



## Prevalence of drug related problems and its associated factors among schizophrenic patients in psychiatric ambulatory clinic of Mettu Karl Referral Hospital, South Western, Ethiopia: A prospective cross sectional study

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### Abstract

**Background:** Drug related problem is defined as any undesirable event experienced by a patient which involves, or is suspected to involve, drug therapy and that interferes with achieving the desired goals of therapy and requires professional judgment to resolve. Worldwide, schizophrenia is associated with considerable disability and may affect educational and occupational performance. The intent of this study was to ascertain prevalence and factors associated with drug related problems among schizophrenia patients in ambulatory clinic of Mettu Karl Referral Hospital.

**Methods:** An Institution based prospective cross sectional study design was carried out from May 07 /2021 to July 19/2021. Data was collected through employing check list and semi-structured questioner, and then the collected data was coded and analyzed by statistical packages for social sciences 25.0 version statistical software. Binary logistic regression analysis was used to identify factors associated with drug therapy problems. Finally, further analyses were carried out using multivariable analysis at a significance level of p-value < 0.05.

**Findings:** From the total 117 study subjects, 96(82.1%) of the respondents were  $\geq 25$  years. The overall incidence of drug therapy problem among schizophrenic patients in psychiatric ambulatory clinic follow up was 45(38.5%). Among seven types of drug therapy problem, 11(24.4%) of the study subjects were unnecessary drug therapy followed 9(20%) of participants had in-compliance. Rural residency (AOR=2.73,95% CI=2.162- 3.428,P=0.004), duration of schizophrenia treatment 6-10 years (AOR=3.85,95% CI=2.790-6.20,P=0.037), patients who had comorbidities (AOR=2.17,95% CI=1.907-3.721, P=0.001), and patients who had taken haloperidol (AOR=2.69,95% CI=1.805-4.381, P=0.009) were associated factors of the outcome(DRPs).

**Conclusion and Recommendation:** Regarding duration of schizophrenia treatment majority of the participants taken the medication one year up to five years and had the frequency of attending follow up appointment every two months. Health care workers especially those who work at psychiatric where counsel the patients about the medication usage and disease behaviors.

**Keywords:** drug related problems, schizophrenia, associated factors, Mettu Karl Referral Hospital, Ethiopia

### Introduction

DTP is any undesirable event experienced by a patient which involves, or is suspected to involve, drug therapy and that interferes with achieving the desired goals of therapy and requires professional judgment to resolve. According to Robert J. Cipolle text book of pharmaceutical care practice (third edition), there are seven basic categories of DTPs. These are: need for additional therapy, unnecessary drug therapy, wrong drug, dosage too low, adverse drug reaction, dosage too high and non-compliance<sup>[1]</sup>. Problems associated with drug use are many and includes inappropriate medication prescribing, discrepancies between prescribed and actual regimens, poor adherence, drug interactions, inappropriate use, patients monitoring and inadequate surveillance for adverse effects etc. Drug related problems are of a major concern in health care because of increased cost, morbidity and mortality. DTP is associated with prolonged medication adverse drug reaction, increased economic burden, and an almost 2-fold increased risk of death<sup>[2]</sup>. In 1990 when drug therapy problem investigated, DTP was described and assessed based on indication, effectiveness, safety, and adherence. The purpose of assessing DTP is to improve an individual patient's quality

of life by decreasing medication-related problems and optimizing therapeutic outcome<sup>[3]</sup>. The term schizophrenia derived from the Greek 'schizo' (splitting) and 'phren' (mind) with the term first coined by Eugen Bleuler in 1908, schizophrenia is a functional psychotic disorder characterized by the presence of delusional beliefs, hallucinations, and disturbances in thought, perception, and behavior. Traditionally, symptoms have divided into two main categories: positive symptoms which include hallucinations, delusions, and formal thought disorders, and negative symptoms such as anhedonia, poverty of speech, and lack of motivation. The diagnosis of schizophrenia is clinical; made exclusively after obtaining a full psychiatric history and excluding other causes of psychosis. Risk factors are maternal influenza in pregnancy, family history, social isolation, cannabis use, minority ethnicity, and urbanization<sup>[4, 5]</sup>. Despite a low prevalence, schizophrenia's global burden of disease is immense. Over half of the patients have significant co-morbidities, both psychiatric and medical, making it one of the leading causes of disability worldwide<sup>[6]</sup>. The diagnosis correlates with a 20% reduction in life expectancy, with up to 40% of deaths attributed to suicide<sup>[7]</sup>.

In 2017 world health organization reported that, schizophrenia affected 21 million people worldwide [8]. According to the reports of WHO one in two people living with schizophrenia does not receive treatments. The life-time prevalence of schizophrenia in Ethiopia is estimated to be 0.5%, according to study done at Butajira, Ethiopia [9]. In the United States, during 2009-2011, an estimated 382,000 emergency department visits related to schizophrenia occurred among adults aged 18-64, with an overall emergency department visit rate of 20.1 per 10,000 [10]. In the same country, the annual prevalence of schizophrenia averages 15 per 100,000, the point prevalence averages approximately 4.5 per population of 1000, and the risk of developing the illness over one's lifetime averages 0.7% [11]. Drug therapy problem cause significant morbidity and mortality in healthcare as well as increasing cost of care and this also applies to mental health care. The pharmaceutical care practitioner is responsible for identifying drug therapy problems which helps the patient to achieve treatment goals and get the best possible out comes from drug therapy. Unfortunately, even in some developed nations, the responsibility of clinical pharmacists in mental health on drug related problems is also under-utilized [12]. Patients with schizophrenia are at increased risk of metabolic and other cardiac risk factors, and most antipsychotic drugs also increase the risk of weight gain and metabolic syndrome for example the well-known atypical anti-psychotic clozapine can cause fatal agranulocytosis that requires immediate medical attention which is age and gender associated [13]. Thus, before treating patients with clozapine, clinicians must consider patients with a clozapine monitoring system and if the patient has a white blood cell count below 2,000 cells per mm<sup>3</sup> or a granulocyte count below 1,000 cells per mm<sup>3</sup>, clozapine must be switched. So it is important for psychiatrists to be aware of cardio metabolic risks in their patients so that appropriate lifestyle and pharmacologic interventions can be planned [14]. In most low and middle income countries mental health services, especially, specialized mental health care are not easily accessible and there are limitation for treatment utilization for people with schizophrenic disorders [15]. This study could also provide information for health care professionals to focus on DTP of medicine and also will help them by providing useful information for development of effective DTP reporting system and for awareness creation forums and training for them, and all essential activities for optimizing patient safety and to control the impact of DTP s on the patients and the society in the study area.

## Methods

**Study design, area and period:** An Institutional based prospective cross sectional study was conducted at MKRH in southwest Oromia, from May 07 /2021 to July 19/2021. MKRH which located at 600 km from Addis Ababa.

**Study participants:** The study population was all patients who attending to the psychiatric ambulatory ward of MKRH during the data collection period & that fulfilled the inclusion criteria. patients who were greater than 18 years age with schizophrenia on treatment follow up at psychiatry ambulatory, patients whose follow up had been on for at least two months on treatment with antipsychotic medication, patients who had complete registration charts

were included in the study. patients who had interrupt their follow up during data collection, patients who had emergency condition such as current aggravated and unconscious condition and capable of impairing response.

**Sample size calculation and sampling technique:** The sample size was determined by using the single population proportion formula: The sample size was determined based on "P" value which was taken from AMSH, P=0.282, or 28.2%  $n = \frac{(Z\alpha/2)^2 P(1-P)}{d^2}$ , n= sample size, P=prevalence of drug therapy problem, d=margin of sampling error tolerated, z=the standard normal value at confidence interval of 95%.  $n = (1.96)^2 (1 - 0.282) \times (0.282) / (0.05)^2 = 311$ . Since the total number of schizophrenic patients was less than 10,000, reduction formula (correction formula) will be applied as follow;  $n_f = n / (1 + (n/N))$ ,  $n_f = 311 / (1 + (311/161)) = 106$ . When 10% contingency is added to minimize non response rate, then final sample size was found to be 117. Consecutive sampling method was conducted to invite all adult patients participate in the study until the total sample size was obtained.

**Data collection and quality control:** A well-structured standard checklist and questionnaire was used to collect relevant information from patients and patient charts. The structured questionnaire contained questions on socio-demographic and socio-economic status of the patients (age, sex, marital status, and educational level, occupation, income and social habit), clinical characteristics such as (duration of treatment, number of drugs, presence of co morbidity, presence of ADR), duration of untreated psychotic disorder and comorbidity: The participants were asked to indicate the duration of time they stayed before they sought therapy at modern health services after the onset of the illness. DRPs were assessed by reviewing and analyzing all medication orders, administration sheets, laboratory test results, and diagnostic test results. DRPs were identified by evaluating the appropriateness of prescriptions in terms of indication, dosage, compliance, and duration of therapy. Appropriateness of drug choice was identified by using the Ethiopian psychiatric guidelines for the Management of DTPs [17]. Potential DDIs were identified using Medscape (WebMD, LLC) online drug interaction checker, Up To Date® (version 21.2, Wolters Kluwer), and Micromedex® (Micromedex 2.0). During data collection, if a DRP was identified, it was recorded and classified using a DRP registration format taken from Cipolle et al. with some modifications. In order to assure quality of data important measures was undertaken including: the patient card number was used, to check for if there is invalid and incomplete pertinent response and these cards were also coded so over or under count was not matter.

**Data management and analysis:** The data collected was checked for completeness and consistency on daily basis. Data was coded, and then analyzed through employing statistical packages for social sciences 25.0 version statistical software. The dependent variable (outcome) and independent variables (predictors) were entered into bivariate logistic regression in order to determine statistical association between dependent and independent variables. All variables associated with the dependent variable with p-

value less than 0.25 in the bivariate analyses of the binary logistic regression were entered into multivariate models of the logistic regression. Variables with p-value < 0.05 in the multivariate analyses were considered significant predictors of drug therapy problem.

**Ethical consideration:** Ethical clearance was obtained from SWAN diagnostic pharmaceutical importer. Informed consent was obtained from each respondent. They were given the right to refuse to participate in the study. participant names were not used at the time of data collection and all other personnel information kept anonymously. Behind the scenes was maintained throughout the study.

### Operational Definitions

**Drug therapy problem:** is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.

**Antipsychotic poly pharmacy:** Two or more combination of antipsychotic drugs prescribed at the same time.

**Wrong Drug:** The drug product is not being effective or sub optimal efficacy at producing the desired response in the patient, the dosage form of the drug product is inappropriate.

**Adverse drug reaction:** The drug product causes an undesirable reaction; a safer drug product is required due to risk factors, the drug product causes an allergic reaction and the drug product is contraindicated due to risk factors.

**Additional drug therapy:** Additional drug therapy is required to treat or prevent a medical condition in the patient.

**Dose High:** Dosage is high, need additional monitoring to determine if dosage is too high, the dosing frequency is too short, the duration of drug therapy is too long.

**Unnecessary drug therapy:** Multiple drug products are being used for a condition that requires only single drug therapy.

**Dose low:** The dosage is low to produce the desired response in the patient, the dosing frequency is long and the duration of drug therapy is short.

### Result

**Socio-demographic characteristics of the patients**  
From the total 117 study subjects, 96(82.1%) of the respondents were  $\geq 25$  years and 75(64.1%) of the participants were male. Above one-half 69(59.0%) of study subjects were live in rural area, 64(54.7%) earn < 500 ETB monthly income, and 70(59.8%) of the participants were uneducated.

A majority 39(33.3%) of the respondents were single and 31(26.5%) of respondents were chewing the khat followed by 29(24.8%) cigarette smokers. The overall incidence of drug therapy problem among schizophrenic patients in psychiatric ambulatory clinic follow up was 45(38.5%) (Table 1).

**Table 1:** Socio-demographic characteristics of the patients in psychiatric ward of MKRH, 2021.

Variables	Category	Frequency	Percent
Age	<25 years	21	17.9
	$\geq 25$ years	96	82.1
Sex	Male	75	64.1
	Female	42	35.9
Residency	Urban	48	41.0
	Rural	69	59.0
Marital status	Single	39	33.3
	Married	32	27.4
	Divorced	25	21.4
	Widowed	21	17.9
Educational status	Educated	70	59.8
	Uneducated	47	40.2
Monthly income	< 500 ETB	64	54.7
	$\geq 500$ ETB	53	45.3
Social habit	Cigarette smokers	29	24.8
	Alcohol drinker	18	15.4
	Khat Chewing	31	26.5
	No social habit	39	33.3
Prevalence of DTP	Yes	45	38.5
	No	72	61.5

Clinical characteristics of the patients

Regarding duration of schizophrenia treatment majority 44(37.6%) of the participants taken the medication one year up to five years and 45(38.5%) of respondents had the frequency of attending follow up appointment every two months. Above one-half 71 (60.7%) of the participants were haven't laboratory values, 66(56.4%) of participants hadn't past medical history, 68(58.1%) of the participants hadn't past medication history, 92(78.6%) of respondents were haven't drug interaction, and 67 (57.3%) of participants hadn't comorbidities. Concerning MMAPS 32(27.4%),34 (29.1%),and 51(43.6%) of the participants were have low, moderate and high respectively, and regarding naranjo adverse effects 35(29.9%), 12(10.3%), 33(28.2%), and 37(31.6%) of the respondents had doubtful, possible, probable, and definite respectively (Table 2).

**Table 2:** Clinical characteristics of the patients in psychiatric ward of MKRH, 2021.

Variables	Category	Frequency	Percent
Duration of schizophrenia treatment	< 1 years	27	23.1
	1-5 years	44	37.6
	6-10 years	33	28.2
	>10 years	13	11.1
Frequency of attending follow up appointment	Twice a month	33	28.2
	Once a month	39	33.3
	Every 2 month	45	38.5
Laboratory values	Yes	46	39.3
	No	71	60.7
Past medical history	Yes	51	43.6
	No	66	56.4
Past medication history	Yes	49	41.9
	No	68	58.1
Drug interaction	Yes	25	21.4
	No	92	78.6
Comorbidities	Yes	50	42.7
	No	67	57.3
MMAPS-8	Low	32	27.4
	Moderate	34	29.1
	High	51	43.6
Naranjo adverse effects	Doubtful	35	29.9
	Possible	21	17.9
	Probable	33	28.2
	Definite	37	31.6

Common comorbidities and treatment related factors of the patients

Among 201 commonly identified comorbidities 41(20.4%) was hypertension followed by 32(16.0%) diabetes mellitus and 26(13.0%) chronic kidney disease. From 167 drug prescribed to schizophrenia about half 78(46.7%) was taken chlorpromazine followed by 54(32.3%) haloperidol and also 22(13.2%) of the participants taken trihexyphenidyl to manage extra-pyramidal side effects of haloperidol. Only 54(46.2%) of the study subjects were experienced side effects (Table 3).

**Table 3:** Common comorbidities and treatment related factors of the patients in psychiatric ward of MKRH, 2021.

Variables	Category	Frequency	Percent
Common comorbidities	Hypertension	41	20.4
	Diabetes mellitus	32	16.0
	Chronic kidney disease	26	13.0
	Meningitis	23	11.4
	Epilepsy	18	9.0
	Hypothyroidism	25	12.4
	Anemia	23	6.4
	Others	13	3.4
Drug name	Chlorpromazine	78	46.7
	Haloperidol	54	32.3
	Trihexyphenidyl	22	13.2
	Others	13	7.8
Experienced side effects	No	63	53.8
	Yes	54	46.2

Type of medication related problems in psychotic patients

Among seven types of drug therapy problem, 11(24.4%) of the study subjects were unnecessary drug therapy followed 9(20.0%) of participants had noncompliance, 7(15.5%) respondents were have dosage too high and 6(13.3%) participants had needs additional drug therapy. And 5(11.2%) of participants were have dosage too low followed by 4(8.9%) of respondents had ineffective drug therapy and 3(6.7%) of participants were have adverse events drug therapy (Table 4).

**Table 4:** Type of DTPs of the patients in psychiatric ward of MKRH, 2021.

Variables	Category	Frequency	Percent
Seven types of drug therapy problem	Indication		
	Unnecessary drug therapy	11	24.4
	Needs additional drug therapy	6	13.3
	Safety		
	Dosage too high	7	15.5
	Adverse events drug therapy	3	6.7
	Effectiveness		
	Ineffective drug therapy	4	8.9
	Dosage too low	5	11.2
	Compliance		
	Noncompliance	9	20.0

Multi-variable logistic regression of factors associated with DTPs

The result of the binary logistic regression showed that association was observed between residency, duration of schizophrenia treatment, frequency of attending follow up appointment, comorbidities, and drug name with the presence of DRPs. Patients who lived in rural area were 2.73 more likely had DRPs (AOR=2.73,95%CI=2.162-3.428,P=0.004) than those who dwelled in urban area, duration of schizophrenia treatment 6-10 years were 1.79 more likely had DRPs (AOR=2.73, 95% CI=1.602-2.850,P=0.014), frequency of attending follow up

appointment in every 2 month were 3.85more likely had DRPs (AOR=3.85,95%CI=2.790-6.20,P=0.037),patients who had comorbidities were 2.17 more likely had DRPs (AOR=2.17,95%CI=1.907-3.721, P=0.001),and patients who taken haloperidol were 2.69 more likely had DRPs (AOR=2.69,95%CI=1.805-4.381,P=0.009) than those who had taken other drugs(Table 5).

**Table 5:** Multi-variable logistic regression of factors associated with DTPs in psychiatric ward of MKRH, 2021.

Variables	Category	N (%)	AOR (95% C.I)	P-value
Age	<25 years	21(17.9)		
	≥25 years	96(82.1)	1.25(1.198-1.724)	0.069
Residency	Urban	48(41.0)		
	Rural	69(59.0)	2.73(2.162-3.428)	0.004
Duration of schizophrenia treatment	< 1 years	27(23.1)		
	1-5 years	44(37.6)	0.94(0.021-1.047)	0.095
	6-10 years	33(28.2)	1.79(1.602-2.850)	0.014
	>10 years	13(11.1)	1.17(1.082-1.6450)	0.67
Frequency of attending follow up appointment	Twice a month	33(28.2)		
	Once a month	39(33.3)	0.45(0.076-1.329)	0.015
	Every 2 month	45(38.5)	3.85(2.790-6.201)	0.037
Comorbidities	No	67(57.3)		
	Yes	50(42.7)	2.17(1.907-3.721)	0.001
Drug interaction	Yes	25(21.4)		
	No	92(78.6)	1.12(1.037-1.805)	0.86
Drug name	Chlorpromazine	78(46.7)		
	Haloperidol	54(32.3)	2.69(1.805-4.381)	0.009
	Trihexyphenidyl	22(13.2)	0.37(0.097-1.017)	0.065
	Others	13(7.8)	1.18(1.074-1.842)	0.437

**Discussion**

Mental disorders are leading causes of disability worldwide, accounting for one-third of the years lost due to disability [16]. About 25% of the world’s population develops mental illness at some stage in their life [17]. Antipsychotic medication are the mainstay of the treatment for schizophrenia and have reduced the number of recurrent episodes among persons with schizophrenia [18].The overall incidence of drug therapy problem among schizophrenic patients in psychiatric ambulatory clinic follow up was 45(38.5%).

The present survey revealed 7(15.5%) respondents were have dosage too high were less than the study done in Australia [19] indicates that a considerable amount of, antipsychotic prescribing did not align with clinical guidelines in particular poly pharmacy 32.5%, and antipsychotic high-dose 20.5%, was seen. The difference was due to in our study subjects majority of participants taken chlorpromazine and haloperidol due to unavailability others antipsychotic medication in the hospital and the participants hadn’t take poly pharmacy rather than taking trihexyphenidyl to manage the extra-pyramidal side effects of haloperidol medication in some patients unless comorbidities.

In our survey study inappropriate dose 26.7% which means 7(15.5%) dosage too high and 5(11.2%) dosage too low), 25(21.4%) drug interaction and 3(6.7%) adverse drug reaction were less than the study conducted in Belgium [20] in a geriatric ward, 304 drug therapy problems were identified by a clinical pharmacist and the most common drug-related problems were, inappropriate dose 31%, drug–drug interaction 20%,and adverse drug reaction 15%.In our study dosage inappropriate were somewhat in line with the study conducted in Belgium [20] but adverse drug reaction were very low compared with the study conducted in Belgium due to no adverse reaction measurement scales

done appropriately and also no skilled person who identified the adverse drug reaction. Drug interaction whose makes the drug therapy problem by cause drug failure or dosage too low and drug toxicity or dosage too high/adverse drug reaction.

The present study showed that among seven types of drug therapy problem, 11(24.4%) of the study subjects were have unnecessary drug therapy followed by 9(20%) of participants had in-compliance, 7(15.5%) respondents were have dosage too high and 6(13.3%) participants had needs additional drug therapy. Because unnecessary drug therapy was occur in some patients due to no medical indication, and non-drug therapy more available, and also noncompliance was occur due to myriad reasons such as drug not available, patient cannot afford the medication, patient does not understand instructions, and patients prefers not to take the medication were the rationale why unnecessary and noncompliance was highly occurred type of drug therapy problems.

Our study showed among the commonly identified comorbidities 41(20.4%) was hypertension followed by 32(16.0%) diabetes mellitus and 26(13.0%) chronic kidney disease in schizophrenic patients. From drug prescribed to schizophrenia about half 78(46.7%) was chlorpromazine followed by 54(32.3%) was haloperidol and also 22(13.2%) of the participants taken trihexyphenidyl to overwhelm extra-pyramidal side effects of haloperidol. Because comorbidities makes the patients to take more medication to treat the comorbidity and precipitation factors then poly pharmacy which the reason for drug therapy problem were occur. The chlorpromazine was commonly prescribed antipsychotic because it can't cause extra-pyramidal symptoms and tardive dyskinesia due to lower binding to D<sub>2</sub> receptors. In haloperidol some patients experienced jerky movement of tongue and face or bucco-lingual masticatory symptoms trihexyphenidyl was prescribed to surmount those side effects.

The result of the binary logistic regression showed that association was observed between residency, duration of schizophrenia treatment, frequency of attending follow up appointment, comorbidities, and drug name with the presence of DRPs. Patients who lived in rural area were 2.73 more likely had DRPs (AOR=2.73,95%CI=2.162-3.428, P=0.004) than those who dwelled in urban area, duration of schizophrenia treatment 6-10 years were 1.79 more likely had DRPs (AOR=2.73,95%CI=1.602-2.850,P=0.014),frequency of attending follow up appointment in every 2 month were 3.85more likely had DRPs (AOR=3.85,95%CI=2.790-6.20,P=0.037), patients who had comorbidities were 2.17 more likely had DRPs (AOR=2.17, 95%CI=1.907-3.721, P=0.001), and patients who taken haloperidol were 2.69 more likely had DRPs (AOR=2.69,95% CI=1.805-4.381,P=0.009) than those who had taken other drugs were somewhat in line with study conducted in Ethiopia<sup>[21]</sup> showed Extra pyramidal side effects, repeated psychiatric hospitalization, history of substance use, longer duration of treatment, and drug non adherence were found to be significantly associated with antipsychotic poly pharmacy<sup>[42]</sup>.

### Conclusion and recommendation

The overall incidence of drug therapy problem among schizophrenic patients in psychiatric ambulatory clinic follow up was high. Regarding duration of schizophrenia

treatment majority of the participants taken the medication one year up to five years and had the frequency of attending follow up appointment every two months. From drug prescribed to schizophrenia slightly about less than one half was chlorpromazine followed by haloperidol and also some of the participants taken trihexyphenidyl to manage extra-pyramidal side effects of haloperidol. Health care workers especially those who work at psychiatric where counsel the patients about the medication usage and disease behaviors.

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