of commonly used paper envelopes for labeling in Ethiopia doesn't even allow writing the required drug information on it. **Methods**: Direct observation supported cross-sectional study was conducted to assess the extent of patients' misunderstanding of dosage instructions and associated factors among patients attending Kenema Pharmacy Number 09 at Addis Ababa by using a pre-specified structured interview questionnaire.**Result**: A total of 398 patients were included in the study and 62.81% were female. Around 34.42% of respondents were found to be in the age range of 25 to 34 years. Two hundred eighty-eight (72.36%) of participants misunderstood one or more dosage regimen instructions, and 269(67.59%) misunderstood the frequency of drug administration. The most commonly misunderstood medications were antibiotics. Moreover, from medication label observations, 273 (68.25%) were dispensed without a medication label. Patient misunderstanding of dosage instructions was significantly associated ($p< 0.001$) with age, residence, and educational level. **Conclusion**: A significant number of patients misunderstood dosage regimen instructions. The majority of drugs were dispensed without label information and pharmacists did not practice the 'tell me back if you know, principle to ensure understanding of communicated information. Age, educational status, sex, and residence of patients were significantly associated with patient misunderstanding of dosage instructions. Therefore, pharmacy professionals should appropriately label, and effectively communicate to ensure patient understanding of the dosage instructions for the patient before dispensing. Future studies involving multiple sectors should be done to identify the ranges of associated factors with patients' misunderstanding of dosage instructions and patient–dispenser communication optimization.
Keywords: Misunderstanding; Dispensed drug labeling; Dosage instruction; Pharmacy-patient communication; Kenema Pharmacy
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1. Background

The appropriate uses of medications through the rational prescription and dispensing, and rational use of dispensed drugs by patients has been taken as the basis for medication therapy. The patient's knowledge of appropriate medication use should be inclusive of the name and purposes of the medication use, the dose, frequency of dosing, and duration of treatment (1, 2). The good dispensing practices which guarantee the correct medications are delivered to the right patients at the right time with required dosage and amounts along with clear instructions and a package that maintains an acceptable standard and quality of drug always plays a central role in the provision of the rational drug therapy (3, 4). An institution-based cross-sectional study conducted to Assess patient's misunderstanding of dosing instructions among outpatients in Dessie Referral Hospital showed that 298 (77.6%) misunderstood more than one dosage instruction, 8.75% misunderstood the dose, 51.3% misunderstood the frequency while 58.6% misunderstood the duration of treatment (5). A systematic review conducted to generate evidence on the prevalence and nature of medication administration errors in healthcare settings involving 91 studies showed that the median error rate was 19.6% of total opportunities for error (6).

A cross-sectional study conducted to evaluate patients' ability to read and understand dosing instructions of their medicines in a community pharmacy setting showed that only a few dispensing labels had the route of administration and the duration of treatment written on them (7). Another study conducted to evaluate the potential and limitations of written drug information showed that oversight and standards are needed so that written drug information can serve as a coherent and organized system to educate patients (8). A cross-sectional study conducted to evaluate dispensed medications labeling patterns and patient knowledge at a tertiary in Southwest Ethiopia showed that labeling of dispensed drugs was the main problem identified (9). Drug information depicted on labels and inserts balances the risks and benefits of drugs and becomes a major source of knowledge for patients.

Failure to follow dosage instructions on labels and inserts could lead to undesired outcomes (10). Counseling and appropriate labeling of each prescribed drug have an important role to make sure that the patients have appropriate information about the use of prescribed drugs (11-13).

Counseling regarding the use of medication should involve both oral and written information (3, 4, 8). Patients' non-compliance that might be due to confusion in medication names and sounds have a lion share of out-patient medications errors. Different studies indicated that patients misunderstood one or more dosage instructions like frequency of dose administration, name, and dose of drugs, duration of treatment, and the precaution of the drugs (8). Among common prescription drugs, nearly half of patients were unable to understand one or more of the label instructions, in Botswana (4). A cross-sectional study conducted in three clinics of America among 395 outpatients showed that 46.3% of patients misunderstood one or more dosage instructions (14).

The focus on health-care delivery continues to shift from inpatient care of patients to managing them on an outpatient basis. In this scenario, the practice of quality control over medication use is becoming more the responsibility of the patient and less the responsibility of the provider. Previous studies have found that many patients are not receiving oral or written instructions from their physicians and pharmacists on how to appropriately deal with prescription medications. The research has established, and it is well accepted that an adequate level of knowledge regarding prescribed medications is associated with an increased level of compliance with drug therapy; consequently, failure to comply with medication instructions commonly leads to serious adverse outcomes (14, 15). The institute of medicine estimates that 90 million adults in the United States may have trouble understanding and acting on health information. In providing drug information, pharmacists less often discuss how the medication should be taken. It is also important to provide information to patients on when to take their medications with food intake (16-18). Every day patients are admitted to the hospital due to complications arising from misuse of prescription drugs. As noted by Terry Davis, Professor of Medicine at Louisiana State University, misunderstanding labels may be an unrecognized contributor to the estimated 2% to 11% of hospital admissions in the United States caused by misuse of prescription medications (17).

Despite the advance in drug development and availability of dozens of drugs in the healthcare system today, knowledge of patients about dispensed medicines is poor to the extent suppositories are swallowed by patients (4). Misunderstanding of dosing instruction is the major problem resulting in adverse drug reactions, drug resistance, drug abuse, and misuse in the case of narcotic and psychotropic drugs. The size of commonly used paper envelopes for labeling in Ethiopia doesn't even allow writing the required drug information on it; making them hard to read, especially for geriatric patients (10, 11). Currently, there is no system for verifying the understanding of medications after providing prescriptions by the clinician and dispensing of the prescribed medications by the pharmacist in Ethiopia. The matter of whether the patient has understood the instructions for medication use and can manage the medications independently at home remains unsolved (18, 19). Misunderstandings of dosage instructions and poor labeling lead to incorrect medication, resulting in many consequences like drug interactions, drug resistance, healthcare cost, and even death. The size of commonly used paper envelopes for labeling in Ethiopia doesn't even allow writing the required drug information on it. Therefore, this direct observation supported cross-sectional study was conducted to assess the extent of patients' misunderstanding of dosage instructions and associated factors among patients attending Kenema Pharmacy Number 09 at Addis Ababa, from October 26- November 26, 2020, by using a pre-specified structured interview questionnaire.

2. Methods

2.1 Study Area and Period

The study was conducted in Kenema Pharmacy Number 09 in Yeka Sub-city, Woreda 11, and Addis Ababa, Ethiopia from October 26-November 26, 2020. The Kenema Pharmacy Number 09 is located in the Yeka Sub-city of Addis Ababa, the capital city of Ethiopia. It serves as the outpatient public pharmacy for more than 13,000 people on an annual basis.

2.2. Study Design

Direct observation supported cross-sectional study was conducted. Descriptive research aims to present a complete description of a subject within its context. Descriptive researches are often used when an amount of knowledge about the subject already exists, this knowledge was then be used to categorize into models and frameworks. Consequently, the approach with in-depth interviews, document review and the use of questionnaires as data collection techniques are very useful in the study of the major constructs. Hence, a descriptive cross-sectional study design was carried out.

2.3 Population

All patients attending the Kenema Pharmacy number 09 of Addis Ababa City Administration were the source population. All patients of selected Kenema Pharmacy number 09 in the City administration during the data collection time were the study population.

2.4 Sample Size Determination and Sampling Technique

2.4.1 Sample Size Determination

The sample size was determined by using a single population proportion formula ($n=\frac{(Z\alpha/2)^2)\,p(1-p)}{d^2}$) with the following assumptions: since there is no local data for the value of p, the prevalence of 50% is taken. "d" is the expected margin of error (5%), Z, the standard score corresponding to a 95% confidence interval and α, the risk of rejecting the null hypothesis (0.05) and 10% non-response rate. Therefore, the total sample size was 423.

2.4.2 Sampling Technique

To reach the study unit systematic sampling technique was used. The sampling interval was determined by dividing the total number of patients who visited the Kenema Pharmacy Number 09 in Yeka Subcity, Woreda 11, at Addis Ababa, Ethiopia the last one year(approximately N=13,000 and calculating to one Month data collection period) to the allocated sample size (N/n) which was 3. The first patient was selected randomly.

2.5. Variables

2.5.1. Dependent Variables

[10] Misunderstanding of dosage instruction

2.5.2. Independent variables

[11] Socio-demographic characteristics (age, sex, job status, residency, marital status educational status, religion)

2.6 Data Collection Tools, Techniques and Quality Control

Data were collected by using pretested, a structured questionnaire which consists of socio-demographic information, patient misunderstanding of dosage, and adverse drug outcomes questions, by reviewing related literature in the English version. A pre-test was done on 5% of a sample size of selected Kenema before actual data collection. Data were collected by trained three pharmacists and one supervisor after being briefed on the purpose of the study and on how to fill adequate information on the questionnaire.

2.7. Data Management and Analysis

The collected data was first checked manually for completeness, missed values, unlikely responses and then coded, entered using Microsoft Excel 2013 Sheets. Then, it was cleaned and analyzed using SPSS version 25. Descriptive statistics were computed to determine frequencies and summary statistics (mean, standard deviation, and percentage) to describe the study population about socio-demographic and other relevant variables. The factors associated with patient misunderstanding of dosage instruction was determined chi-square test (X^2-test). Results were presented by using tables, graphs, and figures.

3. Results

3.1 Socio-demographic characteristics of patients attending Kenema Pharmacy

A total of 398 participants responded to the administered questionnaire with a 94.09% response rate. Of the total respondents, 158(39.71%) of them were Oromo in ethnicity followed by Amhara 105(26.40%), Gurage 40(10.05%), and others 95(23.87%). Regarding respondents' religion, Muslims were 103(25.88%), Orthodox were 95(23.87%), Protestant were 72(18.09%), and Catholics 68 (17.09%). Two hundred fifty (62.8%) of the respondents were females, about 150 (37.69%) were from grades 7-12 and about 137 (34.42%) of the patients were in the age range of 25 to 34 years (Table 1).

3.2. Misunderstanding of dosage instructions

Concerning dosage instruction information provided during dispensing, Majority 352 (88.4%), 253 (63.57%), and 292 (73.37%) received counseling in local languages about dosage instructions, adverse drug reactions, and drug interactions respectively. On the other hand, only 6 (1.51%) of patients received written drug information other than information on dispensing bags, and 18 (4.52%) were asked by the dispensing pharmacist to tell dosage instruction back to ensure understanding of information communicated. Regarding the misunderstandings of the 398 study participants, 288 (72.36%) patients misunderstood one or more dosage regimen instructions and 269(67.59%) misunderstood the frequency of drug administration. One hundred seventy (42.71%) patients misunderstood the duration of treatment and 62 (15.58%) misunderstood the dose of the drug to be administered (Table 2).

During direct observation of medication packages for medication labeling, 270 (67.84%) of patients' medications were dispensed without any label and only 128 (32.16%) were labeled. From a total of 702 dispensed drugs, 501 (71.36%) drugs were misunderstood by study participants. From these, the majority accounted for misunderstanding of frequency of drug administration 269 (53.69%), and the least was a misunderstanding of the

dose of drug therapy 62 (12.37%). Concerning medications commonly misunderstood, among antibiotics prescriptions 25 (40.32%), 125 (46.47%), and 80 (47.06%) dose, frequency and duration were misunderstood respectively. Similarly, among Non-steroidal anti-inflammatory drugs 7 (11.29%), 22 (8.18%), and 16 (9.41%) dose, frequency and duration were misunderstood respectively. Followed by drugs acting on the gastrointestinal tract 5 (8.06%), 30 (11.15%), and 14 (8.24%) dose, frequency, and duration misunderstood respectively (Table 3 and Figure 1).

Concerning factors associated with medication dosage instruction misunderstanding, 23 (37.17%), 34(54.84%), and 52 (83.87%) of patients who misunderstood dosage regimen instructions were in the age range of 45-54 years, females, and those who cannot read and write, respectively. From the patients characteristics educational status had great extent of association with misunderstanding of dose(X^2=267.599, P= 0.000), misunderstanding of frequency (X^2= 112.839, P= 0.000), and duration of treatment (X^2= 176.852, P= 0.000) and sex characteristics has no relation with misunderstanding of dose (X^2 = 2.000, P=0.157) which shows p-value >0.05. This study also revealed that misunderstanding of dosage instruction is higher for those medications which were dispensed without any label (Table 4).

4. Discussion

4.1. General description of the study

The present study described the level of patient misunderstanding of dosage instruction (i.e. patients misunderstood one or more dosage instructions such as frequency of dose administration, name, and dose of drugs, duration of treatment, and the precaution of the drugs) to dispensed drugs in the Kenema Pharmacy Number 09 of Yeka Sub-city, Woreda 11, Addis Ababa, Ethiopia was assessed. Types of medication administration errors include wrong time medication, wrong route medication, wrong dose medication, medication to the wrong patient, wrong medication, and wrong documentation (20, 21).

In this study, the majority of respondents, 67.84%, received the prescribed medication from the dispensary without any medication label written in the appropriate local language. Almost all medications were packed in blisters, strips, bottles, and tubes which were dispensed for the patients without labels, and the drug information was given only verbally. During direct observation of the label, dosing instructions labeled on the container were not enough, simply, morning, evening, etc. rather than the exact time intervals and duration of treatment. This is in line with evidence from a study conducted to assess patients' misunderstanding of Dosage regimen Instructions among adolescent and adult outpatients in Ethiopia showed that 273 (68.25%) of medications were dispensed without a medication label (22). Studies documented that patient misunderstanding can be minimized through additional efforts by healthcare professionals by improving the clarity and comprehensibility of labeling on prescription drugs (14, 19). Communication between pharmacists and patients regarding the use of medication should involve both oral and written information (3, 8, 23). Poor labeling of prescription drugs and patient non-noncompliance to prescribed medicines is major reason for outpatient medication errors and adverse events (2-4)(10, 11). A systematic review conducted to evaluate the impact of textual elements on the comprehensibility of drug label instructions (DLIs) showed that using clear labels about dosage instructions sing plain language can improve patient understanding of dosage instructions (24).

On the other hand, only 18 (4.52%) of participants were asked by the dispensing pharmacist to tell dosage instructions back to ensure understanding of information communicated. This could contribute to a large number of medication dosage instruction misunderstandings in this study. A study conducted to describe the effect of "Tell me so I know you understand" on Pharmacists' verification of patients' comprehension of antiretroviral dosage instructions showed that asking 'tell me so I know you understand' is an effective strategy to address patient misunderstanding by pharmacists (25).

In this study, 72.36% of patients misunderstood one or more dosage regimen instructions given by pharmacy professionals. This is supported by evidence from a study conducted to assess patients' misunderstanding of dosage instructions among adolescent and adult outpatients in Ethiopia showed that 293 (73.3%) of the study participants misunderstood one or more dosage regimen instructions (22). However, this is significantly higher when compared to a study done in the USA, where 46.3% of patients had misunderstood one or more dosing instructions (14). The difference might be due to differences in medication counseling policy between these two countries as well as might be due to differences in the health literacy status of the study populations. The other possible explanation might be the long waiting time spent at health facilities, which could lead to decreased attention to medication counseling provided by pharmacy professionals that can ultimately lead them to misunderstand the instructions (15).

In this study, 67.59% of respondents misunderstood the frequency of drug administration. This is supported by evidence from a study conducted to assess patients' misunderstanding of Dosage regimen instructions among adolescent and adult outpatients in Ethiopia showed that 264 (66%) of patients misunderstood the frequency of administration (22). However, this is lower than a study done in the USA which revealed that 79% of patients

reported taking all three times daily doses within twelve hours (23). This may be due to the reason that the American study was done only on medications prescribed three times in frequency of drug administration, but the present study included all on needed prescription, two times, three times, and four times per day. In addition, 15.58% of patients misunderstood the dose of dispensed medications. In this study also, from 61 patients who cannot read and write, close to 84% misunderstood dose instructions. Similarly, a study conducted in the USA, showed that 65.3% of patients with low literacy could not demonstrate the number of pills to be taken daily (14).

Regarding the rate of misunderstanding of the duration of treatment, it was found that close to 43% of the respondents misunderstood the instruction given. This result is almost similar to a cross-sectional study conducted in Jimma, Ethiopia on assessment of knowledge and practice on the appropriate use of drugs in the rural and urban community. In the above-mentioned study, it was found that 39.9% of patients discontinued taking the drug when the symptoms of disease disappeared (17, 26). Pharmacy professionals can help patients to avoid medication misuse and latent errors at home by providing them with adequate information on medication safety (23). Pharmacy professionals should confirm patients understanding through the "teach-me back" method, in which patients are asked to repeat instructions to demonstrate their understanding, especially for those vulnerable groups of the population, like patients with low health literacy (18). There should also be a mechanism that addresses the legal requirement for medication labeling by dispensers in the local language for patients to refer at home in case of confusion.

4.2. Drugs commonly misunderstood

Concerning medications commonly misunderstood, among antibiotics prescriptions 25 (40.32%), 125 (46.47%), and 80 (47.06%) dose, frequency and duration were misunderstood respectively. Similarly, among Non-steroidal anti-inflammatory drugs 7 (11.29%), 22 (8.18%), and 16 (9.41%) dose, frequency and duration were misunderstood respectively. Followed by drugs acting on the gastrointestinal tract 5 (8.06%), 30 (11.15%), and 14 (8.24%) dose, frequency, and duration misunderstood respectively. Patients who misunderstood dosing instructions will take their medications incorrectly, which results in so many consequences, including adverse drug reactions, drug resistance, increased healthcare costs, and decreased work productivity (3, 4). Misunderstanding of antibiotic dosage instruction could contribute to antimicrobial resistance due to either over/under-dosing, drug interactions. Enhancement of communication skills with patients with the aid of information brochures and labeling is one multifaceted intervention to reduce irrational use of antibiotics and antimicrobial resistance (27). A study conducted to gain better insight on Patients' understanding of prescription drug label instructions in Saudi Arabia showed that the most common features misunderstood were duration of treatment (38.9%) and storage instructions (29.5%) (28).

4.3. Factors associated with medication misunderstanding

Patient misunderstanding of dosage instructions (dose, frequency and duration) was significantly associated with Age ($p<0.000$), educational status ($p <0.000$), sex (dose, $p=0.157$, frequency, $p<0.000$, duration $p=0.002$) and residence ($p <0.001$) of patients. This could be associated with reduced visual acuity and low literacy of the elderly population. This is because misunderstanding of nonprescription acetaminophen product information was common among study participants and independently associated with both impaired visual acuity and low literacy skills (29). A randomized controlled trial conducted to investigate the impact of patient-centered labels on comprehension of medication dosing in a large tertiary care hospital in Brisbane, Queensland, Australia showed that the proportion of participants who were able to correctly comprehend dose instructions provided on all three labels was significantly higher in the group that received PCL; 23.3% standard vs 83.6% PCL, $p<0.001$. This study supports the use of PCL in Australian pharmacy practice. PCL provides simple, clear, and explicit dosing instructions to patients. Implementing PCL may reduce the risk of misinterpreting dosing instructions by patients and improve the quality use of medicines (30).

A cross-sectional study conducted to identify parameters that likely affect ambulatory patients' knowledge of medication(s) provided at the exit of outpatient pharmacy of Federal Harar Police Hospital, Eastern Ethiopia showed that only 37.2, 33.4 and 28.7% of the patients were able to recall the name of the drug(s), common side effects, and actions to be taken for missed doses, respectively. The likelihood of patients' knowledge for dispensed medications was high among patients aged 19–39 years (adjusted odds ratio [AOR]: 5.0; 95% CI: 1.04–24.2) and who thought their communication with dispenser had been polite (AOR: 4.62; 95% CI: 1.48–14.4) (31).

Patient misunderstanding of dosage instructions (dose, frequency, and duration) was significantly associated with the educational status of patients ($p <0.000$). This is in line with findings from a cross-sectional study conducted to assess patients' ability to read and understand dosing instructions of their medicines in a hospital and community pharmacy setting showed that readability scores significantly differed with education level ($P < 0.001$) (32). A study conducted to evaluate misunderstanding prescription physician's oral instructions in patients with low back pain showed that less than diploma educational level (OR=4.17, 1.18, 14. 76, p=0.03) was risk factors for misunderstanding prescription medication oral instructions for patients (33).

Poor knowledge about their medications among patients could result in misuse and poor compliance (2), both of which will negatively impact medication safety. If patients are unaware of their medication names or strengths, they may consume the wrong medication, wrong strength, or even duplicate medicines with different brand names. They will not be able to check if the medicines they bought are appropriate, or communicate to other health professionals about the medications they use when needed. If dosing instructions are incomplete, misread, or misunderstood, patients may consume medication at the wrong time, duration, or even route (3). Simply, outpatient healthcare will completely collapse if patients who are correctly diagnosed with carefully planned treatment regimens, do not take their medication as prescribed. Hence the pharmacists' ability to effectively communicate medicines information to patients is a topic of national importance. The impact of factors such as patient literacy, number of medicines dispensed, format and organization of the medicines label, the complexity of dosing instructions, the precision of writing dosing instructions, and the use of icons, graphics, and pictograms, on the communication of medicines information have been documented in the literature (12-14).

Functional health literacy is the ability to read, understand, and act on health information. This includes reading and comprehending prescription labels, interpreting appointment slips, completing health insurance forms, following instructions for diagnostic tests, and understanding other essential health-related materials required to adequately function as a patient (8, 10, 23). A cross-sectional study conducted to examine patients' abilities to understand and demonstrate instructions found on container labels of common prescription medications showed that low and marginal literacy was significantly associated with misunderstanding (34).

Patient misunderstanding of dosage instructions (dose, frequency, and duration) was significantly associated with sex (frequency, $p<0.000$, duration $p=0.002$) of patients. This is supported by evidence from a cross-sectional study conducted to evaluate factors associated with older patients' misunderstandings of medication dosage regimen instructions after consultation in primary care in Brazil showed that being female was a protective factor against the misunderstanding of medication dosage regimen instructions (35). Another study conducted to evaluate misunderstanding prescription physician's oral instructions in patients with low back pain showed that being male (OR=2.76, 1.08, 7.06, p=0.03) was a risk factor for misunderstanding prescription medication oral instructions for patients (33). A study conducted to gain better insight on patients' understanding of prescription drug label instructions in Saudi Arabia showed that the degree of misunderstanding significantly worsened for the male gender (P-value < 0.001), with low education level (P-value = 0.002), and low monthly income (P-value = 0.012). The most common features misunderstood were duration of treatment (38.9%) and storage instructions (29.5%) (28).

Patient misunderstanding of dosage instructions (dose, frequency, and duration) was significantly associated with the residence ($p <0.001$) of patients. This is also supported by evidence from a cross-sectional study conducted to identify parameters that likely affect ambulatory patients' knowledge of medication(s) provided at the exit of outpatient pharmacy of Federal Harar Police Hospital, Eastern Ethiopia showed that patients who came from rural residence have less outpatient medication knowledge (31).

5. Strength and limitations

The strength of this study relies on its methodology (adequate sample size and direct patient data). However, being a single facility-based study the findings of the study should be extrapolated with due consideration of sociodemographic characteristics of patients.

6. Conclusion

A significant number of patients misunderstood dosage regimen instructions. In addition to this majority of drugs were dispensed without label information and pharmacists did not practice the 'tell me back if you know' principle to ensure understanding of communicated information. Age, sex, educational status, and residence of patients were significantly associated with patient misunderstanding of dosage instructions. From the findings of the present study, the following recommendations were forwarded: Pharmacy professionals should effectively communicate and ensure patients understand the dosage instructions for the drug therapy by considering specific patient groups before dispensing. In addition to this, pharmacy professionals should label dispensed medications clearly to enhance patient understanding. Further extensive studies involving multiple sectors should be done to identify the ranges of associated factors with patients' misunderstanding of dosage instructions and patient–dispenser communication optimization.

Abbreviations

AOR: Adjusted Odd Ratio
CI: Confidence Interval
COR: Crude Odds Ratio
DLIs: Drug Label Instructions
RCT: Randomized Control Trial

PCL: patient Centered label
USA: Unites States of America

Statements and Declarations

Ethics approval and consent to participate

Before data collection, appropriate ethical clearance was obtained from Yanet Health College ethical review committee. A formal letter of permission was obtained from the Addis Ababa health bureau and Kenema pharmacy. Written informed consent was obtained from each healthcare professional after explaining the objective of the study. Confidentiality was assured by using code numbers rather than names in the questionnaire.

Consent for publication

All authors read the full version of this manuscript and agreed to publish

Availability of data and materials

All the data reported in the manuscript are publicly available upon acceptance of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All Authors read and approved the manuscript. *TAD* conceived the research, framed the format design, and analyzed data; *MMS participated in data analysis,* developed the manuscript for publication *and* ZBS polished the language of the manuscript.

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