Antipsychotic Polypharmacy, Health-Related Quality of Life and Associated Factors among Patients with Schizophrenia: A Cross-Sectional Study at Ayder Comprehensive Specialized Hospital, Northern Et

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By

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A thesis submitted to the Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Sciences Addis Ababa University in Partial Fulfillment of the Requirement for the Master of Science Degree in Pharmacy Practice.

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Declaration

This is to certify that the thesis proposal prepared by Elias Fitsum (BPharm) entitled; "**Antipsychotic Polypharmacy, Health-Related Quality of Life and Associated Factors among Patients with Schizophrenia: A Cross-Sectional Study at Ayder Comprehensive Specialized Hospital, Northern Ethiopia** ", for the degree of master science in pharmacy practice complies with the regulations of the university and meets the accepted standard with respect to originality and quality.

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ABSTRACT

Background: Schizophrenia is a highly disabling psychotic disorder that results in significant morbidity and a diminished health-related quality of life (HRQoL) for those affected. Antipsychotic medications are regarded as the primary treatment for patients with schizophrenia. The practice of antipsychotic polypharmacy (APP) has become common in the treatment of schizophrenia, However, there is a paucity of data on APP use, which is associated with several undesirable outcomes, importantly, it is predicted further to impair the health-related quality of life of schizophrenia patients.

Objective: This study aimed to assess the prevalence of antipsychotic polypharmacy, health-related quality of life, and associated factors among outpatients with schizophrenia at Ayder Comprehensive Specialized Hospital (ACSH).

Methods: A hospital-based cross-sectional study was conducted from March 13th to June 11th, 2023 at ACSH. Data were collected from 391 randomly sampled patients with patient interviews and chart reviews. The Tigrigna version of the Euro Quality of Life (EQ-5D-5L) questionnaire was used to assess the HRQOL. A binary logistic regression and multivariate Tobit regression models were used. p-value < 0.05 was considered statistically significant.

Result: A total of 391 study participants were involved in the final study with a mean (±SD) age of 33.97 ±9.061 years. The prevalence of APP was 25.8%. The mean (SD) PANSS scores of the study participants were: positive symptoms 17.18 (3.986); negative symptoms 15.82 (3.246); general psychopathology 28.66 (7.071); and total score 61.66 (12.509). A total of 14.1 % of participants experienced severe side effects, with sedation and CNS-related side effects (77.6%) being the most common type of antipsychotic-related side effects. Early onset of illness (AOR=4.366, 95% CI: 1.956-9.746, p<0.001), duration of illness > 10 years (AOR = 8.664; 95% CI: 1.040-15.15, p<0.046), presence of comorbid mental illness (AOR=4.289, 95% CI: 1.563- 11.77, p=0.005), positive symptoms (AOR=1.216, 95% CI: 1.039 - 1.424, p=0.015), anticholinergic drug use (AOR=2.37, 95% CI: 0.076-0.79, p=0.013), and medication nonadherence (AOR=2.56, 95% CI: 1.10-5.950, p=0.029) were positively associated with APP. In contrast, the use of adjuvant medication is inversely associated with APP (AOR = 0.08; 95% CI: 0.015-0.435, p=0.003). The most frequently reported health problem was the anxiety/depression dimension (97.3%). The median [IQRs] EQ-5D-5L utility value and EQ-VAS score of the study participants were 0.859 [0.774–0.9177] and 65 [55–70], respectively. Being not working (β = -0.033, 95% CI=-0.059, -0.070), presence of comorbid

physical illness (β = -0.060, 95% CI =-0.097, -0.023), having antipsychotic polypharmacy (β = -0.040, 95% CI=-0.075, -0.006), poor medication adherence (β = -0.043, 95% CI=-0.072, -0.013), and experiencing a severe side effect (β = -0.081, 95% CI=-0.135, - 0.028) were significantly negatively associated with the EQ-5D-5L utility score. Conversely, female sex (β = 0.0332, 95% CI = 0.007, 0.059) was significantly positively associated with EQ-5D-5L utility score.

Conclusion: The prevalence of APP was high among the current study participants. Compared with the general population in Ethiopia, outpatients with schizophrenia have a lower HRQoL. Clinicians and other relevant stakeholders should identify and implement targeted interventions to improve antipsychotic prescribing practices and improve the health-related quality of life of schizophrenic patients.

Keywords: *Schizophrenia; Antipsychotic polypharmacy; Health-related quality of life; Medication adherence; Antipsychotic side effects; PANNS.*

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List of Acronyms and Abbreviations

ACSH	Ayder Comprehensive Specialized Hospital
BPRS	Brief Psychiatric Rating Scale
DALYs	Disability-adjusted life years
DSM-V	Diagnostic and Statistical Manual, Fifth Edition
EPS	Extrapyramidal side effects
EQ-5D-5L	Euro Quality of Life Group's five dimensions with five-level
EQ-VAS	Euro Quality of Life Group's visual analogue scale
FGAs	First-generation antipsychotics
GASS	Glasgow Antipsychotics Side Effect Scale
HRQoL	Health-Related Quality of Life
ICD-10	International Classification of Diseases, Tenth Revision
LAI	Long-acting injectable
MMAS-8	Morisky Medication Adherence Scale
NICE	National Institute for Clinical Excellence
PANSS	Positive and Negative Syndrome Scale
QOL	Quality of Life
SF-36	Short Form-36
SGAs	Second-Generation Antipsychotics
SQLS	Schizophrenia Quality of Life Scale
WHO	World Health Organization
WHOQOL-BREF	World Health Organization Quality of Life–Brief Form

1. Introduction

1.1. Background

Schizophrenia is a severe, chronic, and debilitating psychiatric disorder characterized by abnormal thinking, perceptual disturbances, and diminished or exaggerated emotional expression (1, 2). This illness is characterized by an early onset, usually during adolescence, with diagnosis typically occurring between the ages of 15 and 25. It affects various aspects of general health, functioning, autonomy, subjective well-being, and life satisfaction for individuals experiencing the illness. Men are diagnosed with schizophrenia slightly earlier than women. Genetic and environmental factors are believed to be the greatest risk factors for schizophrenia, which is thought to be a multifactorial disorder despite the exact cause not yet known (3, 4).

Schizophrenia has a consistent incidence rate across diverse countries, cultural groups, and genders, with a lifetime prevalence estimated to be between 0.5% and 1% (5, 6). The World Health Organization (WHO) estimates that schizophrenia affects approximately 24 million individuals worldwide (7, 8), whereas Africa, estimates that this psychiatric disorder affects approximately 3.9 million people (9). Schizophrenia has been recognized as one of the top ten burdensome illnesses globally, accounting for 1.1% of the total disability-adjusted life years and 2.8% of the years lived with disability (4, 10). In Ethiopia, mental illness constitutes 11% of the overall burden of non-communicable diseases, with schizophrenia being among the top ten most burdensome conditions (11). The lifetime prevalence of schizophrenia in Ethiopia has been reported as 0.47% (12).

Individuals with schizophrenia can manifest three primary types of symptom: psychotic, negative, and cognitive. Psychotic symptoms include hallucinations, delusions, disorganized speech, and unusual behavior. Negative symptoms comprise alogia, avolition, flat affect, anhedonia, and social isolation. Cognitive impairments involve executive function deficits, memory difficulties, and decreased mental processing speed (3).

The diagnosis of schizophrenia requires confirmation that patients meet the established criteria for the disorder. The two major diagnostic systems for schizophrenia commonly used are the Diagnostic and Statistical Manual, Fifth Edition (DSM-V) and the Tenth Revision of the International Classification of Diseases (ICD-10). According to the DSM-V, the diagnosis of

schizophrenia relies on the presentation of positive and negative symptoms along with social or occupational dysfunction lasting for at least six months. In the ICD-10 the requirement of social or occupational dysfunction is not included, and the duration of illness in the ICD-10 is 1 month, resulting in a narrower definition of schizophrenia in the DSM-V (13, 14).

Schizophrenia can have a profound impact on daily life, often leading to social isolation, marginalization, and difficulties in various areas of functioning. People with this illness may struggle with poor living conditions, limited financial resources, inadequate education, and deficits in vocational and social skills, all of which contribute to poor quality of life (15, 16). Improving health-related quality of life (HRQoL) is indeed an important treatment goal in managing schizophrenia, considering that it is a lifelong disorder. Enhancing HRQoL focuses not only on addressing the symptoms of the illness but also on promoting overall well-being, functional abilities, social relationships, and personal fulfillment for individuals living with schizophrenia (16, 17). Therefore, the treatment of schizophrenia should aim to enhance the HRQoL of patients, as this has been linked to higher levels of satisfaction with care and improved adherence to treatment (18).

The treatment of schizophrenia involves both pharmacological and non-pharmacological approaches. Since their discovery, antipsychotics have been the mainstay of treatment for patients with schizophrenia and enhance recovery by controlling symptoms, improving quality of life(QOL), regaining basic life functioning, and preventing relapse. Antipsychotics are effective in treating acute psychotic episodes and improving symptoms in early schizophrenia patients. Long-term therapy can reduce the risk of psychotic relapses and has also been shown to reduce suicidal behavior. In addition to pharmacological treatment patients with schizophrenia are well-managed non-pharmacologically in the form of basic life training, and psychoeducation for both patients and caregivers. With the optimum dosing of some antipsychotics, the effect of medication therapy is typically observed within hours or days after initiation, but the full outcome is achieved progressively over weeks to months (19, 20, 21).

Several widely recognized clinical practice guidelines, such as the American Psychiatric Association, National Institute for Clinical Excellence, and Texas Medication Algorithm Project, have published clinical practice guidelines that provide evidence-based recommendations for the use of antipsychotic medications to treat schizophrenia (22, 23, 24, 25, 26, 27, 28, 29). These

guidelines suggest that a combination of antipsychotic medications along with appropriate psychotherapy is an effective approach for treating patients with schizophrenia. Additionally, for individuals experiencing their first episode of schizophrenia, the guidelines recommend oral antipsychotic monotherapy with second-generation antipsychotics (SGAs) as the preferred option over first-generation antipsychotics (FGAs). This preference is due to the lower risk of extrapyramidal side effects associated with SGAs. Moreover, these guidelines propose the use of more than one antipsychotic drug for a given patient, only in cases where other monotherapy approaches have been unsuccessful in achieving a satisfactory clinical response (30).

According to the NICE guidelines, the initiation of antipsychotic combinations is generally not recommended, except for brief periods during the transition from one antipsychotic to another. However, suppose a patient does not respond adequately to treatment despite receiving adequate doses of at least two different antipsychotic drugs (at least one of them being a non-clozapine SGA). In these case, the guidelines recommend considering the use of clozapine. The guideline recommends considering antipsychotic polypharmacy (APP) involving clozapine in combination with other SGAs only for patients who have not responded to clozapine treatment alone (31). Similarly, according to the Texas Medication Algorithm Project, antipsychotic monotherapy (APM) is recommended in the initial third stage of treatment. Antipsychotic polypharmacy, specifically the combination of clozapine and SGAs, as well as FGAs or electroconvulsive therapy, is only recommended at the fourth stage of treatment (32). Moreover, the World Federation of Societies of Biological Psychiatry Guidelines preferred APM with SGAs except for treatment-resistant cases for which the combination of clozapine with other SGAs may be considered as a treatment option (24). Therefore, monotherapy with antipsychotics is the evidence-based and recommended approach for treating both acute exacerbations of symptoms and long-term maintenance treatment to prevent future relapses of symptoms (33, 34).

1.2. Statement of the Problem

Schizophrenia poses significant challenges as one of the most disabling psychotic disorders, resulting in considerable morbidity and burden for patients, their families, communities, and countries (35). Its impact extends beyond its prevalence, as it is recognized as one of the top ten burdensome illnesses globally. Schizophrenia accounts for 1.1% of the total disability-adjusted

life years (DALYs). Additionally, it represents 2.8% of the years lived with disability, highlighting its substantial impact on individuals' quality of life and functioning (4, 10, 16).

Despite notable advancements in both pharmacological and non-pharmacological interventions, the treatment of schizophrenia continues to present clinical complexities and difficulties (36). Antipsychotic medications yield modest outcomes as they improve positive symptoms but are less effective at treating negative and cognitive symptoms (37). About one-third of patients with schizophrenia experience symptomatic and functional benefits from antipsychotic monotherapy, meaning that those with poor responses may need other treatment alternatives to improve outcomes (38).

Evidence-based international guidelines recommend monotherapy as the ideal treatment option and advise against antipsychotic polypharmacy, which is defined as the co-prescription of more than one antipsychotic drug for a given patient (22, 23, 24, 25, 26, 27, 28, 29). These guidelines suggest that the combination of two or more antipsychotics should be only considered as a strategy of last resort for treatment-resistant schizophrenia after multiple trials of monotherapy have failed to adequately control the symptoms.

Despite these recommendations and the limited evidence supporting its effectiveness, APP has become a common practice in the treatment of schizophrenia. The reported figures point to an increase in antipsychotic polypharmacy use over recent decades (39) . The estimated prevalence rate varies across countries and clinical settings, ranging from 12.7%-70.4% (40, 41, 42, 43, 44, 45).

A Systematic review and meta-Analysis of six studies carried out in Africa that involving 2154 schizophrenia patients reported that the pooled prevalence of APP is 40.6% (46). Similarly, A systematic review of the global and regional trends of the prevalence of APP based on 147 studies reported prevalence of 19.6%(39) .

The use of APP appears to be associated with a range of problematic outcomes that can negatively impact patients treatment outcomes, such as medication non-adherence due to the complexity of the medication regimen, a higher risk of side effects attributable to exposure to higher total dosages, challenges in evaluating individual antipsychotic responses when multiple medications are administered concurrently, increasing treatment cost, increased likelihood of

drug-drug interactions, and increased anticholinergic effects, which can have negative cognitive and physical impacts (47, 48, 49, 50, 51, 52, 53). Moreover, owing to the increased risk of adverse effects, including dose-related problems such as extrapyramidal symptoms, medication non-adherence, and its association with increased disease severity, it is predicted that patients receiving APP will experience a decrease in health-related quality of life compared with those treated with APM (54).

Several studies have reported that the benefit of APP is superior to that of antipsychotic monotherapy in terms of total symptom reduction, a lower daily dose, and fewer side effects (30, 55, 56). However, most of these studies lack a clear rationale and documentation for therapeutic benefit (57). Moreover, most of these studies are conducted in developed countries and are limited to a combination of clozapine with other SGAs or SGAs with SGAs. However, studies from developing countries such as Ethiopia show a high percentage of concomitant use of two or more FGAs in clinical practice, which is highly associated with several adverse outcomes (46, 58).

Schizophrenia patients have a lower HRQoL than the general population, which could be attributed to factors such as the chronic nature of the illness, limited effective treatments, poor treatment outcomes, lack of awareness, societal stigma, and side effects of medications (59, 60, 61, 62). Therefore, the treatment approach for this disorder aims to go beyond merely alleviating symptoms, also focusing on enhancing the patient's overall HRQoL. However, clinicians often prioritize treating psychotic symptoms in patients with schizophrenia while overlooking the factors directly linked to patients' quality of life (17). As a result, this study was conducted to assess antipsychotic polypharmacy and health-related quality of life among patients with schizophrenia at Ayder Comprehensive Specialized Hospital Psychiatry Clinic, in Mekelle, Tigray, Ethiopia.

1.3. Significance of the Study

Schizophrenia is a prevalent psychiatric disorder in Ethiopia, and antipsychotic medications are commonly prescribed in psychiatric clinics. APP for treating schizophrenia has always been a subject of debate in clinical practice. Some clinicians criticize this practice as being more expensive, lacking proven efficacy, causing increased side effects, and reducing patients' quality of life. Others argue that APP is preferable to antipsychotic monotherapy in terms of achieving total symptom reduction, facilitating rapid response, and improving quality of life. This study focused on schizophrenia patients and aimed to assess antipsychotic polypharmacy and its associated factors. Therefore, this study provides insight for health professionals concerning APP practices and could also serve as a source of direction by identifying areas for intervention.

In addition, this study aimed to assess HRQoL and identify associated factors, providing clinicians with valuable information about their patients' overall health status, which might otherwise be unnoticed. Additionally, evaluating patients' perspectives on their health status through self-reported HRQoL measures is crucial for evaluating treatment outcomes, providing patient-centered care, and enhancing satisfaction, adherence, and health outcomes. Furthermore, identifying the factors that are associated with HRQoL in patients with schizophrenia can help clinicians select the most suitable and effective interventions.

The findings of this study are expected to contribute to the existing knowledge of schizophrenia treatment, medication adherence, and the side effects of antipsychotic drugs. Furthermore, they can serve as valuable resources for researchers conducting further investigations in these areas. The utility values derived from the current study, have significant implications for future economic evaluations. These values can serve as crucial inputs in health economic models, enabling the assessment of various interventions' cost-effectiveness in schizophrenia care.

In Ethiopia, only a limited number of studies have been conducted on antipsychotic polypharmacy and health-related quality of life among people with schizophrenia, and no study has been conducted specifically in this area. To the best of our knowledge, only one study in Ethiopia has examined the associations between antipsychotic polypharmacy and HRQoL, side effect burden, and medication non-adherence.

2. Literature Review

2.1. Prevalence of Antipsychotic Polypharmacy

Since their introduction, antipsychotics have remained the mainstay treatment for schizophrenia. Despite the recommendation of antipsychotic monotherapy, the use of APP in the treatment of schizophrenia is a common clinical practice with varying prevalence.

A higher prevalence of APP (43.2%) was reported in a retrospective study conducted in Australia. Among these, 88.9% were on two antipsychotics and 11.1% were on three different antipsychotics. The long-acting injectables (LAI) risperidone and zuclopenthixol, and oral clozapine, quetiapine, amisulpride, aripiprazole, and chlorpromazine were significantly more likely to be used as part of an APP regime (63). Another retrospective, cross-sectional study from Australia reported a prevalence of APP of 39.0% (64).

A study involving 31,435 patients with schizophrenia was conducted in the USA and reported a prevalence rate of APP (23%). The most common drug class involved in APP therapy was SGA with FGA (15.7%) followed by SGA with SGA (3.9%). Additionally, combinations consisting of FGAs accounted for 2.8% of the observed combinations (65). However, a study conducted in the USA, that examined the annual rate and duration of antipsychotic polypharmacy reported that more (57.7%) of the participants experienced at least one prolonged period of APP lasting at least more than 60 consecutive days (66).

A nationwide cohort study conducted in Finland (n = 62,250) revealed that up to 57.5% of patients with schizophrenia were receiving APP for at least 90 days (67). Similarly, a study conducted in Poland that examined the prevalence of APP among schizophrenic patients discharged from psychiatric units reported that 47.3% of APP. Among those patients, 46% received a combination of two SGAs, whereas 48% received a combination of both FGAs and SGAs. The SGAs olanzapine and risperidone were the most prescribed (68).

In a study conducted in Spain, the prevalence of APP was reported to be 13.9%. Among these, 62.0% were prescribed a combination of both FGAs and SGAs (69). However, a study conducted on outpatients with schizophrenia in Turkey reported that 70.71% were on APP. Among these, 44.4% had two antipsychotics, 24.4% had three, 1.4% had four, and 0.7% had five (70).

Another cross-sectional study conducted in Norway, involving 329 patients with schizophrenia, reported that 30.7% of the APP. The most commonly observed combinations of drug classes were SGAs with SGAs, accounting for 60.4%, followed by combinations of SGAs with FGAs (36.6%). A combination of three antipsychotics was used by only 3.2% of the patients (71).

A three-year study conducted in Serbia reported a higher prevalence rate of APP at 67.7%. Among the participants using the APP, 63.3% were prescribed a combination of two medications, whereas 4.1% were prescribed a combination of three medications (72).

A nationwide study, which included 45 psychiatric hospitals/centers across China and involved 4,239 patients with schizophrenia, revealed a prevalence rate of 34.2% for APP. Among these, 91.1% were prescribed two antipsychotics, 8.6% were prescribed three, and 0.3% were prescribed four or more antipsychotics (73). In a recent cohort study conducted in Japan involving 448 patients, the prevalence of APP was reported to be 23.6% (74). However, another large prospective study in Japan reported a higher prevalence of APP(56.8%) (75).

A multicentre comparative study in East Asia that involving 2399 patients with schizophrenia reported a 45.7% prevalence of APP (76). Similarly, a recent multicenter survey conducted to investigate the prescription pattern of psychotropic medications in patients with schizophrenia across Asia that involved 879 older adults with schizophrenia reported that the proportion of APP was 40.5 %, with the most common type of APP being SGA + SGA (22%) and 12.9% received FGA + SG and only 5.7% received FGA + FGA (77).

A retrospective cross-sectional study carried out in Palestine on schizophrenic patients reported a 53.1 % prevalence rate of APP. The most common drugs involved in APP were chlorpromazine (77.9%), fluphenazine decanoate depot (44.1%), and haloperidol (41.2%). FGA with FGA (31.2%), three FGAs (9.6%), and SGA with FGA (6.8%) were the most common combination (78). Similarly, a cross-sectional study carried out in Hong Kong to investigate the prevalence and correlates of APP showed that 26% of schizophrenia patients are treated with APP. The most widely used APP prescription fell within the atypical/atypical combination (79). However, another multicenter study conducted in Korea reported a relatively low APP rate(20.4%). Among the patients receiving APP, only 6.4% had been prescribed polypharmacy with FGAs, whereas 46.82% were prescribed FGAs+SGAs (80).

A recent retrospective study carried out in India among patients with schizophrenia reported a 43.9 % prevalence rate of APP. The most common combination was FGA and SGA which comprised 54.4 % of the sample, followed by SGA + SGA combination (43 %). A combination of FGA + FGA was uncommon (2.6 %) (81). Another retrospective study conducted in Bahrain to assess antipsychotic prescribing patterns in a psychiatric referral hospital reported a relatively low APP(10.8%) prevalence rate. Among these, 10.4% were on two antipsychotics, whereas 0.4% were on three antipsychotics. The combination of SGAs with FGAs (76.6%), two SGAs (17%), and two FGAs (6.4%). The three antipsychotics most commonly prescribed as polytherapy were risperidone (73.5%), followed by haloperidol (22.4 %), and trifluoperazine (22.4%) (82).

A study conducted in South Africa on patients with serious mental illness revealed that 56.7 % of schizophrenic patients were taking APP. Regarding the nature of polypharmacy, oral FGA + LAI (long-acting Injectables) FGA combinations predominated, being found in 55.49% of patients discharged on APP, followed by oral SGA + LAI FGA in 35.97% and a combination of two oral SGA agents in 5.49% (41). Similarly, a cross-sectional study carried out in Nigeria on outpatients with schizophrenia reported a prevalence of APP of 50.9%. Of these, nearly all (98.2%) combinations include an LAI. The common combinations were intramuscular (IM) fluphenazine + trifluoperazine (22.7%) and 52.1% of the respondents received FGAs + SGAs, while 47.9% recived SGAs + SGAs combinations (83). However, the APP rate was relatively higher in a another study conducted in Nigeria with a prevalence rate of 70.4%. The most common form of polypharmacy comprises a combination of FGA depot antipsychotic plus FGA oral antipsychotic and was found in 44.4% of participants (42).

A recent multicentered cross-sectional study of 422 patients with schizophrenia at specialized hospitals in Northwest Ethiopia reported that the overall prevalence of APP was 22.7%. Regarding the nature of polypharmacy, FGAs with FGAs predominated (80.2%), followed by SGAs + FGAs 19.8% (44). Another institution-based cross-sectional study carried out in Ethiopia at Amanuel Mental Specialized Hospital (AMSH) that involved 423 schizophrenia outpatients reported a 28.2% prevalence of APP. Among these patients, 23.3% were on FGA + FGA, 4.6% were on FGA + SGA, and only 1 patient took 3 different antipsychotics(45) .

2.2. Factors Associated with Antipsychotic Polypharmacy

Various studies have attempted to identify factors associated with antipsychotic polypharmacy. These factors can be broadly categorized into several domains**:** patients' sociodemographic characteristics, clinical characteristics, and medication-related characteristics.

Studies conducted in South Africa and Hong Kong, have shown that older age is associated with APP (41, 79). However, studies from China have reported the opposite, showing that young age is associated with APP (73). Furthermore, a study from Japan conducted by Ye et al. revealed that older age is associated with APM (75). A multicenter study conducted across six Asian countries revealed that the male sex is associated with antipsychotic polypharmacy (76). Similarly, a study conducted in South Africa also supports this finding (41).

A multicenter study conducted in Europe revealed that patients who were separated or widowed, as well as those living alone, had a higher likelihood of receiving APP (84). Similarly, studies conducted in the United States and Italy also revealed that unmarried patients were more likely to receive APP (85, 86). Moreover, another finding was that patients residing in areas with low population density were associated with APP (87).

The association between working status and APP has been explored in various studies, a cross-sectional study conducted in Korea revealed a positive correlation between unemployment and APP (88). Furthermore, a study from Hong Kong reported a significant association between monthly income and APP (89). However, a study in Ethiopia and Palestine lacked the association of APP with employment status and income (45, 78).

Different studies have established the association between substance use and APP. A study conducted in South Africa and Nigeria revealed that comorbid substance use is associated with APP (41, 42, 83). This finding is supported by two separate studies from Ethiopia, which also reported a significant association between substance use and the use of APP (44, 45).

Diverse clinical characteristics are associated with antipsychotic polypharmacy. A cross-sectional study conducted in China, which defines the early onset of illness as being younger than 25 years, revealed that individuals with a younger age of onset of schizophrenia are more likely to receive APP (73). Similarly, a multicenter cohort study conducted in France and a cross-sectional study carried out in Korea reported that the age of illness onset was significantly lower

in the polypharmacy group than in the monotherapy group (88, 90). However, a study from Norway found that early onset of illness was not associated with APP (71).

Antipsychotic polypharmacy is associated with schizophrenia patients who have a longer duration of illness and treatment. A multi-country study conducted in 15 Asian countries revealed that patients with a longer duration of illness were positively correlated with APP (77). This finding is supported by similar studies conducted in Finland, Singapore, and Ethiopia, which also reported a significant association between a longer duration of schizophrenia and APP (44, 91, 92). Furthermore, studies from Ethiopia and Malaysia have also demonstrated that APP is associated with a longer duration of treatment (44, 45, 93).

Schizophrenia patients who experienced frequent psychiatric-related hospital admissions were more likely to be prescribed APP, as evidenced by a studies conducted in South Africa (41), India (81), Norway (71), and Poland (68). Furthermore, a retrospective cohort study conducted in the USA revealed that patients with a higher burden of psychiatric comorbidity were a significant predictor of APP (94).

Patients who experienced severe symptoms associated with APP, as indicated by studies conducted in Norway (71), were found to have significantly higher scores on both positive and negative symptoms measured by the Positive and Negative Syndrome Scale (PANSS). Similarly, in another study conducted in Korea, higher scores on the Brief Psychiatric Rating Scale (BPRS), specifically BPRS -positive and affective symptom scores, were reported in the APP group than in the APM group (88). Moreover, a cross-sectional study in Nigeria reported that patients on APP scored significantly higher on the negative syndrome subscale of the PANSS than those on monotherapy (42). In contrast, a study from Palestine showed no difference between APP and monotherapy in the positive and negative symptom scale (78).

Different medication-related variables are associated with antipsychotic polypharmacy. Studies from Canada (95), China (73), Asia countries (77), Japan (79), and South Africa (41) reported that higher antipsychotic doses are associated with APP. Moreover, a multicenter study from Asian countries (77), Palestine (78), and South Africa (41) showed that anticholinergic use is associated with APP. Similarly, a study from Japan reported that patients on antipsychotic monotherapy are associated with no anticholinergic use (75). In addition, co-treatment with other adjuvant

medications, such as antidepressants (96), anxiolytics (97), and mood stabilizers (65, 79) has also been associated with APP. However, a study conducted in China reported that patients on APP were less likely to receive benzodiazepines (73).

Side effects due to medication are more common in patients receiving antipsychotic polypharmacy. Studies carried out in India have shown that extrapyramidal side effects (EPS), excessive sedation, and weight gain, were significantly more in APP than AMP (81). A study in China also revealed that compared to those on antipsychotic monotherapy, patients on APP had a higher side effect burden which was measured by the Treatment Emergent Symptom Scale (73). A study in Japan on the effects of APP schizophrenia outpatients showed a higher number of side effects in polypharmacy than in monotherapy groups (98). Similarly, a study from Nigeria reported that participants in polypharmacy had a significantly higher side-effect profile than those on monotherapy, which was measured by the Liverpool University Neuroleptic Side Effect Rating Scale (42).

A study conducted in Nigeria utilizing the eight-item Morisky Medication Adherence Scale (MMAS-8) reported an association between APP use and poor medication adherence (99). This finding is consistent with research from Switzerland (100), Ethiopia (45), and India (81), which also identified an association between APP and poor medication adherence.

2.3. Health-Related Quality of Life and Associated Factors

Schizophrenia not only impairs psychosocial functioning, but it also significantly impacts the quality of life of patients through both positive and negative symptoms (101). In psychiatry, quality of life has emerged as a widely accepted outcome indicator over the past few decades, as it effectively captures the therapeutic efficacy of psychosocial interventions and pharmacological treatments. Moreover, QOL provides a more comprehensive assessment of an individual's well-being, moving beyond mere symptom reduction to encompass a fuller understanding of their overall quality of life (73). Therefore, treatment regimens for schizophrenia involve antipsychotic medication, with a primary focus on reducing both positive and negative symptoms. However, improving patients' quality of life has also been acknowledged as a crucial therapeutic objective (102). Assessing the factors associated with the quality of life of people with schizophrenia is

crucial to mitigate the impact of the disorder and optimize treatment outcomes, ultimately enhancing their overall well-being.

When evaluating the quality of life of patients on antipsychotic medication, it is important to consider several factors that may impact their QOL outcomes. These factors include the side effects and dosage of antipsychotic medication, the presence and severity of depressive and negative symptoms, and the duration of treatment (103).

A multicenter observational study was conducted to examine the relationships between socio-demographic and clinical factors and the HRQoL of outpatients with schizophrenia in eight countries. The study used three measures to assess HRQoL, including the Schizophrenia Quality of Life Scale (SQLS), the Short Form-36 (SF-36), and the EuroQol-5 Dimension (EQ-5D). The results revealed that higher ratings of positive symptoms, as measured by the positive and negative syndrome scale positive dimension, were associated with worse HRQoL across all four measures. Higher PANSS negative dimension ratings were associated with worse HRQoL on the EQ-5D VAS, and SF-36, but not on the SQLS or the EQ-5D utility score. PANSS depression ratings were associated with lower HRQoL in all the scales (104).

A cross-sectional study of hospitalized schizophrenia patients in Japan using the EQ-5D-5L and the subjective well-being under neuroleptic treatment scale (SWNS) to evaluate HRQOL. The study revealed that the mean (SD) EQ-5D score and SWNS total score were 0.776 (0.177) and 83.5 (16.5), respectively. The EQ-5D score was significantly and negatively associated with the female sex, benzodiazepine use, and drug-induced extrapyramidal symptoms scale scores. In contrast, the SWNS total score was significantly and negatively associated with first-generation antipsychotic use, brief psychiatric rating scale scores, drug-induced extrapyramidal symptoms scale scores, and global assessment of functioning scale scores (105).

A multicenter cross-sectional study was conducted in the United Kingdom on 304 schizophrenia patients. The study revaled that schizophrenia patients had poor HRQOL as compared to the general population. The mean EQ-5D tariff score of 0.69 and the median of 0.74 which is lower than the general population (106).

A study investigating the link between antipsychotic side effects and HRQoL in individuals with schizophrenia used the EuroQoL five-dimensional 5-level (EQ-5D-5L) utility scores to measure

HRQoL. The results showed that patients who experienced drug-induced parkinsonism and tardive dyskinesia had a poorer HRQoL compared to those without these side effects(107).

A longitudinal study conducted in the USA, evaluated the self-perceived quality of life of schizophrenia patients using the quality of life (QLI) Index and found that 55% of the participants had a poor quality of life. The study found that high PANSS anxiety scores, high PANSS positive scores, higher levels of depression symptoms, and lower levels of insight were significantly associated with poor quality of life (108).

A meta-analysis of 56 studies on psychiatric symptoms and quality of life in individuals with schizophrenia revealed that both positive and negative symptoms had a significant association with reduced quality of life, whereas general psychopathology showed a consistent negative relationship with QoL (109).

A cross-sectional study carried out in Brazil to investigate the sociodemographic and clinical variables related to low quality of life reported that low QOL is associated with male gender, single marital status, low income plus low schooling, and use of three or more prescribed psychoactive drugs (110). Another study from Brazil also reported that being employed and having had no hospitalization within the last 5 years were positively correlated with one or more WHOQOL-Bref domains (111).

A study conducted in China used the World Health Organization Quality of Life – brief form (WHOQOL-BREF) and the SQLS to assess the generic and disease-specific quality of life of inpatients with schizophrenia. The study revealed that participants had a higher perceived QOL in the environmental and physical health domains compared to the psychological health and social relationships domains. Participants reported better specific quality of life in the symptom and side-effects domain compared to other domains. The study found that monthly household income and subjective social support were statistically significant predictors of both generic and disease-specific quality of life. Duration of hospitalization, degree of support use, and negative and general psychopathology symptoms were also significant predictors of disease-specific quality of life (112).

A study in China that evaluated the quality of life of schizophrenia patients using the WHOQOL-BREF found that compared to the general population, patients had significantly lower scores in

the physical and psychological QOL domains. Having better social support was associated with higher QOL in all domains, while more severe positive symptoms were linked to worse psychological and environmental QOL. Overall psychopathology negatively impacted both physical and psychological domains, while depressive symptoms predicted worse physical QOL, and being married was associated with worse social QOL (113).

In a cross-sectional study conducted in Singapore, it was found that older patients with schizophrenia had better mental health and physical functioning compared to their younger counterparts. However, a longer duration of mental illness was associated with worse mental health, poorer physical functioning, and lower scores on role limitations due to physical health problems (114).

The study carried out in China reported that poor or low physical domain of QOL is associated with older age, being unemployed, major medical conditions, no smoking, more severe depressive and negative symptoms, more frequent insomnia, and suicidality. Male gender, more severe depressive and anxiety symptoms, more frequent insomnia, and suicidality were independently associated with poor mental QOL (73).

Another study in China also revealed a positive association between the age of mental illness onset and quality of life, as well as with mutuality, employment, and monthly household income. On the other hand, the length of mental illness, symptom severity, and health status were negatively associated with QOL. Specifically, health status, mutuality, symptom severity, monthly household income, and employment status were identified as significant predictors of QOL, with mutuality having the greatest impact (115).

A cross-sectional study conducted in Jordan investigated the relationship between quality of life and various clinical factors among patients with schizophrenia. The study found that quality of life was negatively correlated with advanced age, male gender, longer duration of illness, higher body mass index, and the use of FGAs. However, quality of life was positively related to employment and being married. Duration of illness, history of hospitalization, level of knowledge about schizophrenia, psychiatric symptoms, and coping strategies were identified as significant predictors of quality of life among the participants (116).

A study conducted in Nigeria that assesses QOL of schizophrenia patients reported that showed that high functionality, and medication adherence, were associated with good QoL in schizophrenia (117). Furthermore, a different study in Nigeria reported that medication nonadherence was significantly associated with lower scores in all areas and aspects of quality of life, as measured by the WHOQOL-BREF (118).

The study conducted in Ethiopia aimed to examine the QOL among patients with schizophrenia using the WHOQOL-BREF tool. The results showed that positive symptoms, negative symptoms, general psychopathologies, comorbid physical illness, khat use disorder, tobacco use disorder, and medication nonadherence were negatively associated with the quality of life of patients with schizophrenia. On the other hand, monthly income was found to be positively associated with quality of life (119).

A multi-center cross-sectional study was conducted in Ethiopia to evaluate the HRQoL among patients with schizophrenia. The study found that the no formal education, longer duration of treatment, comorbidity, substance use, extrapyramidal side effects, nonadherence, and antipsychotic polypharmacy were all negatively associated with quality of life (54).

Another cross-sectional study conducted in Ethiopia also found that 48.6% of the participants had poor quality of life and educational status, occupation, risperidone use, depression, and sexual dysfunction were significantly associated with the quality of life of patients with schizophrenia (59).

Different studies have reported varying results regarding the impact of APP on HRQoL in patients with schizophrenia. Study carried out in Hong Kong, the QOL of outpatients with schizophrenia was evaluated using WHOQOL-BREF, and the results showed no significant difference in QOL between the APP and APM groups (89). However, another study carried out in China that assessed the QOL of schizophrenic patients by using SF-12 reported that the mean of SF 12 physical domain and mental domain was slightly higher in the APM group than APP group(PF 19.2% vs. 18.3% and MF 20.5% vs.20.2% respectively). However, there was no significant difference between the two groups in the other QOL domain (120).

Another nationwide cross-sectional study carried out in China that involved 4239 schizophrenic patients found that compared to those on APM, patients on APP and their families had lower

satisfaction with treatment, had higher QOL in the mental domain QOL, and no decreased QOL in the physical domain (73).

A Prospective observational study from Germany that examines the effects of antipsychotic treatment on the quality of life of schizophrenic patients shows that the APM treatment had a more positive effect on the SF-36 mental health-related quality of life (MCS) in comparison to treatment with APP treatment. AMP depot-antipsychotic drugs had a more positive effect on the SF-36 physical health-related quality of life (PCS) in comparison to APP treatment (121).

The study that explored the relationship between antipsychotic polypharmacy and quality of life in schizophrenia patients, using the quality of life scale (QLS), found that the total QLS scores of the APP group were significantly lower than those in the monotherapy group (APM). Specifically, patients who were receiving APP had poorer quality of life compared to those who were receiving monotherapy (122)

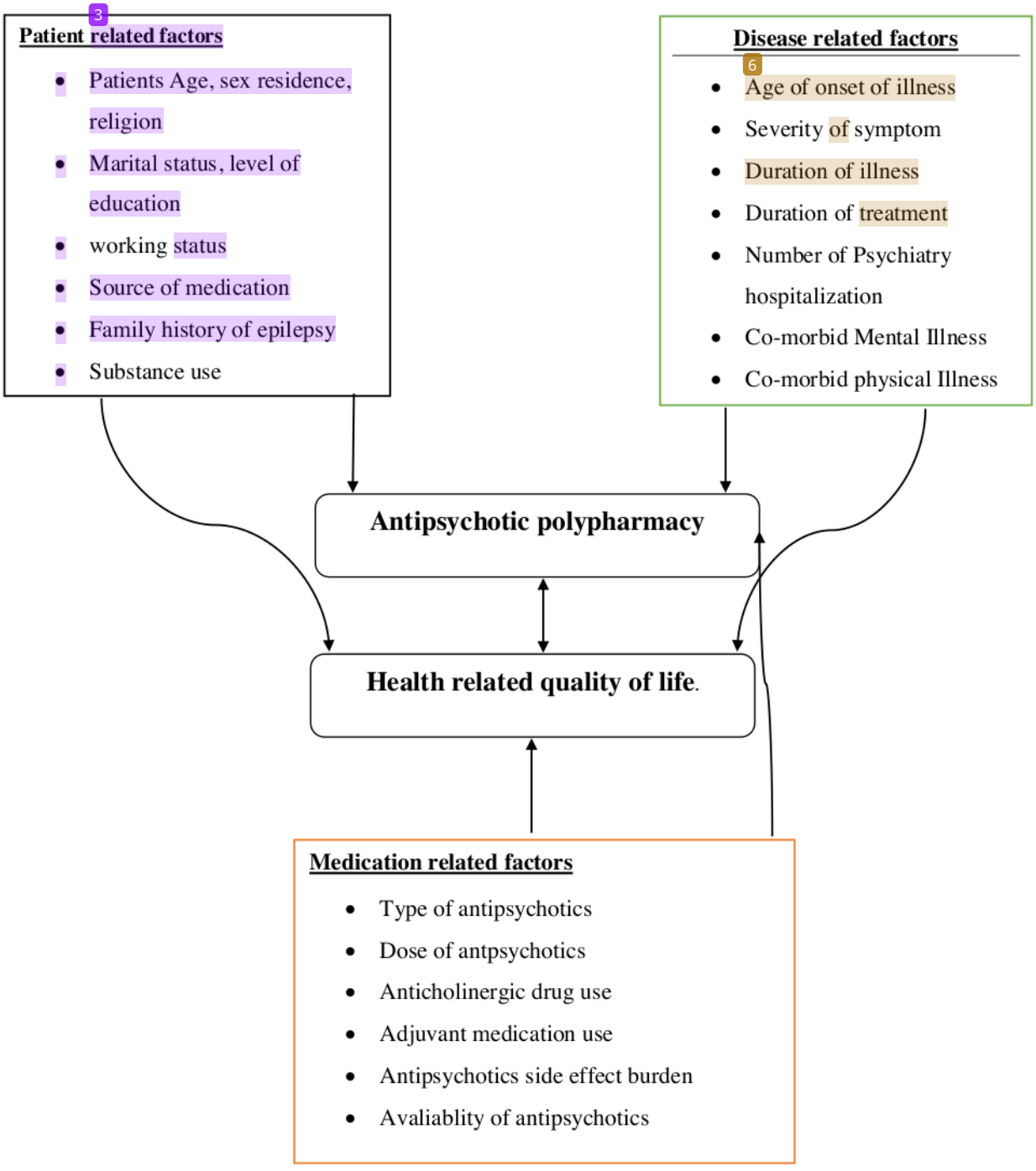

Figure 1: Conceptual framework that shows the expected associations between the variables involved in the study.

3. Objectives

3.1. General Objective

- To assess the prevalence of antipsychotic polypharmacy, health-related quality of life, and associated factors among outpatients with schizophrenia on follow-up at Ayder Comprehensive Specialized Hospitals of Psychiatry clinics, Mekelle, Tigray, Ethiopia from March–June2023 G.C.

3.2. Specific Objectives

- To determine the prevalence of antipsychotic polypharmacy among outpatients with schizophrenia at ACSH, Mekelle, Tigray, Ethiopia.
- To identify factors associated with antipsychotic polypharmacy therapy among outpatients with schizophrenia at ACSH, Mekelle, Tigray, Ethiopia.
- To determine the magnitude of antipsychotic-related side effect burdens among outpatients with schizophrenia at ACSH, Mekelle, Tigray, Ethiopia.
- To assess the level of health-related quality of life using the EQ-5D-5L among outpatients with schizophrenia at ACSH, Mekelle, Tigray, Ethiopia.
- To assess factors associated with health-related quality of life among outpatients with schizophrenia at ACSH, Mekelle, Tigray, Ethiopia.

4. Methods

4.1. Study Setting

The study was conducted at ACSH, Mekelle City, Tigray Regional State, Northern Ethiopia, which is 783 kilometers far way from capital city of Ethiopia, Addis Ababa. It is a government-owned teaching hospital and research center, under the administration of Mekelle University College of Health Sciences. It provides referral and specialized medical services to more than 8 million people in its catchment areas of Tigray, Afar, and some parts of the Amhara Regional States. It is one of the largest hospitals in the nation, with a total capacity of approximately 472 inpatient beds in all departments and more than 170,000 patient flows per year.

The hospital has psychiatric outpatient and inpatient units (16 beds). All patients presenting with psychiatric symptoms are initially evaluated at the psychiatric outpatient department, and severe cases are admitted to the inpatient psychiatry wards. The psychiatric units at Ayder Comprehensive Specialized Hospital are staffed by 5 psychiatrists, 26 psychiatry nurses (including 5 with master's degrees), and 1 clinical nurse who services patients five days a week.

4.2. Study Design and Period

A hospital-based cross-sectional study design was conducted among adult patients with schizophrenia through patient interviews and medical chart review. The study was conducted from March 13 to June 11, 2023, to assess antipsychotic polypharmacy, health-related quality of life, and associated factors among schizophrenia outpatients on follow-up at ACSH.

4.3. Source and Study Population

All adult patients with schizophrenia who were in follow-up at the outpatient psychiatry clinic of ACSH were the source population. The study population included all adult schizophrenia patients who were in follow-up and who visited the outpatient psychiatry unit at the time of the data collection period and fulfilled the eligibility criteria.

4.4. Eligibility Criteria

4.4.1. Inclusion Criteria

Adult patients (aged ≥18 years) with a diagnosis of schizophrenia who had been followed with a minimum of one or more previous visits, and were on antipsychotics for at least three months before the initiation of the study were included.

4.4.2 Exclusion Criteria

The study excluded patients who were acutely disturbed, unable to communicate, unable to speak and read, whose medication was collected by others on the behalf of the patients, who were unwilling to participate in the study, who were unable to complete the interview, and whose medical charts had incomplete records.

4.5. Sample Size Determination and Sampling Technique

The sample size was calculated using a single population proportion formula, with Z values of 1.96, 95% CI, and 5% marginal error. Since we had two dependent variables, antipsychotic polypharmacy and health-related quality of life, we computed the sample size as follows. For antipsychotic polypharmacy, the proportion (P) for sample size determination was obtained from a cross-sectional study conducted in Ethiopia on the prevalence of antipsychotic polypharmacy and associated factors among outpatients with schizophrenia, and the reported prevalence of APP was 28.2% (45). The calculated sample size was 311, and considering 5% of the contingency value, the total calculated sample size was ≈327. For the health-related quality of life, due to the absence of studies done using EQ-5D-5L in schizophrenia patients and to obtain a maximum sample size, an estimated proportion of patients who had utility values above the average was considered to be 50%, was used to calculate the sample size.

$n = [(Z\ \alpha/2)2 \times p\ (1-p)]\ \sqrt{}\ d^2 = [(1.96)^2 \times 0.5 \times 0.5]/0.05^2 = 384$

Hence; n = Sample size; Zα/2 = Confidence level at 95% = 1.96, P = proportion of patients with utility above the average is 50%, d = margin of error of 5% =0.05

The calculated sample size was 384, and considering 5% of the contingency value, the total calculated sample size was 404. Then we took the largest sample size of 404.

Based on the patient registration book, 866 schizophrenia patients visited the psychiatry outpatient clinic three months before this study (Fig.2). A systematic random sampling technique was used to recruit the study population. The sampling fraction (k) was calculated to be 866/404 ≈2. Therefore, every two patients on the list were selected as sample patients, and a total of 404 study participants were recruited; however, 13 patients were excluded, and 391 patients were selected and included in the final analysis.

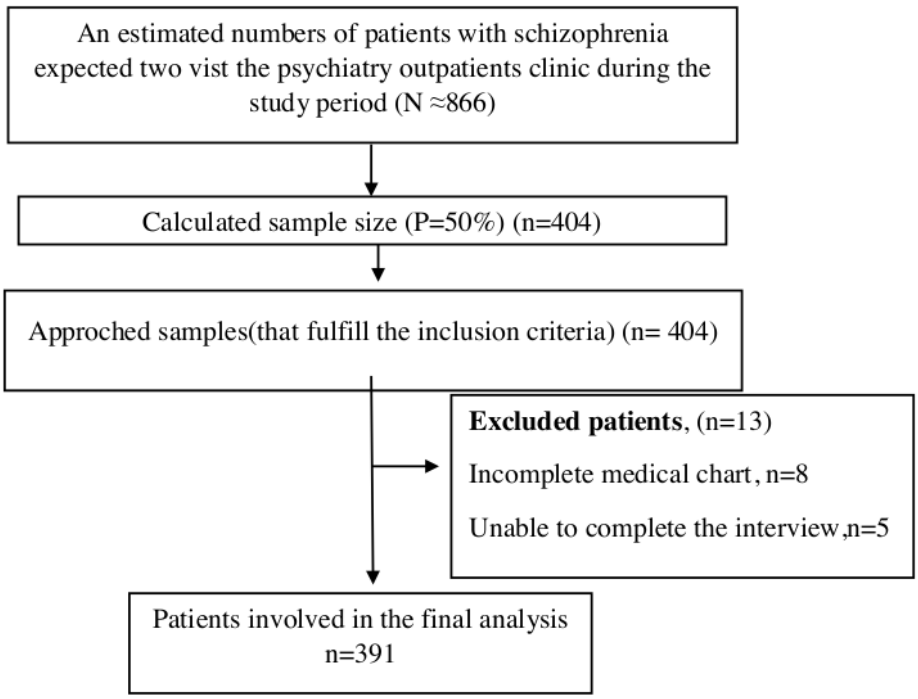

Figure 2: Study participant recruitment flow chart in the psychiatry outpatient clinic at ACSH, Mekelle, Ethiopia, march to June 2023 (n=391)

4.6. Study Variables

4.6.1. Dependent Variable

- Antipsychotic polypharmacy.
- Health-related quality of life.

4.6.2. Independent Variables

- Socio-demographic and behavioral characteristics such as sex, age, marital status, educational status, residence, working status, and current substance use.
- Clinical factors such as the onset of illness, duration of illness, duration of treatment, number of previous psychiatric hospitalizations, comorbid mental illness, comorbid physical illness, and severity of psychotic symptoms.
- Medication-related characteristics such as anticholinergic drug use, adjuvant medication use, total daily antipsychotic dose, and antipsychotic medication adherence.

4.7. Data Collection Procedures and Data Collection Instruments.

Data were collected using a pretested structured questionnaire (Annex I) from the patient prospectively after they were translated to the Tigrinya version (Annex III) and back-translated into English to check the consistency of the questionnaire. The questionnaire used for the interview to collect the data of sociodemographic and behavioral characteristics, clinical characteristics (onset of illness), the Morisky Medication Adherence Predictor Scale (MMAS-8), the Glasgow Antipsychotic Side Effect Scale (GASS), the Positive and Negative Syndrome Scale (PANSS), the EQ-5D-5L and the Euro Quality of Life Group's visual analogue scale (EQ-VAS). After the interview, the patients' charts were reviewed retrospectively using a data extraction format. The data extraction format was employed to collect the data on clinical factors and medication-related factors.

The data collectors identified appropriate participants and approached them for consent. After they secured their written consent, they conducted the data collection. All the necessary data, including the patient's demographic details and clinical informationsuch as age of onset of illness were collected and documented in data collection tools by interviewing the patient through the translated Tigrinya questionnaire for socio-demographic and behavioral characteristics. Then, with the assistance and guidance of the interviewers, the patients themselves completed the

Tigrinya language versions of the MMAS-8, GASS, EQ-5D-5L, and EQ-VAS. The positive and negative syndrome scale, which was used to assess the psychiatric symptom profiles of the patients, was completed by two psychiatrists who were directly involved in the data collection process and intimately familiar with the patient cases. Finally, after the interview was completed, data was extracted from the patient's clinical records using a data extraction format to obtain the following information: duration of illness, duration of treatment, number of psychiatric-related hospital admissions, co-morbid mental illnesses, comorbid physical illness, and medication profiles of the patient including the prescription pattern of antipsychotics, duration of APP, total daily dose of antipsychotics, anticholinergic drug use, and adjuvant medication use.

I. Glasgow Antipsychotic Side Effect Scale

The Glasgow Antipsychotic Side-effect Scale is an easy-to-use patient self-reported measurement scale consisting of twenty-two questions that cover a wide range of antipsychotic medication-related side effects (123). The GASS assesses side effects such as sedation, cardiovascular side effects, extrapyramidal side effects, anticholinergic side effects, and weight gain. For the first 20 questions, the frequency of side effects was rated on a 4-point scale, ranging from "none" (0 points) to "every day" (3 points), and for the final 2 questions (21-22), no (0) and yes (3 points). The severity of the side effects experienced by the participants was categorized based on their total GASS score. A score of 0–12 indicated absent or mild side effects, a score of 13–26 indicated moderate side effects, and a score greater than 26 indicated severe side effects. This tool has been used in various studies conducted in Ethiopia to assess antipsychotic side effects (124, 125, 126). In the present study, the GASS was used to assess the types and severity of antipsychotic side effects. It also compared the side effect burdens experienced by patients receiving APP with those experienced by patients receiving APM.

Even though the GASS has been used in different studies conducted in Ethiopia, the instrument has not been validated. Therefore, the psychometric properties of the Tigrinya version of the GASS; its reliability, validity, clinical feasibility, and acceptability were tested before conducting the main study at Mekelle General Hospital and ACSH. To test reliability we examined internal consistency by calculating Cronbach's α which yielded a total score of 0.792 (good internal consistency when ≥0.7) Separate calculations for males and females resulted in 0.88 and 0.84, respectively (127). We also computed inter-item Spearman's ρ correlations, revealing a range of -0.249 to 0.678 and the average inter-item correlation was 0.484. Moreover, we examined the

constract validity by investigating the relationship between the total GASS score and health related quality of life (measured with the EQ-5D-5L utilites and VAS) by using Spearman's ρ (good construct validity when $|\rho| \geq 0.5$) (128). We found a moderate inverse correlation between a higher GASS total score and reduced quality of life as indicated by a lower EQ-5D-5L utilite score ($\rho = -0.445$, $p < 0.001$), and lower scores on the EQ-VAS ($\rho = -0.413$, $p < 0.001$). The clinical feasibility and acceptability of the instrument were tested by recording the timing of the administration and the questions that the participants asked the data collectors when answering the GASS. All participants (n=220) finished all items on the questionnaire, with an average completion time of 7:44 minutes (ranging from 4 to 13 minutes). The item that generated the most questions from the participants was item 2, "I felt drugged or like a zombie".

II. Morisky Medication Adherence Scale-8

The Morisky Medication Adherence Scale-8 (MMAS-8) is a self-reported scale designed to assess patients' medication-taking behaviors. It consists of eight questions that focus on past medication use patterns. The scoring scheme assigns "Yes" = 1 and "No" = 0 for the first seven items, except for item number five, where the values are reversed (i.e., "Yes" = 0 and "No" = 1). The last question was a 5-point Likert scale, with "never/rarely" = 1 and all other responses scored as 0 (129). The Morisky Medication Adherence Scale has been shown to have good psychometric properties for use in psychiatric patients and is widely used in patients with schizophrenia (130, 131). In accordance with the scoring system of the MMAS-8, adherence was rated as follows: high (= 8), medium (6 - <8), and low (< 6). Patients were categorized as adherent or non-adherent on the basis of their total scores on the MMAS-8. Those achieving high or medium adherence scores were classified as adherent in the current study.

III. Positive and Negative Syndrome Scale

The PANSS is a well-validated instrument that is widely used for assessing the severity of positive and negative symptoms in schizophrenia patients as well as global psychopathology in schizophrenia patients. It has a total of 30 items (7 items for the positive scale, 7 items for the negative scale, and 16 items for the general psychopathology scale). Each item is scored from 1 to 7 depending on the severity level of psychopathology, with higher scores indicating greater severity of the symptom (132). The PANSS has been employed in research conducted in Ethiopia among patients with schizophrenia (133, 134, 135).

IV. EQ-5D-5L, and EQ-VAS

The EQ-5D-5L is a simple, generic, and standardized instrument for assessing patient health states for clinical and economic appraisal. (136). The EQ-5D-5L is the new version of the original EQ-5D-3L (three levels for each dimension), which essentially consists of two parts: the descriptive system and the EQ visual analogue Scale (EQ-VAS). The descriptive system examines five dimensions of HRQoL: mobility (MO), self-care (SC), usual activities (UA), pain/discomfort (PD), and anxiety/depression (AD), with a 5-level response (from 1= no problem to 5= extreme problem). The responses to the five dimensions generated 3125 (55) combinations of HRQoL states, with '11111' indicating 'no problems at all' and '55555' indicating 'extreme problems' in all five dimensions. Each combination was then given a single score using a scoring algorithm based on public preference. The EQ-VAS scale on which the overall state of health is marked by the patient in the form of a number (0 = worst imaginable state of health, 100 = best imaginable state of health). The utility value between the worst and best on to 0-1, 0 is for death and 1 is for perfect health. The self-completed Tigrinya versions of EQ-5D-5L were translated validated, and culturally adapted into the local Tigrinya language (TRF 2225) by the EuroQol Groups Version Management Committee (VMC) (137).

4.8. Data Collectors Recruitment and Training

For the interviews, data were collected by four data collectors who have a Master's degree in psychiatry nursing and work in the psychiatry department of ACSH. The data collectors were trained about the purpose of the study, the identification of patients based on the inclusion/exclusion criteria, the data collection tools and terminologies, and the ethical principles of confidentiality and data management before their involvement in data collection. The principal investigator and a senior psychiatrist trained the data collectors on PANSS rating, assessing patient adherence through self-reporting, and measuring antipsychotic side effects. For the retrospective chart review, two pharmacists with a Master of Science in clinical pharmacy were trained on how to collect the necessary data using a data extraction format and review patient medical records.

4.9. Data Quality Control and Assurance

To ensure the quality of the data, structured questionnaires were utilized. The data collection instrument was assessed by a senior psychiatrist for the clarity and comprehensiveness of its contents. Based on his recommendations, the Simpson-Angus Scale, which was originally intended to assess extrapyramidal side effects of antipsychotics, was removed from the questionnaires. A pretest of the questionnaires was carried out on 5% [21] of schizophrenia patients from Mekelle General Hospital to ensure the quality of the questionnaires. After pre-testing, all the necessary modifications and adjustments were performed before implementation in the main study. Family monthly income was removed from the questionnaire, and the onset of illness was shifted from the data abstraction format to an interview- questionnaire. Pretest respondents were not involved in the data analysis. The supervisor (principal investigator) provided daily supervision throughout the data collection process, and questionnaires with incomplete information were excluded.

4.10. Data Processing and Analysis

The study data were entered into Epi-data version 3.1 software and then exported and analyzed using two statistical packages - the Statistical Package for Social Sciences (SPSS) version 27.0 and STATA v. 14. STATA v. 14 was specifically used to perform a multivariable Tobit regression model analysis. Additionally, Microsoft Office Excel 2016 was used to analyze the EQ-5D-5L utility mean score. To summarize the study participant data, descriptive statistics were computed using SPSS, including the mean (standard deviation) and/or median (interquartile range) for continuous variables, and frequency and percentage for categorical variables. The variables summarized in this way included sociodemographic characteristics, clinical characteristics, medication-related variables, EQ-5D-5L scores, and EQ-VAS scores. Independent samples mean t-tests were used to compare the mean differences in continuous variables between the APP and APM groups. Furthermore, multivariable binary logistic regression was carried out to identify factors associated with APP. The dependent variables were coded as 0 for APM and 1 for APP in SPSS regression analysis. Variables with p-value <0.2 in the univariate analysis were included in the multivariate regression to control the effect of confounders. The level of significance of association was determined at p-value <0.05 and results were reported as odds ratios (ORs) with 95% confidence intervals.

The utility score was calculated using Microsoft Excel 2016. Patient health profiles from EQ-5D-5L were converted into a single index (utility) based on the preference of the general population of Ethiopia, and coefficients that represented level-specific disutility values obtained from the general population were used for computing utility values (138). Four dummies were created for each dimension by considering level one as a reference to represent a decrease in utility in moving from one level to the next higher level (e.g. moving from AD1 to AD2 resulted in a utility decrement of 0.0258862) (Eq.1). As the EQ-5D-5L utility and EQ-VAS scores were nonnormally distributed (Kolmogorov–Smirnov test and Shapiro-Wilk test, $p< 0.05$) and histogram inspection revealed skewed towards 1(Fig. 7), we presented median (IQR) scores. The Kruskal-Wallis and Mann-Whitney U tests were used to determine the significant differences in the EQ-5D-5L utility value and EQ-VAS score across the sociodemographic, clinical characteristics, and medication-related variables between patient subgroups. Spearman-rank correlation coefficient was used to assess the correlation between the EQ-VAS score, EQ-5D-5L utility index, and PANSS scores We then established a multivariate Tobit regression model on the EQ-5D-5L utility score, to identify variables associated with study participants' HRQoL, including all of the independent variables that showed statistical significance ($p<0.05$) in the Kruskal-Wallis and Mann-Whitney U tests (139). The ceiling effect is common in HRQoL studies, which is particularly evident with the EQ-5D instruments, leading to some utility scores censored at a point. A general linear regression model is inappropriate for censored data. Therefore, for censored data, the Tobit regression model is advised(140, 141). The level of statistical significance was declared at a p-value less than 0.05 at a 95% CI. The results were presented with text, tables, graphs, and charts.

$$\begin{aligned}\text{Utility value} = 1 - (&MO2 * 0.0337341 + MO3 * 0.0644715 + MO4 * 0.2276493 + MO5 * 0.3598963) + \\ &(SC2 * 0.0235125 + SC3 * 0.0394815 + SC4 * 0.1419238 + SC5 * 0.2223553) + \\ &(UA2 * 0.0323013 + UA3 * 0.0482993 + UA4 * 0.1573934 + UA5 * 0.2721253) + \\ &(PD2 * 0.0360808 + PD3 * 0.0515949 + PD4 * 0.2703189 + PD5 * 0.4063984) + \\ &(AD2 * 0.0258862 + AD3 * 0.0848133 + AD4 * 0.2987388 + AD5 * 0.4577938)\end{aligned}$$

MO-mobility; SC-self-care; UA-usual activity; P/D-pain/discomfort; A/D-anxiety/depression

Equation 1: The equation for computing the utility score.

4.11. Ethical Clearance

Before the initiation of the study, a letter of ethical approval (Ref No; ERB/SOP/282/13/2021) was obtained from the ethical review committee, School of Pharmacy, Addis Ababa University, and an official letter of support was provided to ACSH to obtain approval for data collection and to Mekelle University. The College of Health Science, Institutional Review Board gave expedited approval (Ref. NO MU-IRB-1871/2021), and a formal approval letter was also obtained from the medical director of ACSH. Informed consent was obtained from the study participants after the purpose of the study was explained. The participants were assured of anonymity and the confidentiality of the information obtained in the study by excluding any personal identifiers in the data collection form and that their answers would remain confidential. The data were collected by psychiatry nurses recruited from the same department to ensure the confidentiality of the patient information. Patients were also told about their right to withdraw from the study at any time.

4.12. Operational Definitions

Antipsychotic Polypharmacy: defined as the co-prescription of more than one antipsychotic drug, including a combination of parenteral (depot) and oral antipsychotics, for at least 30 days before the initiation of the study (45, 72, 83).

Total Daily Dose: The antipsychotic daily dose was converted to the traditional equivalent dose of 100 mg of chlorpromazine (CPZeq) as indicated in Annex IV (21, 142, 143, 144). The total daily chlorpromazine equivalent dose can be classified as follows: Subtherapeutic is less than 300 mg, optimum is between 300-600 mg, high is between 600-1000 mg, and very high is above 1000 mg.

Antipsychotic Medication Adherence: Study participants were classified as highly adherent, medium adherent, or low adherent based on their MMAS-8 score. Those with scores of 8 were considered highly adherent, those with scores between 6 and 8 were considered medium adherent, and those with scores below 6 were considered low adherent. Patients with high or medium adherence were considered adherent overall.

Early Onset of Illness: Age at onset of illness younger than 25 years is defined as early-onset schizophrenia(73, 145).

5. Results

5.1. Sociodemographic and Behavioral Characteristics of the Study Participants.

A total of 391 patients with schizophrenia were included in the study. Among these participants, more than half (54.7%, 214) of them were female, and the mean age (± SD) of the participants was 33.97 (±9.061), ranging from 21-58 years. About half of the participants (49.1%, 192) had completed secondary education, and more than two-thirds (86.2%, 337) were from urban areas. About three-fifths of the study participants (58.3%, 228) were unmarried, and about two-thirds (64.7%, 253) did not have an active working status. Nearly a quarter of the participants (24.8%, 97) were active substance users, who had engaged in at least one behavior such as alcohol drinking, cigarette smoking, or chewing khat (Table 1).

Table 1: Sociodemographic and behavioral characteristics of the participant's follow-up at the outpatient psychiatry clinic of ACSH, Mekelle, Ethiopia, March - June, 2023 (n= 391).

Variables	Categories	Frequency	Percentage (%)
Sex	Male	177	45.3
	Female	214	54.7
Age(years)	Mean± SD	33.97±9.061	
	≤25	67	17.1
	26-35	189	48.3
	≥ 36	135	34.5
Marital status	Unmarried	228	58.3
	Married	122	31.2
	Divorced	29	7.4
	Widowed	12	3.1
Educational status	No formal education	27	6.9
	Primary	72	18.4
	Secondary	192	49.1
	Higher education	100	25.6
Residence	Urban	337	86.2
	Rural	54	13.8
Working Status	Working	138	35.3
	Not working	253	64.7
Current substance use	Yes	97	24.8
	No	294	75.2

5.2. Clinical Characteristics of the Study Participants

As indicated in Table 2, , nearly fourty percent (41.7%, 163) of the particpants had an earlier age of onset illness with a mean (±SD) of 29.1(±8.89) years. Over half of the participants (59.1%, 231) had an illness duration of < 5 years whereas only 42 (10.7%) participants had an illness duration > 10 years. More than two-thirds of the participants (267, 68.3%) had been receiving antipsychotic treatment for less than five years, whereas only 14 (3.6%) participants had been receiving antipsychotic treatment for more than 10 years. The mean (±SD) psychiatry admission history of these patients was 1.14 (±1.34), ranging from no admission to five times. More than half of the study participants (54.7%, 241) had at least one previous psychiatric hospital admission. About one-fifth of the study participants (17.6%, 69) and (14.3%, 56) had co-morbid mental and physical illnesses, respectively.

Table 2: Clinical characteristics of the participants at the outpatient psychiatry clinic of ACSH, Mekelle, Ethiopia, from March–June 2023 (n= 391).

Variables	Categories	Frequency	Percentage (%)
Onset of illness(years)	Mean±SD	29.1±8.89	
	< 25	163	41.7
	≥ 25	228	58.3
Duration of illness	< 5years	231	59.1
	5-10 years	118	30.2
	> 10 years	42	10.7
Duration of treatment	< 5 years	267	68.3
	5-10 years	110	28.1
	> 10 years	14	3.6
Number of psychiatric hospitalizations	No Admission	177	45.3
	One Admission	74	18.9
	≥ Two Admission	140	35.8
Co-morbid Mental Illness	Yes*	69	17.6
	No	322	82.4
Co-morbid physical Illness	Yes**	56	14.3
	No	335	85.7

** Major depressive disorder, Sleep disorder, Anxiety disorder, Substance use disorder*
*** Epilepsy, Diabetes mellitus, Retroviral infection and Hypertension.*

The independent sample mean t-test results revealed statistically significant differences in the PANSS scores between the participants on APP and APM. The mean scores for the PANSS positive, PANSS negative, PANSS general psychopathology, and PANSS total score were slightly higher in the patients receiving APP than in those receving monotherapy, as shown in Table 3.

Table 3: Comparison of PANSS Scores between Participants on APP and APM at the Outpatient Psychiatry Clinic of ACSH, Mekelle, Ethiopia, March – June 2023 (n=391)

Variables	All patients (N=391) M±SD	APP(n=101) M±SD	AMP(n=290) M±SD	t-test (P-value)
PANSS Positive Score	17.18±3.986	19.93±4.407	16.22±3.339	P< 0.001
PANSS Negative Score	15.82±3.246	17.39±4.084	15.28±2.701	P< 0.001
PANSS General Psychopathology Score	28.66±7.071	31.58±8.956	27.64±5.975	P< 0.001
PANSS Total Score	61.66±12.509	68.90±16.232	59.14±9.761	P< 0.001

APP: antipsychotic polypharmacy; AMP: antipsychotic monotherapy.

5.3. Medication-Related Characteristics and Prevalence of Antipsychotic Polypharmacy.

In this study, the prevalence of APP was 101 (25.8%) (Figure 3) and of these, more than two-thirds 71 (70.29%) constituted the use of combined FGAs. More than half of the study participants 219 (56%) took a single FGA, and only 71 (18.2%) took a single SGA. On the other hand, the most frequently prescribed FGA and SGA for the study participants were haloperidol (101, 25.8%) and risperidone (59, 15.1%), respectively. Assessment of patients' responses to the 8-item Morisky Medication Adherence Scale revaled that 215 (55%) and 176 (45%) patients exhibited good and poor adherence to the antipsychotics medications , respectively. Moreover, 71 (18.2%) and 68 (17.4%) patients used anticholinergic and other adjuvant medications, respectively (Tables 4&5).

Table 4: Medication-related characteristics of the participants at the outpatient psychiatry clinic of ACSH, Mekelle, Ethiopia, from March–June 2023 (n= 391).

Variables	Categories	Frequency (n 391)	Percentage (%)
Type of antipsychotics class	FGA	219	56%
	SGA	71	18.2
	FGA+FGA	71	18.2
	FGA+SGA	24	6.1
	FGA+FGA+SGA	4	1
	FGA+FGA+FGA	2	0.5
Anticholinergic drug use	Yes	71	18.2
	No	320	81.8
Adjuvant medication use	Yes	68	17.4
	No	323	81.8
Total Daily Dose in CPZeq dose (mg)	Mean± SD	360.73±301.813	
	Subtherapeutic(<300 mg)	236	60.4
	Optimum(300-600 mg)	75	19.2
	High(600-1000 mg)	69	17.6
	Very High(>1000 mg)	11	2.8
Medication adherence	Good	215	55
	Poor	176	45
Severity of side effects based on GASS	Absent/mild side effects	181	46.3
	Moderate side effects	155	39.6
	Severe side effects	55	14.1
Variables	**APP(n=101),%**	**AMP(n=290),%**	**t-test (P-value)**
Total Daily Dose in CPZeq dose (mg) Mean±SD	508.66±252.696	309.21±300.864	P< 0.001
Subtherapeutic(<300 mg)	24(23.7)	212(73.1)	
Optimum(300-600 mg)	34(33.7)	41(14.2)	
High(600-1000 mg)	38(37.7)	31(10.7)	
Very High(>1000 mg)	5(4.9)	6(2)	

APP: antipsychotic polypharmacy; AMP: antipsychotic monotherapy; FGA: first generation antipsychotics; SGA: second generation antipsychotics.

With respect to polypharmacy patterns, chlorpromazine combined with fluphenazine depot was the most used combination regimen (36.2%), followed by chlorpromazine combined with haloperidol orally (27.2%). The most common medication used in antipsychotic polypharmacy was oral chlorpromazine (86.1%), followed by fluphenazine decanoate depot (55.4%) (Table 5).

The doses of antipsychotic drugs were converted into chlorpromazine-equivalent doses, and the mean total daily doses of the study participants were 360.73(SD 301.813) ranging from 38 to 1580 milligrams. About two-thirds were in the subtherapeutic dose category as indicated in Table 4.

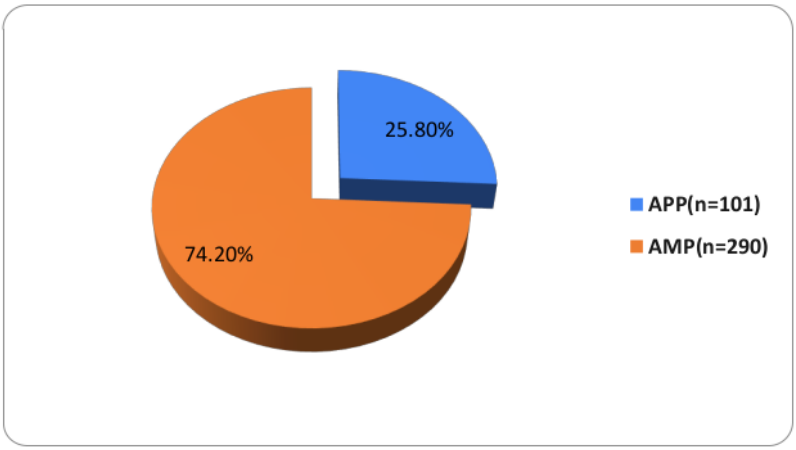

Figure 3: The prevalence of antipsychotic polypharmacy among the participants on follow-up at the outpatient psychiatry clinic of ACSH, Mekelle, Ethiopia, March–June 2023 (n=391).

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The mean (±SD) chlorpromazine equivalent dose for patients on APP and AMP was 508.66 mg (±252.696) and 309.21 mg (±300.864), respectively. In addition, about three-fourths of the (73.1%, 212) participants on AMP were taking subtherapeutic doses. In contrast, only (23.7%, 24) participants on APP were on subtherapeutic doses. On the other hand, (37.7%, 38) and (4.9%, 5) participants on APP were on high and very high doses, respectively; on the other hand, only (10.7%, 31) and (2%, 6) participants on AMP received high and very high doses of antipsychotics, respectively (Table 4).

Table 5: The pattern of antipsychotic prescription and frequency of antipsychotic medications involved in antipsychotic polypharmacy among the participants on follow-up at the outpatient psychiatry clinic of ACSH, Mekelle, Ethiopia, March–June 2023.

Variables	Antipsychotics	Frequency (%)
The pattern of antipsychotic prescription, (n=391)	Haloperidol	101(25.8)
	Chlorpromazine	80(20.5)
	Risperidone	59(15.1)
	Fluphenazine Depot	32(8.2)
	Olanzapine	12(3.1)
	Trifluoperazine	4(1)
	Thioridazine	2(0.5)
	Chlorpromazine+ Fluphenazine Depot	36(9.2%)
	Chlorpromazine+ Haloperidol	28(7.2)
	Risperidone+ Chlorpromazine	13(3.3)
	Haloperidol+ Fluphenazine Depot	7(1.8)
	Risperidone+ Fluphenazine Depot	5(1.3)
	Olanzapine+ Chlorpromazine	4(1)
	Risperidone+ Chlorpromazine+ Fluphenazine Depot	4(1)
	Olanzapine+ Fluphenazine Depot	2(0.5)
	Chlorpromazine+ Haloperidol+ Fluphenazine Depot	2(0.5)
Frequency of antipsychotic medications involved in APP, (n=101)	Chlorpromazine	87(86.1)
	Fluphenazine Depot	56(55.4)
	Haloperidol	37(36.6)
	Risperidone	22(21.8)
	Olanzapine	6(5.9)
	Chlorpromazine	87(86.1)

5.4. The Magnitude of Antipsychotic-Related Side Effect Burdens

The severity of the side effects was assessed and rated as absent-mild, moderate, and severe based on the Glasgow Antipsychotic Side-effect Scale. Among the total participants (46.3%, 181) reported experiencing absent/mild side effects, (39.6%, 155) reported experiencing moderate side effects, and (14.1%, 55) reported experiencing severe side effects (Table 4).

The most common types of antipsychotic-related side effects were sedation and CNS side effects 77.6%;, anticholinergic side effects 54.1%, and cardiovascular side effects 50.9% (Fig.4).

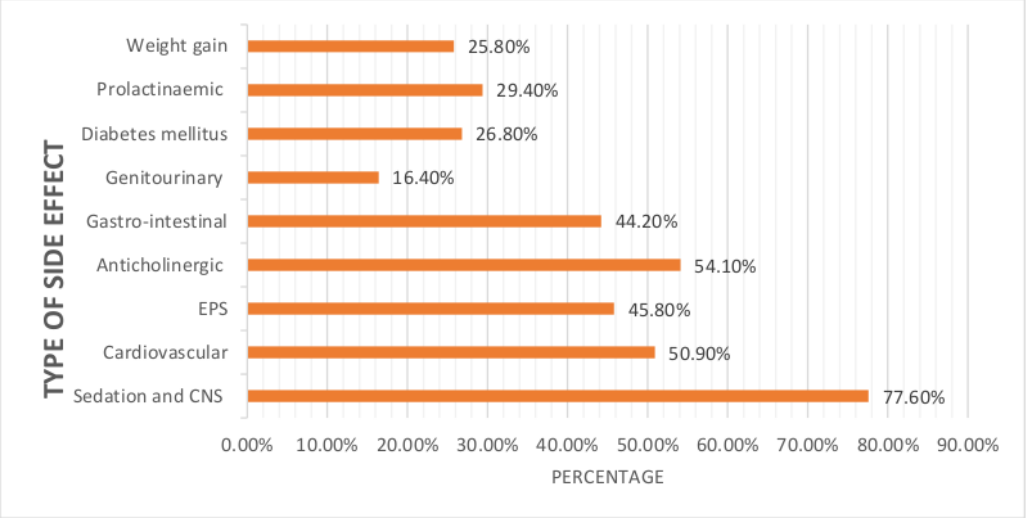


Figure 4: Type of antipsychotic side effects among the participants on follow-up at the outpatient psychiatry clinic of ACSH, Mekelle, Ethiopia, March–June 2023 (n=391).

As indicated in Figure 5, around one-third of people (32.6%, 33) using APP had experienced severe side effects. On the other hand only (7.6%, 22) of those on AMP had severe side effects. Conversely, more than half of the participants in AMP (58%, 168) reported either no side effects or only mild ones, whereas only (12.9%, 13) of those using APP experienced absent or mild side effects.

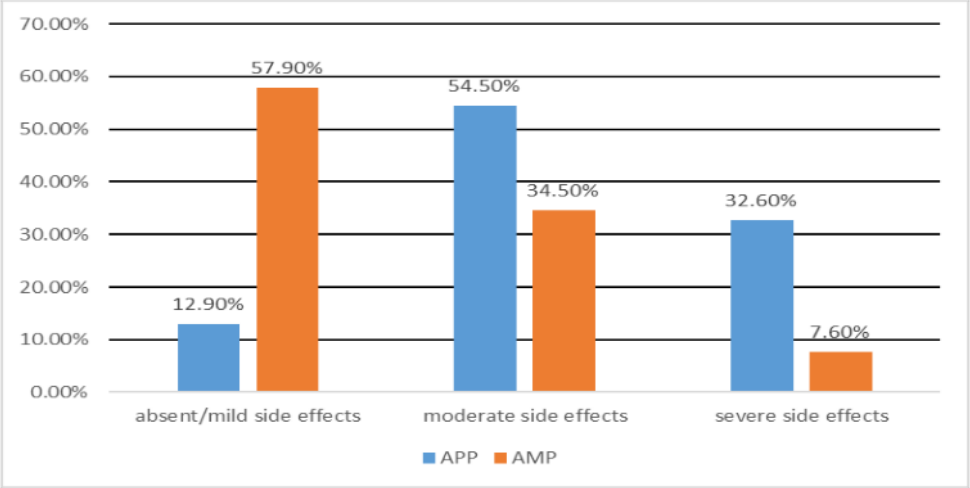


Figure 5: Comparison of antipsychotic side effects between patients on APP and AMP among the participants on follow-up at the outpatient psychiatry clinic of ACSH, Mekelle, Ethiopia, March–June 2023 (n=391).

5.5. Factors Associated with Antipsychotic Polypharmacy

Univariate analysis revealed that working status, current substance use, onset of illness, duration of treatment, duration of illness, psychiatric hospitalization, comorbid mental illness, PANNS score, anticholinergic use, total daily dose, medication adherence, and side effect burden had p values less than 0.2 and were subsequently incorporated for multivariate binary logistic regression. Accordingly, there was a significant association found between seven variables and antipsychotic polypharmacy. The variables that showed a statistically significant association with APP were early onset of illness, duration of illness, comorbid mental illness, PANNS-positive symptoms, anticholinergic drug use, adjuvant medication use, and medication adherence.

Patients who had an early onset of illness (<25 years) had a significant association with APP and were about four times (AOR=4.366, 95% CI: 1.956-9.746, p<0.001) more likely to be on antipsychotic polypharmacy as than those who had late onset of illness (≥25 years). With respect to duration of illness, patients who had more than ten years of illness were 8.664 times more likely to be on APP than those who had a duration of illness of less than five years (AOR = 8.664; 95% CI: 1.040-15.15, p<0.046) (Table 6).

Patients with co-morbid mental illness were found to be about four (AOR=4.289, 95% CI: 1.563-11.77, p=0.005) times more likely to be on APP as compared to those who did not have comorbid mental illness. On the other hand, patients prescribed anticholinergic drugs were 2.37 times more likely to be on APP as compared to those who had no concomitant anticholinergic use (AOR=2.37, 95% CI: 0.076-0.79, p=0.013). Interm of adjuvant medication use, a patient taking adjuvant medication is 12.5 times more likely to be on APM than patients not taking adjuvant medication, or the odds of a patient being on adjuvant medication 92% lower in the APP group than the APM group (AOR = 0.08; 95% CI: 0.015-0.435, p=0.003) (Table 6).

Interm of medication adherence, patients who were nonadherent to their antipsychotic treatment were found to be 2.56 times more likely to be on APP as compared to those who had good adherence to antipsychotic treatment (AOR=2.56, 95% CI: 1.10-5.950, p=0.029). The multivariate logistic regression analysis also revealed a significant positive association between the PANSS positive symptom scores and the odds of APP, with (AOR=1.216, 95% CI: 1.039 - 1.424, p=0.015). This finding suggests that patients with higher positive symptoms are at increased odds of receiving APP.

Table 6: Univariate and multivariate logistic regression analysis results of factors associated with antipsychotic polypharmacy among the participants on follow-up at the outpatient psychiatry clinic of ACSH, Mekelle, Ethiopia, March - June 2023 (n=391).

Antipsychotic polypharmacy Variables		Yes	No	Odds Ratios COR (95% CI)	P value	AOR (95% CI)	P value
Working status	Not working	75	178	1.815(1.096-3.007)	0.021	1.243(0.544-2.834)	0.605
	Working	26	112	1.00		1.00	
Current substance use	Yes	41	56	2.85(1.745-4.673)	0.001	0.535(0.213-1.339)	0.181
	No	60	234	1.00		1.00	
Onset of illness(years)	< 25	71	92	5.09(3.11-8.34)	0.001	4.366(1.956-9.746)	**0.001***
	≥ 25	30	198	1.00		1.00	
Duration of illness	< 5years	20	211	1.00		1.00	
	5-10 years	53	65	8.60(3.79-9.43)	0.001	3.59(0.960-13.42)	0.226
	> 10 years	28	14	21.1(4.59-12.42)	0.001	8.664(1.040-15.15)	**0.046***
Duration of treatment	< 5 years	27	240	1.00		1.00	
	5-10 years	62	48	11.48(4.63-12.86	0.001	3.59(0.96-9.442)	0.057
	> 10 years	12	2	53.33(5.33-32.00)	0.001	4.8(0.352-18.42)	0.239
Psychiatry hospitalizations	No Admission	17	160	1.00		1.00	
	One Admission	18	56	3.025(1.459-6.274)	0.003	1.61(0.556-4.668)	0.380
	≥ Two Admission	66	74	8.394(4.607-15.29)	0.001	1.175(0.424-3.255)	0.756
Co-morbid Mental Illness	Yes	42	27	6.934(3.96-12.13)	0.001	4.289(1.563-11.77)	**0.005***
	No	59	263	1.00		1.00	
Anticholinergic drug use	Yes	31	40	2.76(1.61-4.74)	0.001	2.37(0.076-0.79)	**0.013***
	No	70	250	1.00		1.00	
Adjuvant medication use	Yes	7	61	0.28(0.123-0.634)	0.002	0.080(0.015-0.435)	**0.003***
	No	94	229	1.00		1.00	

**Variables significantly associated with APP.*

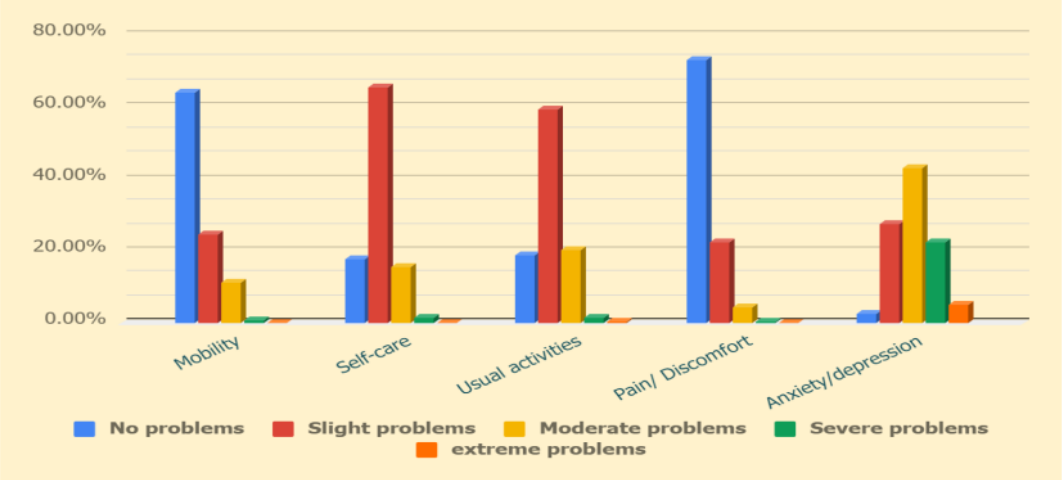
Table 6: **Continued…**

Total daily dose	Subtherapeutic	24	212	1.00		1.00	
	Optimum	34	41	7.325(3.93-13.622)	0.001	2.314(0.855-6.264)	0.099
	High	38	31	10.828(3.73-12.43)	0.001	6.236(2.976-19.39)	0.072
	Very High	5	6	7.36(2.08-16.94)	0.002	1.361(0.183-7.147)	0.763
Medication Adherence	Poor	81	95	8.31(4.80-14.37)	0.001	**2.560(1.101-5.950)**	**0.029***
	Good	20	195	1.00		1.00	
Side effect burden	absent/mild	13	168	1.00		1.00	
	Moderate	55	100	7.10(3.69-13.65)	0.001	1.994(0.747-5.321)	0.168
	Severe	33	22	19.38(8.88-42.31)	0.001	1.754(0.366-8.41)	0.482
		Mean ±SD		**COR (95% CI)**	**P value**	**AOR (95% CI)**	**P value**
PANSS	Positive	17.18±3.986		1.28(1.19-1.37)	0.001	**1.216(1.039-1.424)**	**0.015***
	Negative	15.82±3.246		1.23(1.14-1.32)	0.001	1.131(0.967-1.323)	0.123
	General Psychopathology	28.66±7.071		1.076(1.043-1.11)	0.001	0.988(0.919-1.339)	0.738

**Variables significantly associated with APP.*

5.6. Health-Related Quality of Life of the Study Participants

Patients' self-reported health status for the five dimensions of EQ-5D-5L is presented in Figure 4. From the the total participants, 73.1% and 63.9% reported "no problem" in the pain/discomfort and mobility dimension, respectively. In contrast, the most frequent health problems were reported for the "anxiety/depression dimension" (97.3%, all levels) followed by "self-care" (82.4%, all levels), and "usual activity" (81.1%, all levels). The study participants had an EQ-VAS score median (IQR) of 65 (55-70), and their median (IQR) EQ-5D-5L utility value was 0.859 (0.774-0.917). Conversely, the mean (SD) EQ-VAS score and EQ-5D-5L utility value were 64.6 ± 10.12 and 0.813 ± 0.137 respectively (Figure 6).



	Mobility	Self-care	Usual activities	Pain/ Discomfort	Anxiety/depression
No problems	63.90%	17.60%	18.90%	73.10%	2.30%
Slight problems	24.60%	65.20%	59.30%	22.50%	27.30%
Moderate problems	11.00%	15.60%	20.20%	4.10%	43%
Severe problems	0.50%	1.50%	1.30%	0.30%	22.30%
extreme problems	0%	0%	0.30%	0%	5.10%

Figure 6*:* Percentage distribution of self-reported health problems using the EQ-5D-5L descriptive dimensions of patients with schizophrenia on follow-up at the outpatient psychiatry clinic of ACSH, Mekelle, Ethiopia, March – June 2023 (n=391).

The Mann–Whitney U test and the Kruskal–Wallis H test revealed significant differences in the median (IQR) EQ-5D-5L utility and EQ-VAS score across different variables: sex, marital status, working status, current substance use, duration of illness, duration of treatment, psychiatric hospitalization, comorbid mental illness, comorbid physical illness, antipsychotic polypharmacy, total daily dose, medication adherence, and side effect burden, with a p-value of <0.05 (Table 7).

Table 7: Median(IQR) differences in the EQ-5D-5L utility and EQ-VAS scores with patient demographic, clinical, and medication characteristics among the participants at the outpatient psychiatry clinic of ACSH, Mekelle, Ethiopia, March - June 2023 (n=391).

Variables	EQ-VAS score median (IQR)	Mean rank	P value	EQ-5D-5L index score median (IQR)	Mean rank	P value
Overall scores	65(55-70)			0.859 (0.774-0.917)		
Sex						
Male	60(55-70)	176.18	**0.001**	0.843(0.646-0.885)	175.03	**0.001**
Female	65(60-75)	212.39		0.859(0.810-0.918)	213.31	
Age(years)						
≤25	70(60-70)	218.74	0.169	0.882(0.831-0.938)	227.86	0.015
26-35	65(55-70)	188.93		0.859(0.646-0.885)	181.89	
≥ 36	65(55-70)	194.61		0.859(0.795-0.918)	199.94	
Marital status						
Unmarried	65(60-70)	204.42	**0.011**	0.859(0.795-0.917)	202.52	**0.04**
Married	65(58.75-70)	195.38		0.859(0.774-0.918)	196.85	
Divorced	60(50-65)	131.02		0.803(0.612-0.882)	138.53	
Widowed	62.5(55-78.75)	199.42		0.863(0.798-0.916)	202.42	
Educational status						
No formal education	65(60-70)	185.57	0.585	0.833(0.790-0.918)	194.20	**0.031**
Primary	65(56.25-70)	209.26		0.822(0.801-0.939)	231.23	
Secondary	65(55-70)	190.14		0.859(0.698-0.980)	189.47	
Higher education	65(55-75)	200.5		0.847(0.779-0.890)	183.67	
Residence						
Urban	65(55-70)	198.79	0.217	0.859(0.776-0.917)	196.98	0.667
Rural	62.5(55-70)	178.58		0.859(0.742-0.898)	189.86	
Working Status						
Working	65(60-75)	215.61	**0.010**	0.863(0.815-0.918)	217.44	**0.006**
Not working	65(55-70)	185.31		0.858(0.669-0.908)	184.30	

Table 7: **Continued…**

Variables	EQ-VAS score median (IQR)	Mean rank	P value	EQ-5D-5L index score median (IQR)	Mean rank	P value
Current substance use						
Yes	60(55-65)	157.94	**0.001**	0.826(0.635-0.880)	158.56	**0.001**
No	65(60-75)	208.56		0.859(0.801-0.918)	208.35	
Onset of illness						
< 25	70(55-70)	189.44	0.326	0.859(0.646-0.918)	194.14	0.783
≥ 25	65(60-70)	200.69		0.859(0.795-0.915)	197.33	
Duration of illness						
< 5years	70(60-75)	225.87	**0.001**	0.882(0.831-0.918)	226.71	**0.001**
5-10 years	60(55-65)	148.59		0.810(0.629-0.867)	148.79	
> 10 years	60(55-70)	164.92		0.826(0.743-0.874)	159.73	
Duration of treatment						
< 5 years	65(60-75)	216.77	**0.001**	0.867(0.802-0.918)	215.74	**0.001**
5-10 years	60(55-65)	147.37		0.819(0.634-0.867)	151.09	
> 10 years	62.5(55-70)	182		0.826(0.617-0.918)	172.36	
Number of psychiatry hospitalizations						
No Admission	70(60-75)	226.98	**0.001**	0.882(0.826-0.918)	230.68	**0.001**
One Admission	65(55-75)	202.64		0.859(0.797-0.915)	200.51	
≥ Two Admission	60(55-65)	153.32		0.826(0.613-0.872)	149.77	
Co-morbid Mental Illness						
Yes	60(55-70)	152.51	**0.001**	0.831(0.635-0.883)	173.66	0.070
No	65(60-70)	205.32		0.859(0.790-0.918)	200.79	
Co-morbid physical Illness						
Yes	60(50-65)	133.95	**0.001**	0.800(0.640-0.859)	139.02	**0.001**
No	65(60-70)	206.37		0.859(0.795-0.918)	205.53	

Table 7: **Continued…**

Variables	EQ-VAS score median (IQR)	Mean rank	P value	EQ-5D-5L index score median (IQR)	Mean rank	P value
Antipsychotic polypharmacy						
Yes	60(55-65)	141.71	**0.001**	0.810(0.610-0.859)	136.50	**0.001**
No	65(60-75)	214.94		0.867(0.810-0.918)	216.72	
Anticholinergic drug use						
Yes	60(55-65)	145.42	**0.001**	0.810(0.596-0.859)	131.35	**0.001**
No	65(60-70)	207.22		0.859(0.797-0.918)	210.35	
Adjuvant medication use						
Yes	60(60-70)	190.15	0.635	0.859(0.791-0.892)	195.99	0.999
No	65(55-70)	197.23		0.859(0.774-0.918)	196	
Total Daily Dose						
Subtherapeutic	70(60-75)	223.97	**0.001**	0.872(0.823-0.918)	223.69	**0.001**
Optimum	60(55-70)	174		0.831(0.612-0.882)	164.04	
High	60(55-65)	129.38		0.813(0.656-0.863)	147.71	
Very High	65(50-70)	163.77		0.599(0.513-0.885)	122.64	
Drug adherence						
Good	70(60-75)	226.47	**0.001**	0.882(0.843-0.918	229.54	**0.001**
Poor	60(55-65)	158.78		0.811(0.613-0.882)	155.03	
Side effect burden						
absent/mild	70(60-75)	232.69	**0.001**	0.883(0.859-0.918)	239.78	**0.001**
Moderate	65(55-70)	182.87		0.833(0.767-0.885)	178.63	
Severe	55(50-65)	112.25		0.635(0.583-0.833)	100.89	

EQ-5D-5L: EuroQoL life questionnaires with five dimensions and five levels; EQ-VAS: EuroQoL visual analogue scale; HRQoL: health-related quality of life.

There were significant modest negative correlations between PANSS positive score with the EQ-5D-5L utility and the EQ-VAS scores and significant weak negative correlations between negative, and general psychopathology symptoms scores with EQ-5D-5L utility and EQ-VAS scores. The Spearman rank correlation coefficient between mean scores of PANSS positive, negative, and general psychopathology symptoms scores and the EQ-5D-5L utility score was -0.329, -0.178, and-0.214 respectively. The correlation between PANSS positive, negative, and general psychopathology symptoms scores and EQ-VAS scores were -0.321, -0.149, and-0.216 respectively (Table 8).

Table 8: Spearman rank correlation coefficient between the PANSS score and HRQoL scale (EQ-5D-5L and EQ-VAS).

PANSS SCORE	EQ-VAS score	P value	EQ-VAS score	P value
Positive symptoms score	-0.329	<0.01	-0.321	<0.01
Negative symptoms score	-0.178	<0.01	-0.149	<0.003
General Psychopathology symptoms score	-0.214	<0.01	-0.216	<0.01

EQ-5D-5L: EuroQoL life questionnaires five dimensions with five levels; EQ-VAS: EuroQoL visual analog scale HRQoL: health-related quality of life.

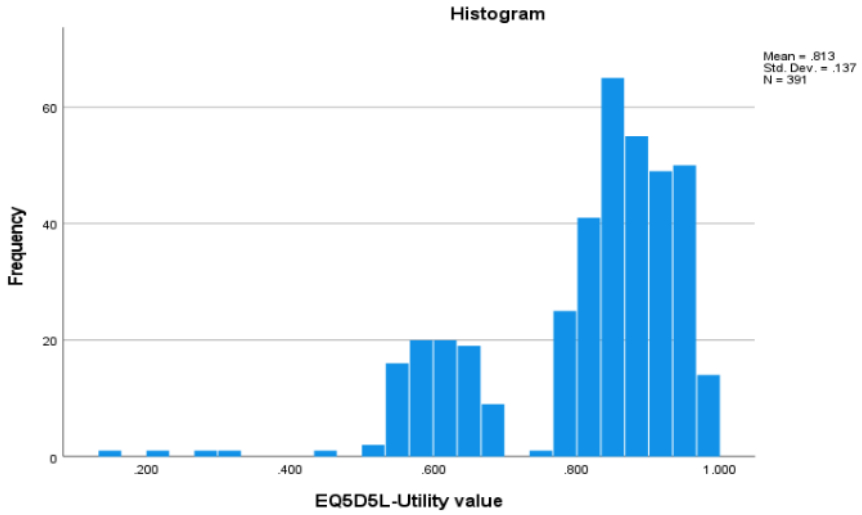


Figure 7: Distribution of the mean EQ-5D-5L utility scores of patients with schizophrenia at the outpatient psychiatry clinic of ACSH, Mekelle, Ethiopia, March – June 2023 (n=391).

5.7. Factors Associated with Health-Related Quality of Life.

A multivariate Tobit regression model was used to identify variables associated with the HRQoL, and it revealed that being not working (β = -0.033, 95% CI=-0.059, -0.070), presence of comorbid physical illness (β = -0.060, 95% CI =-0.097, -0.023), have antipsychotic polypharmacy (β = -0.040, 95% CI=-0.075, -0.006), poor medication adherence (β = -0.043, 95% CI=-0.072, -0.013), and experiencing a severe side effect (β = -0.081, 95% CI=-0.135, -0.028) were significantly negatively associated with the EQ-5D-5L utility score. Conversely,

female sex (β = 0.0332, 95% CI = 0.007, 0.059) was significantly positively associated with the EQ-5D-5L utility score. Similarly, divorce (β = -4.035, 95% CI = -7.737, -0.334) and the presence of comorbid medical illness (β = -5.462, 95% CI = -8.263, -2.661) were negatively associated with the EQ-VAS score, whereas female sex (β = 3.323, 95% CI = 1.373, 5.273) was positively associated with the EQ-VAS score (Table 9).

Table 9: Factors associated with HRQoL in patients with schizophrenia at the outpatient psychiatry clinic of ACSH, Mekelle, Ethiopia, March - June 2023 (n=391).

	EQ-5D-5L utility score		**EQ-VAS score**	
Variables	**β-Coefficient [95% CI]**	**P-value**	**β-Coefficient [95% CI]**	**P-value**
Sex, female Ref (male)	0.0332(0.007;0.059)	**0.012**	3.323(1.373;5.273)	**0.001**
Marital status (Ref=single)				
Married	-		-0.388(-2.471;1.694)	0.714
Divorced	-		-4.035(-7.737; -0.334)	**0.033**
Widowed	-		0.708(-4.637;6.055)	0.794
Working status, Ref (working)				
Not working	-0.033(-0.059; -0.070)	**0.013**		
Comorbid physical illness, Ref (No)				
Yes	-0.060(-0.097; -0.023)	**0.001**	-5.462(-8.263; -2.661)	**0.001**
Antipsychotic polypharmacy, Ref (No)				
Yes	-0.040(-0.075; -0.006)	**0.021**		
Medication adherence, Ref (Good adherence)				
Poor adherence	-0.043(-0.072; -0.013)	**0.004**		
Side effect burden, Ref(absent/mild)				
Moderate	-0.011(-0.042;0.019)	0.466		
Severe	-0.081(-0.135;-0.028)	**0.003**		

EQ-5D-5L: EuroQoL life questionnaires five dimensions with five levels; EQ-VAS: EuroQoL visual analog scale

6. Discussion

This cross-sectional study aimed to assess antipsychotic polypharmacy and health-related quality of life among patients with schizophrenia on follow-up at Ayder Comprehensive Specialized Hospital (ACSH) in Mekelle, Tigray, Ethiopia.

The study's findings revealed a prevalence of APP was 25.8%. This prevalence was comparable to reports from Japan (23.6%), and Hong Kong (26%) (74, 79). but higher than those reported in studies in Spain (13.9%), Bahrain (10.8%), Korea (20.4%), and Ethiopia (22.7%) (44, 69, 80, 82). Additionally, the APP rate in this study was fairly high compared with the global median prevalence of 19.6% reported in a systematic review (39). The higher APP prevalence could be attributed to an insufficient response to monotherapy (146). The limited availability of clozapine and newer antipsychotic medications in the study setting may also contribute to the higher prevalence of APP in the current study setting. These finding may imply that prescribers should be cautious when prescribing multiple antipsychotics and patients receiving APP require close monitoring to reduce the risk of adverse effects associated with combined antipsychotic use. Moreover, a thorough review of medication regimens may be necessary to optimize treatment outcomes and improve patient safety.

Another Ethiopian study reported a somewhat higher APP prevalence of 28.2% (45). In addition, this finding was lower than multicenter findings from Asia (40.5%), Australia (39%), India (43.9%), Nigeria (50.9%, and 70.4%), South Africa (56.7%), Finland (57.5%), and Turkey (70.71%) (41, 42, 64, 67, 70, 81, 83). It is also lower than a review and meta-analysis of African countries in which the prevalence of APP was 40.6% (27.6% to 53.7%) (46).

The difference in reported APP prevalence across studies can be attributed to several factors. Differences in study characteristics, such as sociodemographic profiles, methodologies, populations studied, sample sizes, study areas, and durations, may contribute to these discrepancies. Additionally, clinician expertise and experience can influence prescribing patterns. Furthermore, some studies have examined APP in a broader range of psychiatric disorders, including schizoaffective, acute psychosis, and mood disorders, as well as in hospitalized patients (41, 64, 67, 74, 79, 82). In contrast, participants in this study were outpatients who are usually less severly ill and had a lower persistent symptoms compared to

inpatients, APP rates were expected to be lower as studies have also reported a direct correlation between the illness severity and APP prescription (147).

Variations in inclusion and exclusion criteria, as well as the operationalization of APP, may also account for the differences. While some studies define APP as the use of two or more antipsychotics concurrently (70) others may use a longer duration threshold, such as more than 90 days (41). Moreover, the exclusion of severely ill schizophrenic patients in this study, and the varying proportions of LAI antipsychotic use across studies, could further contribute to the observed prevalence disparities (83).

Prescribing trends have shifted toward SGAs, as they are preferred over FGAs because of their fewer side effects (148). However, the majority of participants in this study were prescribed FGAs. Regarding patterns of APP, most participants on APP (94%) were taking two antipsychotics, and among these, 73.3% were taking a combination of two FGAs which remains unsupported by strong evidence. The common FGA combination was fluphenazine depot with oral chlorpromazine, which aligns with findings from studies in Ethiopia, Palestine, and Nigeria (42, 44, 45, 83), but differs significantly from the report of Kim et al. in which only 6.4% had FGA combinations, 46.82% received FGAs-SGAs combinations, whereas SGAs combinations were prescribed to another 46.82% (80). Similarly, most other studies reported more combinations of SGAs and SGAs with FGAs (68, 71, 77, 81, 82). A possible explanation for the greater use of FGA in this study setting may be attributed to their relatively better affordability and accessibility compared with those of SGAs. Therefore, clinicians prefer to prescribe FGAs for these reasons. These findings may suggest that improving the availability and accessibility of newer antipsychotics may serve as a crucial strategy to reduce APP and promote the use of safer, more effective antipsychotic treatments.

In this study, early onset of illness, duration of illness, comorbid mental illness, positive symptom, anticholinergic drug use, adjuvant medication use, and medication adherence were found to be significantly associated with antipsychotic polypharmacy.

Regarding the onset of illness, our study found that participants with an early onset of schizophrenia symptoms were more likely to be prescribed APP. This finding is consistent with previous studies conducted in China, Korea, and France (73, 88, 90). This association may be

explained by the fact that an earlier onset of schizophrenia is often accompanied by a poorer response to treatment (149), which may prompt clinicians to prescribe multiple antipsychotic medications in an attempt to achieve better symptom control. These findings suggest that early intervention and treatment strategies may be crucial for improving treatment outcomes in patients with early-onset schizophrenia.

A significant association was found between longer illness duration (>10 years) and APP, which aligns with previous findings (44, 77, 91). These could indicate that the patients in the APP might have had a longer illness which could have influenced the decision of clinicians on prescribing APP. A plausible explanation for this association is that extended duration of illness may also be accompanied by more likely to experience treatment resistance (150). This can lead clinicians to prescribe multiple antipsychotic medications, in an attempt to improve patient outcomes. This suggests the importance of early and sustained treatment interventions, as well as regular monitoring and adjustment of medication regimens, to optimize treatment outcomes and minimize the need for APP in patients with longer illness durations.

Several studies have reported the benefits of APP in reducing symptoms in patients with schizophrenia, with a review, meta-analysis, and RCTs showing APP superiority over APM in total symptom reduction (151). However, most of the included studies were clozapine-augmentation studies. The current study revealed associations between APP and higher scores on the positive subscale of the PANSS, suggesting that clinicians may prescribe combinations when monotherapy fails to manage positive symptoms. While the cross-sectional design causality cannot be established, future longitudinal studies are needed to determine whether APP causes or results from persistent positive symptoms in schizophrenia.

Our study's findings raise concerns regarding the safety of APP, as we observed a significant positive association between APP and co-prescription of anticholinergic medications, which may suggest a risk for increased extrapyramidal side effects (EPS) with APP. The findings of our studies are supported by those other studies (41, 73, 77, 78, 79). The use of higher antipsychotic doses, which is more common with APP, may be a key contributing factor to the increased likelihood and severity of side effects (152). The predominance of FGA + FGA polypharmacy in our study, and the co-prescription of anticholinergic medications observed in our study may be

explained by the increased likelihood of requiring anticholinergic agents to manage and prophylactic treatment of EPS.

Our study found that patients on antipsychotic polypharmacy were less likely to be co-prescribed with other adjuvant medications, and anxiolytics/hypnotics (Benzodiazepine) were the common adjuvant medication prescribed in our study. This aligns with another study that reported similar findings (73). The lower use of adjuvant medications in APP patients may be due to the polypharmacy approach itself, which could be targeted at addressing specific comorbid symptoms, such as anxiety, violent behavior, and sleep disturbances, rather than relying on additional medications typically used to manage these symptoms (30, 153). The findings of the study indicate that prescribers may utilize APP to target additional symptoms, such as insomnia, alongside the management of psychotic symptoms. These suggest that prescribers should be aware of the importance of alternative adjunctive therapies, to target symptoms rather than relying on APP for these purposes. A further implication of the research this that prescribers' preferences for APP over other treatments should be examined in more detail, including the potential influence of clinical experience, patient characteristics, and perceived treatment outcomes, as well as the availability of newer antipsychotic medications.

The results of our study revealed a statistically significant association between poor medication adherence and APP. This finding aligns with previous research in Ethiopia (45), Nigeria (99), India (81), and Switzerland (100). The possible reason could be the likelihood of more drug-induced side effects due to multiple drug combinations, a more complicated regimen, and the high pill burden in patients taking APP. The findings suggest that pharmacists, as integral members of the healthcare team, can play a vital role in patient care by facilitating informed treatment decisions, providing education on potential adverse events, and offering guidance on mitigation strategies. Such activities along with providing psycho-education can enhance treatment adherence and overall well-being.

According to the GASS, all patients reported at least one side effect from their medication, with sedation and CNS side effects, anticholinergic side effects, and cardiovascular side effects being the most common. These findings align with previous studies in Ethiopia and a cross-sectional study of 7 countries, where most patients (71.3% and 83.2%, respectively) reported sleep disturbances (154, 155). The findings of the present study on align with those of a prior study in

Ethiopia, which reported that 53.2% of patients experienced anticholinergic effects (156). Evidence indicates that EPS and sedation are the most common side effects of FGAs, which are the most commonly prescribed antipsychotics for the current study participants (157). In addition, anticholinergic agents, which were prescribed for 18.2% of the study participants in the current study, may produce adverse effects, including sedation, cognitive impairment, and increased total anticholinergic drug burden. Therefore, it is important to regularly monitor the side effects of antipsychotics to optimize treatment and minimize adverse effects. We also recommend conducting further studies to evaluate anticholinergic burden and its impact on cognitive impairment in schizophrenic patients.

The current study found a higher CV side effect similar to the study conducted in Ethiopia (126). While FGAs generally have lower cardiovascular risk than second-generation antipsychotics, certain FGAs like chlorpromazine and fluphenazine have higher cardiovascular risks, including orthostatic hypotension (158). The high CV side effects in this study may be due to the use of chlorpromazine and fluphenazine depot, which were the most commonly prescribed medications among the participants. The current study reported lower rates of weight gain, metabolic, and prolactin-related side effects compared to previous findings of high prevalence of these side effects (159). This may be because the majority of participants were treated with FGAs, which have a lower risk of weight

This study examined the HRQoL of outpatients with schizophrenia using the EQ-5D-5L. The median EQ-VAS score (65%) was lower than the general Ethiopian population (median of 90%) (138). This reduced quality of life aligns with evidence that schizophrenia patients typically have a lower HRQoL compared to the general population (105, 106, 108, 113). Similar to previous studies, the current study revealed that patients with schizophrenia reported problems with all descriptive dimensions of the EQ-5D-5L (160, 161, 162). A significant proportion of outpatients in our study reported problems with anxiety/depression, self-care, and daily activities, which suggests their HRQoL is impacted not only by mental function, but also by daily functioning. To support social reintegration and daily functioning, a safe and secure living environment that addresses their physical, social, and mental needs is crucial. Clinicians and family members must understand their specific challenges and take targeted steps to address them.

The study revealed that the mean EQ-5D-5L utility value for patients with schizophrenia was 0.813, which was lower than the mean for the general Ethiopian population (0.94) (138). This difference can be attributed to the multitude of challenges faced by individuals with schizophrenia. These include positive and negative symptoms, a chronic nature, and long-term treatment of the illness, as well as its debilitating medication side effects and social stigma, leading to marginalized living conditions, poor housing, low income, limited education, and inadequate vocational and social skills (15, 163).

Compared with previous studies, our mean EQ-5D-5L utility score (0.81) was lower than that reported in the Serbian study (0.86) (164), and approximately similar to that reported in two studies from Singapore (0.82 and 0.81) (165, 166), and Taiwan (0.80) (167), but higher than reported in Europeans (0.57) (168), the UK (0.69) (106), and Japan (0.77) (105). These discrepancies may be attributed to differences in patient characteristics, sociocultural beliefs, medication availability, healthcare systems, and access, as well as the value set used, which could have contributed to these variations.

Furthermore, our study identified factors associated with HRQoL. A statistically significant association was found between the EQ-5D-5L utility score and female sex, being not working, the presence of comorbid physical illness, antipsychotic polypharmacy, poor medication adherence, and experiencing a severe side effects.

The findings of the present study are consistent with those of other studies that revealed the female sex was associated with higher QOL when compared to males with schizophrenia (110, 116, 169). One possible explanation is that the early onset of psychosis in males, which is often associated with a more severe clinical presentation, can also have devastating consequences, including disadvantages in schooling, employment, friendships, and intimate relationships may contribute to poor HRQoL in males (149, 170). The other possible reason could be that females tend to have higher estrogen levels, which have an antidopaminergic effect that may contribute to a milder course of illness (171). This could explain why females have a better HRQoL than males with schizophrenia, which is supported by a literature review suggesting that, compared to males, females with schizophrenia have a better response to medications, a more favorable prognosis of illness, and better social functioning (172).

Another factor that was negatively associated with HRQOL in the current study was that participants who were not working had a lower HRQoL compared to those who were working. This finding was supported by studies done in China (169) and Jordan (116). The chronic nature of schizophrenia and its clinical symptoms, such as a lack of motivation and goal-oriented activity, often make it challenging for individuals to consistently perform job duties. This can lead to job loss and unemployment, which in turn can contribute to financial hardship, social isolation, decreased self-esteem, and a loss of daily structure. Our results suggest that having a job plays a key role in the daily life of the individual, which is supported by the previous literature, showing that occupation not only results in financial gain but also promotes individual integration in the community and supports the perception of self-worth and growth (173).

The presence of co-morbid physical illness was also a factor that negatively affected HRQoL in our study. Our finding was consistent with studies done in Ethiopia (54, 119), Nigeria (174), and A multi-centered study of eight countries (104). Chronic medical conditions can negatively impact HRQoL by causing physical impairments, such as pain, balance issues, and reduced strength, which limit physical function and activity, leading to overall HRQoL deterioration. (175). Our findings indicate that early detection and treatment of comorbid physical illnesses in individuals with schizophrenia are crucial for achieving better treatment outcomes and improving their overall quality of life.

This study also revealed that non-adherence to antipsychotic medications is significantly and negatively associated with HRQoL and this result is in line with the previous studies in Nigeria (118), and Ethiopia (54, 119). Similarly, another study from Nigeria showed that good medication adherence is positively associated with good HRQoL (117). This could be because non-adherence to medication may contribute to poor symptom control, increased risk of relapse, and decreased functionality, ultimately leading to a further decline in mental health and health-related quality of life. These findings indicate that medication adherence plays a crucial role in the quality of life of individuals with schizophrenia and that improving medication adherence through counselling and follow-up is a promising approach to enhancing the quality of life of individuals with schizophrenia.

In the present study experiencing severe side effects, as reflected by higher GASS scores was found to be a factor that is significantly and negatively associated with patients' HRQoL and our

finding is consistent with those of previous studies, including a multicenter study across seven countries (155), and Japan (105). The adverse effects of antipsychotics (including EPS, sexual dysfunction, sedation, and weight gain) have also been reported to be associated with lower EQ-5D scores and decreased utility scores (176, 177). Our finding suggests that the burden of antipsychotic side effects can significantly impact patients' HRQoL. The negative impact of side effects on quality of life can be attributed to reduced functional capacity, emotional distress, decreased adherence, stigma, and social withdrawal. Therefore, effective side effect management is essential, and strategies such as regular monitoring and dose optimization are necessary to alleviate the burden of antipsychotic side effects and enhance HRQoL.

Antipsychotic polypharmacy was also another factor that was significantly and negatively associated with HRQoL in the current study. This finding is consistent with studies done in Germany (121), Turkey (122), and Ethiopia (54). This might be due to that APP, which is associated with greater illness severity, treatment resistance, higher overall doses, side effects, higher use of concurrent anticholinergic medications, drug interaction, non-adherence, and increasing cost of treatment (39, 52, 53), may contribute to a negative impact on the HRQoL for individuals with schizophrenia. In addition, attributed to the fact that the most common combination of APP in our participants was FGA with FGA, which is known to increase the risk of EPS and other side effects (157). Furthermore, patients on APP exhibited higher symptom scores on measurement scales compared to those on APM, and a significant proportion (32.6%) of APP users experienced severe side effects, which may have contributed to the lower HRQoL observed in this group. Consequently, implementing targeted programs for optimal antipsychotic utilization and regular follow-up care may need to improve the HRQoL for individuals with schizophrenia receiving APP.

Contrary to our findings, a study done in China reported that APP was associated with higher QOL (73). This discrepancy could be attributed to the difference in the HRQoL measurement tool used and the influence of social support from family members, which the author suggested as a possible explanation for the better mental health-related QOL in the APP group. Another possible explanation could be that the difference in HRQoL between the two groups could be difficult to detect in clinically stable outpatients.

7. Strengths and Limitations of the Study

7.1. Strengths of the Study

The strengths of this study, which include a fairly large sample size and systematically randomly selected representative sample, use of a validated HRQoL measurement tool, and it also evaluated the burden of antipsychotic side effects, the onset of illness, disease severity, medication adherence, and their associations with antipsychotic polypharmacy and health-related quality of life. Importantly, the study also assessed the associations between APP and HRQoL. To the best of our knowledge, the current study is the first to establish the utility value for outpatients with schizophrenia in Ethiopia, and also assess the practice of APP in the study setting.

7.2. Limitations of the Study

Despite its strengths, this study has several limitations. One of the main limitations of this study is the cross-sectional nature of the study design which prevented the exploration of the causality of associations between the dependent variables (APP, and HRQOL) its correlates could not be ascertained. Another limitation of this study is the applicability of the results, which may be restricted to clinically stable schizophrenia outpatients because it excludes severely ill and hospitalized schizophrenia patients, the findings may have reduced generalizability, as they may not be fully applicable to schizophrenia patients. The other limitation that reduces the generalizability of the study is that it involved one setting, the result of this study may not apply to other health facilities in Ethiopia because of differences in the availability of antipsychotics and psychiatry services. Another limitation of this study is that the reasons or rationale for APP was not explored, and due to budget and time constraints, extrapyramidal side effects of antipsychotics were not investigated. Moreover, the study did not assess important factors such as social support and stigma, which could significantly influence HRQoL in schizophrenia patients. Lastly, the HRQoL of the study participants was evaluated using only a generic QOL instrument rather than a disease-specific measure, which may not accurately capture the unique experiences and challenges faced by this population.

8. Conclusion and Recommendations

8.1. Conclusions

The prevalence of APP was found to be high among the current study participants, with about one in four outpatients with schizophrenia receiving APP. The most common combination was two first-generation antipsychotics. Patients with an early onset of illness, longer duration of illness, comorbid mental illness, PANNS-positive symptoms, anticholinergic drug use, adjuvant medication use, and medication non-adherence were found to have a significant association with antipsychotic polypharmacy. The findings of this research indicate that sedation and central nervous system-related side effects were the most common type of antipsychotic-related side effects. The study also found that outpatients with schizophrenia had lower HRQoL compared to the non-schizophrenic-general population in Ethiopia, as measured by the EQ-5D-5L utility and EQ-VAS scores. Most patients reported problems in the Anxiety/depression and self-care dimension of EQ-5D-5L. Being not working, presence of comorbid medical illness, antipsychotic polypharmacy, poor medication adherence, and experiencing a severe side effect were significantly negatively associated with poor HRQoL. Conversely, the female sex was significantly positively associated with good HRQoL.

8.2. Recommendations

- ✓ The authority bodies in Ethiopia should develop clear guidelines to guide clinicians on the appropriate use of antipsychotics while considering the benefits and risks of APP.
- ✓ We suggest implementing regular medication reviews and optimizing medication regimens to minimize the use of APP, especially in patients with longer duration of treatment, comorbid mental illness, poor adherence, and severe psychotic symptoms.
- ✓ Clinical pharmacy services should be delivered in the psychiatry ward for comprehensive monitoring of antipsychotic-related side effects, particularly in patients on APP, to proactively identify and manage these adverse events and to develop standardized protocols for the assessment and management of common antipsychotic side effects.
- ✓ Healthcare providers should encourage the implementation of patient-centered approaches that empower individuals to actively participate in their treatment decisions, which helps to enhance patient medication adherence.
- ✓ Clinicians consider alternative treatment strategies that use evidence-based, symptom-specific medications for comorbid conditions, rather than relying on APP.
- ✓ Clinicians treating patients with schizophrenia should focus not only on reducing symptoms but also on improving HRQoL, which is a crucial component of treatment strategies that can help achieve a more holistic approach to patient care.
- ✓ Clinicians should advise patients and caregivers on methods to reduce anxiety and depression, which include exercising, sleep hygiene, and cessation of substance use. They should also recommend psychosocial and emotional support to improve self-care.
- ✓ Policymakers should prioritize improving the availability and accessibility of newer-generation antipsychotics with better side effect profiles and efficacy in treating treatment-resistant schizophrenia, which could help reduce the need for APP.
- ✓ Furthermore, multi-centered follow-up research should be undertaken by including inpatients with schizophrenia, which explores the rationale, benefits, and risks of APP, and the prognosis of HRQoL of schizophrenia patients by using both generic and disease-specific tools, and the risk factors for common antipsychotic-induced side effects. This approach allows for a more comprehensive understanding of the causal relationships between the variables and their correlates.

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ANNEXES

Annex I. Participant information sheet and consent form (English version)

Dear respondent my name is _____. I am here to collect data for a study entitled **"Assessment of Antipsychotic Polypharmacy, Health-Related Quality of Life, and Associated Factors among Schizophrenia Outpatients".** The research investigator is **Elias fitsum**, a master's student in Pharmacy Practice at Addis Ababa University, Department of Pharmacology and Clinical Pharmacy. The purpose of this study is to assess Antipsychotic Polypharmacy and health-related quality of life, associated factors among Schizophrenia patients in Ayder Comprehensive Specialized Hospital. The results obtained from this study are useful in directing decision makers' of Schizophrenia patients' related treatments and programs, to know Schizophrenia patients' health-related quality of life, Schizophrenia patients' health utility, and the factors affecting HRQoL and utility of Schizophrenia patients. To achieve the study objective, your honest and genuine participation in responding to the question prepared is very important and highly appreciated.

You will not receive any payment or other personal benefit for participation in this study. But study findings will add input on decisions made by policymakers that might positively or negatively affect your Health-related quality of life and the health amount of utility gained from your health services. There is also no cost to you for participating in this study but it will take 30-45 minutes of your time. Your selection to participate in this study is by chance and there is no specific issue targeting you as a participant. You do not have any harm because of participating in this study. Your participation in this study is completely voluntary. You have the right to be in the study or to withdraw at any time; no influence insists you to participate unless you voluntarily confirm to participate.

We would like to assure you that privacy will strictly be maintained throughout. Your personal information will be maintained through the use of unique identifiers, through restricting access to the data set to the principal investigator and those working directly with him and you don't need to write your name or any special identification that might disclose who you are. If you have any questions or would like to receive further information about the study; please contact the following responsible bodies:

Persons to contact:

Elias Fitsum Yigezaw

Mob: +251-9-85-75-78-32

E-mail: Eliasbisrat16@gmail.com

Are you willing to participate in this study?

Yes☐ No ☐

If agreed to participate and give his/her oral consent confirm with his/her signature and then conduct the interview, if not willing to participate thank him/her and proceed to the next participant.

Participant's signature: _____

Thank you for your time.

Annex II: Data Collection Tool

Card No._____

Part I. Participant Socio demographics and behavioral data.

1. Sex A. Female ❑ B. Male ❑

2. Age (years) _____

3. Age of onset of illness (Year) _____

4. Marital status A. Single ❑ B. Married ❑ C. Divorced ❑ D. Widowed ❑

5. Educational status

A. No formal education ❑ B. Primary ❑ C. Secondary ❑ D. Higher education ❑

6. Residence A. Urban ❑ B. Rural ❑

7. Working status A. Working ❑ B. Not working ❑

8. Current substance use A. Yes ❑ B. No ❑

8.1 Alcohol A. Yes ❑ B. No ❑

8.2 Smoking cigarette A. Yes ❑ B. No ❑

8.3 Khat A. Yes ❑ B. No ❑

Part II: Positive and Negative Syndrome (PANSS) Rating

		Absent	Minimal	Mild	Moderate	Moderate severe	Severe	Extreme
P1	Delusions	1	2	3	4	5	6	7
P2	Conceptual disorganization	1	2	3	4	5	6	7
P3	Hallucinatory behavior	1	2	3	4	5	6	7
P4	Excitement	1	2	3	4	5	6	7
P5	Grandiosity	1	2	3	4	5	6	7
P6	Suspiciousness/Persecution	1	2	3	4	5	6	7
P7	Hostility	1	2	3	4	5	6	7
N1	Blunted affect	1	2	3	4	5	6	7
N2	Emotional withdrawal	1	2	3	4	5	6	7
N3	Poor rapport	1	2	3	4	5	6	7
N4	Passive/apathetic social withdrawal	1	2	3	4	5	6	7
N5	Difficulty in abstract thinking	1	2	3	4	5	6	7
N6	Lack of spontaneity & flow of conversation	1	2	3	4	5	6	7
N7	Stereotyped thinking	1	2	3	4	5	6	7
G2	Anxiety	1	2	3	4	5	6	7
G3	Guilt feelings	1	2	3	4	5	6	7
G4	Tension	1	2	3	4	5	6	7
G5	Mannerisms & posturing	1	2	3	4	5	6	7
G6	Depression	1	2	3	4	5	6	7
G7	Motor retardation	1	2	3	4	5	6	7
G8	Uncooperativeness	1	2	3	4	5	6	7
G9	Unusual thought content	1	2	3	4	5	6	7
G10	Disorientation	1	2	3	4	5	6	7
G11	Poor attention	1	2	3	4	5	6	7
G12	Lack of judgment & insight	1	2	3	4	5	6	7
G13	Disturbance of volition	1	2	3	4	5	6	7
G14	Poor impulse control	1	2	3	4	5	6	7
G15	Preoccupation	1	2	3	4	5	6	7
G16	Active social avoidance	1	2	3	4	5	6	7

Part III: Glasgow Antipsychotic Side-Effect Scale (GASS)

S no.	Over the past week	Never	Once	A few times	Everyday	If you feel distress tick this box
1	I felt sleepy during the day					
2	I felt drugged or like a zombie					
3	I felt dizzy when I stood up and/or have fainted					
4	I have felt my heart beating irregularly or unusually fast					
5	My muscles have been tense or jerky					
6	My hands or arms have been shaky					
7	My legs have felt restless and/or I couldn't sit still					
8	I have been drooling					
9	My movements or walking have been slower than usual					
10	I have had, or people have noticed uncontrollable movements of my face or body					
11	My vision has been blurry					
12	My mouth has been dry					
13	I have had difficulty passing urine					
14.	I have felt like I am going to be sick or have vomited					
15.	I have wet the bed					
16	I have been very thirsty and/or passing urine frequently					
17	The areas around my nipples have been sore and swollen					
18	I have noticed fluid coming from my nipples					
19	I have had problems enjoying sex					
20	Men only: I have had problems getting an erection					
For the last three months		**YES**	**NO**	**Thick this box if distressing**		
21	Women only: I have noticed a change in my periods					
22	Men and women: I have been gaining weight					

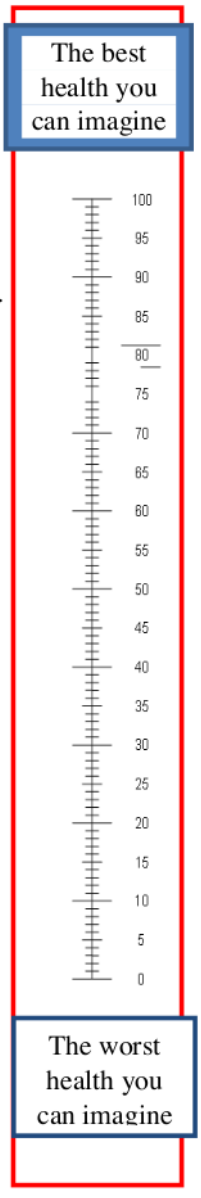
IV: Health-Related Quality of Life Questionnaire Self Completed (EQ-5D-5L) UK (English) © 2009 EuroQol

MOBILITY	
I have no problems walking about	❑
I have slight problems in walking about	❑
I have moderate problems in walking about	❑
I have severe problems in walking about	❑
I am unable to walk about	❑
SELF-CARE	
I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑
USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	
I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑
PAIN / DISCOMFORT	
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑
ANXIETY / DEPRESSION	
I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

Health-Related Quality of Life Questionnaire (EQ-VAS) UK (English) © 2009 EuroQol

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
- 0 means the worst health you can imagine.
- Mark an X on the scale to indicate
- How your health is TODAY
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY ☐



	Part V: 8-Item Morisky Medication adherence(AEDs) scale (MMAS-8)	Yes	No
1	Do you sometimes forget to take your AED/s?		
2	People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your AED/s?		
3	Have you ever cut back or stopped taking your AED/s without telling your doctor because you felt worse when you took it?		
4	When you travel or leave home, do you sometimes forget to bring along your mAED/s?		
5	Did you take all your AED/s yesterday?		
6	When you feel like your symptoms are under control, do you sometimes stop taking your AED/s?		
7	Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?		
8	How often do you have difficulty remembering to take all your AED/s? A) Never/rarely❑ B) Once in a while ❑ C) Sometimes ❑ D) Usually ❑ E) All the time ❑		

Part VI: Data Abstraction Format from Patients' Medical Chart

I. Clinical Characteristics

1. Duration of illness _____

2. Duration of treatment_____

3. Other co-morbid mental illness _____

4. Other co-morbid physical illness _____

5. Number of psychiatry hospital Admission(s) _____

II. Medication Profile

Indication	Drug product (Generic Name)	Full Dosage regimen	Started Date	Stopped Date

Annex III. Participant Information Sheet and Consent form (Tigrinya version)

ቅጥዒ- 3 ኣብ መፅናዕቲ ንምስታፍ ናይ ፍቃደኝነት መግለፂ ቅጥዒ

ዝተከበርኩም/ክን ናይዚ መፅናዕቲ ተሳተፍቲ ኣነ ሽመይ _____ይብሃል። ሕዚ ኣብዚ ዝተረከብኩሉ ምክንያት "ኣብ ዓይደር ኩለመዳያዊ ፍሉይ ሆስፒታል ዝርከቡ ኣብ ምክትታል ዝርከቡ ናይ ደገ ሕሙማት ናይ ስኪዞፍረኒያ ተሓካሚ ዘለዎም ጥዕና ተንከፍን ተዛመድትን ዝኮኑ ናይ ብዛዕባ ኣጠቓቕማ መድሃኒትን ሂወት ምኞት ኣነባብራን ፤ ኣብዚኦም ፅልዋ ከሕድሩ ዝክእሉ ምክንያታትን ናይ ጥዕና መሕትት ብምጥቃም ንዝግበር መፅናዕቲ" ሓበሬታ ንምእካብ እዩ። ናይዚ መፅናዕቲ ብዓልዋና ኣይተ ኤልያስ ፍፁም እንትኮኑ ኣብ ኣዲስ ኣበባ ዩኒቨርስቲ ፋርማሲ ቤት ትምህርቲ ናይ ፋርማስን ድሕረ- ምረቃ ተምሃራይ እዮም። ናይዚ መፅናዕቲ ዋና ዕላማ ናይ ስኪዞፍረኒያ ተሓካሚ ዘለዎም ጥዕናን ጥዕና ተንከፍ ዝኮኑ ናይ ሂወት ምኞት ኣነባብራን ከምኡ እውን ኣብዚኦም ፅልዋ ከሕድሩ ዝክእሉ ምክንያታትን ንምፅናዕ እዩ። ብተወሳኪ ስኪዞፍረኒያ ተሓካሚ ካብ ዝግበረሎም ናይ ጥዕና ኣገልግሎት ክንደይ ዝኣክል ተጠቀምቲ ከምዝኮኑ ንምፍላጥ እዩ። ናይዚ መፅናዕቲ ውፅኢት ናይ ስኪዞፍረኒያ ተሓካሚ ዝምልከት ሕክምናን ነዚ ኣመልኪቱ ንዝቅረፅ ፕሮግራምን ንዝውሰኑ ናይ ፖሊስ ቀረፅቲ ብመረዳእታ ዝተደገፈ ንክከውን ይሕግዝ። ካብዚ ብተወሳኪ ናይ ስኪዞፍረኒያ ተሓካሚ ካብ ዝግበረሎም ናይ ጥዕና ኣገልግሎት ክንደይ ዝኣክል ጥዕነኦም ኣብ ምምሕያሽ ተጠቃሚ ከምዝኮኑ ፣ ከምኡ እውን ነዚ ናይ ጥዕነኦም ምኞት ብኣሉታዊ ወይ ድማ ብኣወንታ መንገዲ ፅልዋ ዘሕድሩ ተዛመድቲ ምክንያታት ንምፍላጥን ነዞም ምክንያታት መሰረት ዝገበረ መአረምታ ንምግባርን ዘኽእል እዩ።

ኣብዚ መፅናዕቲ ብምስታፎም ምክንያት ዝክፈሎም ነገር የለን። ነገር ግን ናይዚ መፅናዕቲ ውፅኢት ንናይ ልቢ ጥዕናን ጥዕና ተንከፍ ዝኮኑ ጉዳያትን መሰረት ዝገበረ ፖሊስ ንዝቀርፁ ኣካላት ተወሳኪ መረዳእታ ብምሃብ ርኡይ ኣስተዋፅኦ ኣለዎ። ካብዚ ብተወሳኪ በቲ ዝግበረሎም ናይ ጥዕና ኣገልግሎት ክንደይ ዝኣክል ተጠቃሚ ምኳኖም ንምርዳእን በዚ መሰረት ድማ መስተካካሊ ንምግባርን ይሕግዝ። ብካሊእ ወገን ኣብዚ መፅናዕቲ ብምስታፎም ምክንያት ዝበፅሖም ምንም ዓይነት ጉድኣት የለን። እንተበዝሐ ካብ ግዘኦም ካብ 30-45 ደቂቃ ክወስደሎም ይክእል እዩ።

ኣብዚ መፅናዕቲ ንምስታፍ ዝተመረፅሉ ምክንያት ብኣጋጣሚ እምበር ካሊእ ንዐኦም መሰረት ዝገበረ ዝተፈለየ ምክንያት የለን። ኣብዚ መፅናዕቲ ንመስታፍ ሙሉእ ብሙሉእ ብናቶም/ተን ነፃ ፍቃደኝነት እዩ ዝውሰን። ኣብዚ መፅናዕቲ ንምስታፍ ኮነ ኣብ ዝደለይዎ/ኦ ስዓት ካብቲ መፅናዕቲ ናይ ምቁራፅ ዘይተገደበ መሰል ኣለዎም። ስለዚ ኣብዚ መፅናዕቲ ንምስታፍ ፍቃደኛ እንተዘይኮይኖም/ነን ማንም ኣገዲዱ ንክሳተፉ ኣይገብሮምን/ንን።

ንሶም/ሰን ዝሀቡና/ባና መረዳእታ ምስጥራዊነቱ ሙሉእ ብሙሉእ ክንሕሉ ኢና። ናቶም/ተን ናይ ብሕቶም/ተን መረዳእታ ካብቲ መፅናዕቲ ብዓል ዋናን ምስኡ ብቀጥታ ዝሰርሑን ሰባት ወፃኢ ካሊእ ሰብ ክረክቦ ኣይክእልን። ናቶም/ተን መንነት ክገልፁ ዝክእሉ ከም ሽሞም ምፅሓፍን ምግላፅን ዝኣመሳሰሉ ነገራት ፍፁም ኣይህልውን። ዝኮነ ዓይነት ሕቶ ይኹን ሪኢቶ እንተሃልይዎም/ወን ወይ ስለ እቲ መፅናዕቲ ተወሳኪ መረዳእታ ንምሕታት ኣብ ዝደለይሉ ስዓት ነዞም ዝስዕቡ ሓላፍነት ንዝተውሃቦም ኣካላት በቲ ዝሰዕብ ኣድራሻኦም ምዝርራብ ይክእሉ እዮም።

ኤልያስ ፍፁም (ሞቫይል 09-85-75-78-32 ኢሜይል eliasbisrat16@gmail.com

ኣብዚ መፅናዕቲ ንምስታፍ ፍቃደኛ ድዮም/የን? እወ ☐ ኣይፋሉን ☐

ኣብዚ መፅናዕቲ ንምስታፍ ፍቃደኛ እንተኮይኖም/ነን ናይ ቃልን ናይ ፅሑፍን ፍቃደኝነቶም/ተን እንተሂቦም እቲ ቃለ መሕተት ይጀምሩ።

ኣብቲ መፅናዕቲ ንምስታፍ ፍቃደኛ እንተዘይኮይኖም/ነን ናብቲ ዝቅፅል ተገልጋሊ ይሕለፉ/ፋ።

ናይዚ መፅናዕቲ ተሳታፊ ፌርማ _____

ንግዚኦም/አን ነመስግን!

ካርድ ቁጽሪ _____

ቀዳማይ ክፋል: ናይ ተሳታፊ ማሕበረ-ስነ-ህዝብን ባህርያዊ መረዳእታን።

1. ጾታ 1. ተባዕታይ 2. አንስታይ

2. ዕድመ _____ዓመት

3. ዕድመ ምጅማር ሕማም_____ዓመት

4. ኩነታት ሓዳር 1. ዘይተመርዐወ/ት 2. ዝተመርዐወ/ት 3. ዝፈትሐ/ት 4. ሰብኣያ/ሰበይቱ ዝሞታ/ተት

5. ደረጃ ትምህርቲ 1. ስሩዕ ትምህርቲ ዘይተምሃረ/ት 2. ቀዳማይ ብርኪ 3. ካልኣይ ብርኪ 4. ዲፕሎማን ልዕሊኡን

6. መንበሪ 1.ከተማ 2. ገጠር

7. ናይ ስራሕ ኩነታት 1. ሰራሕተኛ 2. ዘይሰርሕ

8. ህሉው ኣጠቓቕማ ንጥረ ነገራት. 1.እዎ 2. አይፋሉን

8.1 ኣልኮላዊ መስተ 1.እዎ 2. አይፋሉን
8.2 ሽጋራ ምትካኽ 1.እዎ 2. አይፋሉን
8.3 ጫት ምሕካኽ 1.እዎ 2. አይፋሉን

ካልኣይ ክፋል: ናይ ተሓከምቲ ናይ መድሓኒት ኣዎሳስዳ ዝምልክት

1. ሓደ ሓደ ጊዜ መድሓኒት ምውሳድ ረሲዖም ይፈልጡዶ ? 1. እዎ 2. አይፋሉን

2. ሓደ ሓደ ጊዜ ሰባት ካብ ምርሳዕ ወጻኢ መድሓኒት ከይወሰዱ ይተርፉ እዮም። አብዝሓለፈ ክልተ ሰሙን መድሓኒት ከይወሰዱ ዘሕለፍዎ መዓልቲ ነይሮም ዶ? 1. እዎ 2. አይፋሉን

3. ሕማሞም ስለ ዝተባኣኣሰ ሓኪሞም ከየማኽሩ መድሓኒቶም አቓሪጾም ዶ ይፈልጡ ? 1. እዎ 2. አይፋሉን

4. ኣብ መንገሻ ጊዜ መድሓኒቶም ብትክክል ዶ ይዎስዱ ? 1. እዎ 2. አይፋሉን

5. ትማሊ ኩሉ መድሓኒቶም ዎሲዶም ዶ ? 1. እዎ 2. አይፋሉን

6. ሕማመይ ቀኒሱ/ሕሹኒ ኢሎም መደሓኒቶም ጠጠው ኣቢሎም ዶ ይፈልጡ ? 1. እዎ 2. አይፋሉን

7. መድሓኒት ዘይምዉሳድ ናይ ሓደ ሓደ ሰባት ፀገም እዩ። መድሓኒቶም ብትእዛዝ መሰረት ንምዉሳድ ይሰላቸዉ ዶ ? 1. እዎ 2. አይፋሉን

8. ኩሉ መድሓኒቶም ንምዉሳድ ዝኽበደኩም ክንደይ ጊዜ እዩ ?

1. ፈፂሙ 2. ብዝኾነ ጊዜ ሓደ ጊዜ 3. ሓደ ሓደ ጊዜ 4. ብተደጋጋሚ ግዜ 5. ኩሉ ግዜ

ግላስኮ ጸረ-ኣእምሮኣዊ ጎናዊ ሳዕቤን መለክዒ

	ኣብ ዝሓለፈ ሰሙን	**ፈጺሙ**	**ሓንሳዕ**	**ኣብ ውሑዳት ግዜ**	**መዓልታዊ**	**በቲ ጎናዊ ሳዕቤን ጭንቀት ይስመዓካ ነዚ ሳጹን ምልክት ግበር**
1	ኣብ ግዜ ቀትሪ ድቃስ ይስምዓኒ ነይሩ።					
2	ምድንዛዝ ወይባህርያዊ ድሌት ዝዋሳእ ዘለኹ ይመስለኒ።					
3	ደው ምስ በልኩን/ወይ ደው ክብል ከለኹ ምድንዛዝ ተሰሚዑኒ።					
4	ልበይ ብዘይስሩዕ ወይ ብዘይተለምደ ፍጥነት ክትሃርም ተሰሚዑኒ።					
5	ጭዋዳታተይ ውጥረት ወይ ምውጥዋጥ ተሰሚዑኒ።።					
6	ኣእዳወይ ተንቀጥቂጠን እየን።					
7	ኣእጋረይ ዕረፍቲ ዘይብሉ ኮይኑ ተሰሚዑኒ'ዩ/ወይ'ውን ኮፍ ክብል ኣይከኣልኩን።					
8	ምራቕ ምፍሳስ የሸግረኒ					
9	ምንቅስቓሰይ ወይ ምጉዓዘይ ካብቲ ልሙድ ዝሓሰረ ኮይኑ ኣሎ።					
10	ኣብ ገጸይ ወይ ኣካላተይ ዘይቆጻጸሮ ምንቅስቓስ ነይሩኒ ወይ ሰባት ኣስተብሂሎም እዮም።					
11	ራእየይ ድብዝዝ ኢሉ እዩ ጸኒሑ					
12	ኣፈይ ነቒጹ ኣሎ					
13	ሽንቲ ንምሕላፍ ተጸጊመ እየ					
14	ክሓምም ወይ ተምላስ ከም ዝኾንኩ ኮይኑ ተሰሚዑኒ።					
15	ኣብ ድቃሰይ ኣብ ዓራት ሽንቲ ምፍሳስ ኣጋጢሙኒ።					
16	ኣዝየ ጽምኢን/ወይ ድማ ብተደጋጋሚ ሽንቲ ምሕላፍን ጸኒሐ					
17	ኣብ ከባቢ ጡበይ ዝነበረ ከባቢታት ቆሲሉን ሓቢጡን ኣሎ።					
18	ካብ ጡበይ ፈሳሲ ክመጽእ ኣስተብሂለ ኣለኹ					
19	ጾታዊ ርክብ ከስተማቕር ጸገም ኣጋጢሙኒ እዩ					
20	ደቂ ተባዕትዮ ጥራይ: ብልዕቲ ምትንሳእ ጸገም ኣጋጢሙኒ እዩ።					
	ንዝሓለፉ ሰለስተ ኣዋርሕ	**እዎ**	**ኣይፋሉን**			
21	ደቂ ኣንስትዮ ጥራይ፡- ኣብ ወርሓዊ ጽግያት ለውጢ ኣስተብሂለ ኣለኹ					
21	ደቂ ተባዕትዮን ደቂ ኣንስትዮን፡- ክብደት ክውስኽ ጸኒሐ					

EQ-5D-5L

ናይ ጥዕና መሕተት/ ብትግርኛ

ትግርኛ ትርጉም ንኢትዮጵያ

(Tigrigna version for Ethiopia)

EQ-5D-5L

ኣብ ትሕቲ ሕድሕድ ርኣሲ **ንናይ ሎምዓንት** ጥዕነኣም/ኣን ብደንቢ ዝገልፅ ዝሓዘ **ሓደ** መማረፂ ብምርኣይ ኣብ ቅድሚቱ ዘሎ ሳፁን ይኣርሙ/ማ

ምንቅስቓስ

ብእግረይ ንምጉዓዝ ፀገም የብለይን	❑
ብእግረይ ንምጉዓዝ ንእሽተይ ፀገም ኣለኒ	❑
ብእግረይ ንምጉዓዝ ማእኸላይ ፀገም ኣለኒ	❑
ብእግረይ ንምጉዓዝ ብርቱዕ ፀገም ኣለኒ	❑
ብእግረይ ምጉዓዝ አይክእልን	❑

ዓርሰ-ምንክብኻብ

ዓርሰይ ንምሕፃብ ወይ ክዳነይ ንምክዳን ፀገም የብለይን	❑
ዓርሰይ ንምሕፃብ ወይ ክዳነይ ንምክዳን ንእሽተይ ፀገም ኣለኒ	❑
ዓርሰይ ንምሕፃብ ወይ ክዳነይ ንምክዳን ማእኸላይ ፀገም ኣለኒ	❑
ዓርሰይ ንምሕፃብ ወይ ክዳነይ ንምክዳን ብርቱዕ ፀገም ኣለኒ	❑
ዓርሰይ ንምሕፃብ ወይ ክዳነይ ምክዳን አይክእልን	❑

ዝውቱራት ተግባራት (ንኣብነት ስራሕ፣ መጽናዕቲ፣ ስራሕቲ-ገዛ፣ ቤተሰብ ወይ መዝናነይቲ ተግባራት)

ዝውቱራት ተግባራተይ ኣብ ምትግባር ፀገም የብለይን	❑
ዝውቱራት ተግባራተይ ንምትግባር ንእሽተይ ፀገም ኣለኒ	❑
ዝውቱራት ተግባራተይ ንምትግባር ማእኸላይ ፀገም ኣለኒ	❑
ዝውቱራት ተግባራተይ ንምትግባር ብርቱዕ ፀገም ኣለኒ	❑
ዝውቱራት ተግባራተይ ምትግባር አይክእልን	❑

ቃንዛ/ ስእነት-ምኞት

ቃንዛ ወይ ስእነት-ምኞት የብለይን	❑
ንእሽተይ ቃንዛ ወይ ስእነት-ምኞት ኣለኒ	❑
ማእኸላይ ቃንዛ ወይ ስእነት-ምኞት ኣለኒ	❑
ብርቱዕ ቃንዛ ወይ ስእነት-ምኞት ኣለኒ	❑
ብጣዕሚ ከቢድ ቃንዛ ወይ ስእነት-ምኞት ኣለኒ	❑

ጭንቀት / ዝን-ምባል

ጭኦቕ ወይ ዝን-ዝበልኩ ኣይኮንኩን ❑

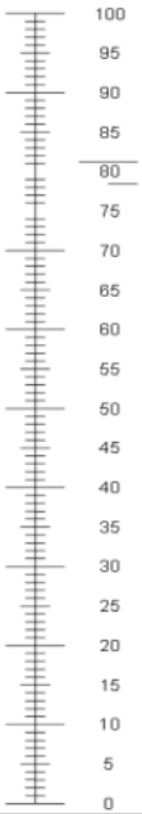
ንእሽተይ ጭኦቕ ወይ ዝን-ዝበልኩ እየ ❑

ብማእኸላይ ጭኦቕ ወይ ዝን-ዝበልኩ እየ ❑

ብርቱዕ ጭኦቕ ወይ ዝን-ዝበልኩ እየ ❑

ብጣዕሚ ከቢድ ጭኦቕ ወይ ዝን-ዝበልኩ እየ ❑

እቲ ብሓሳብኩም/ክን ዝበለፀ ኢልኩም/ክን ትሓስብዎ/ኦ ጥዕና



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- እዚ መለክዒ ካብ 0 እስካብ 100 ‘ቁፅሪ ተውሂብዎ ኣሎ።
- 100 ማለት እቲ ብሓሳብኩም/ክን ዝበለፀ ኢልኩም/ክን ትሓስብዎ/ኦ ጥዕና እዩ።
- 0 ማለት እቲ ብሓሳብኩም/ክን ዝኸፍአ ኢልኩም/ክን ትሓስብዎ/ኦ ጥዕና እዩ።

- ናይ ሎምዓንቲ ጥዕነኦም/አን ከመይ ከምዝኾነ ንምምልካት ኣብቲ መ
- ሕዚ በይዘኦም/አን እቲ ኣብቲ መለክዒ ዘቕመጥዎ/ኦ ቁፅሪ ኣብቲ ታሕቲ ዘሎ ሳፁን ውሽጢ ይፅሓፉ/ፋ ።

ናይ ሎምዓንቲ ጥዕነኦም/አን =

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Annex IV: Chlorpromazine Equivalent Dose for Antipsychotics Involved in the Current Study.

Antipsychotic	**Equivalent dose of 100 mg Chlorpromazine**
Chlorpromazine	100 mg PO per day
Haloperidol	2 mg PO per day
Risperidone	2 mg PO per day
Fluphenazine Depot	2.5 mg IM per 3 Weeks
Olanzapine	5 mg PO per day
Trifluoperazine	5 mg PO per day
Thioridazine	100 mg PO per day

(DiPiro et al., 2017, Woods, 2003, Danivas and Venkatasubramanian, 2013, Schooler et al., 1976)

Antipsychotic Polypharmacy, Health-Related Quality of Life and Associated Factors among Patients with Schizophrenia: A Cross-Sectional Study at Ayder Comprehensive Specialized Hospital, Northern Et

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