Assessment of Antipsychotic Combination Therapy among Patients with Schizophrenia on Follow-up at Amanuel Specialized Mental Hospital

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This is to certify that the thesis prepared by Chalelgn Kassaw entitled: "*Assessment of Antipsychotic Combination Therapy among Patients with Schizophrenia on Follow-up at Amanuel Specialized Mental Hospital*" and submitted in partial fulfillment of the requirements for the degree of master of Pharmacy in pharmacy practice complies with respect to originality and quality.

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Abstract

Assessment of Antipsychotic Combination Therapy among Patients with Schizophrenia on Follow-up at Amanuel Specialized Mental Hospital, Addis Ababa, Ethiopia

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Antipsychotic medications are first line for the treatment of patients with schizophrenia. Although monotherapy is supported, antipsychotic combination therapy in schizophrenia is common in clinical practices. However, there are issues with this treatment approach regarding safety, nonadherence, increment in daily dose and cost. This study aimed to assess the practice of antipsychotic combination therapy among patients with schizophrenia on follow-up. Cross-sectional study was conducted from August 10 to September 10, 2015 at Amanuel Specialized Mental Hospital. Data was collected through a two stage process. First, patients were interviewed using a pretested structured questionnaire. In the second stage, information on diagnosis and treatment was extracted from the medical records of patients who were interviewed face to face. A total of 423 patients participated in the study. The prevalence of antipsychotic combination therapy was 21.8%. The drug most frequently involved in combination therapy was fluphenazine decanoate depot while the frequently drug combination type was chlorpromazine orally with fluphenazine decanoate depot. The most common reason for combination was inadequate response (52.8%) to treatment. Younger age (25-34 years), male sex, greater than ten years duration of illness, frequent hospital admissions, severe side effect burdens and anticholinergic use had positive association with antipsychotic combination therapy. On the other hand, age group of 35-44 years had an inverse relation with antipsychotic combination therapy. From this study, antipsychotic combination therapy was practiced on a fifth of the study participants. As a result, development of treatment guideline and broadening the availability of other second generation antipsychotics should be warranted.

Key Words: Antipsychotic medications, Combination therapy, Schizophrenia, Follow-up

Abbreviations/Acronyms

ACT	Antipsychotic Combination Therapy
AMT	Antipsychotics Monotherapy
AOR	Adjusted Odds Ratio
APA	American Psychiatry Association
ASMH	Amanuel Specialized Mental Hospital
CI	Confidence Interval
COR	Crude Odds Ratio
CPZeq dose	Chlorpromazine equivalent dose
FGA	First Generation Antipsychotics
FMOH	Federal Ministry of Health
GASS	Glasgow Antipsychotics Side effect Scale
IPAP	International Psychopharmacotherapy Algorithm Project
NICE	National Institute for Health and Care Excellence
PANSS	Positive and Negative Syndrome Scale
SGA	Second Generation Antipsychotics
SPSS	Statistical Package Software for Social Sciences
TMAP	Texas Medication Algorithm Project
WFMH	World Federation of Mental Health
WHO	World Health Organization

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1. Introduction

1.1. Background

Schizophrenia is a psychotic disorder characterized by impaired thinking, emotions, and behaviors that affect family relationships, social functioning and employment. The most common onset of this illness is in the age of twenties to age of forty but its onset is rare before late adolescence and after the age of forty (Picchioni & Murray, 2007; Kasper, *et al*., 2015). Schizophrenia occurs more frequently in males than females (male to female ratio 1.4:1) and mostly appears in the early twenties in males but in late twenties in females. Schizophrenia is more common in males because during birth and at early life boys might face different injuries as well as men have smaller inferior partial lobule that may lead to manifestation of symptoms if misfired (Picchioni & Murray, 2007; WFMH, 2014). The life time affection of schizophrenia may reach up to 1.0% and around 26 million people are living with schizophrenia worldwide (WFMH, 2014).

According to the Mental Health Gap Action Program working group report, "The prevalence of schizophrenia is 0.5% in Ethiopia. Mental illness is non- communicable disorder in terms of burden in Ethiopia, where in rural area it comprised of 11% of the total burden of disease with schizophrenia included in the top ten most burdensome conditions" (FMOH, 2012).

The causative agent of this disease condition is not definitely known but it is assumed that the risk is associated with both genetic and different environmental factors. Schizophrenia is more common from patients of first degree relatives. Different environmental factors like obstetric complications, childhood trauma, early life infections etc. can also lead the incident of schizophrenia at a later age where schizophrenia is developed (WHO, 1998; Picchioni & Murray, 2007).

Patients with schizophrenia may clinically present with distortion to the reality (positive symptoms) like hallucinations, delusions, disorganized speech or unusual behavior. Negative symptoms including lack of emotional expression, poor grooming, decreased socialization can be manifested along with those positive symptoms, Cognitive impairment and mood or anxiety symptoms (Picchioni & Murray, 2007; APA, 2013; Kasper, *et al*., 2015).The diagnosis of schizophrenia is relied on the presenting positive and negative symptoms along with social or occupational dysfunction lasting for at least six months using the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria of the American Psychiatric

Association (APA, 2013) or the International Statistical Classification of Diseases and Related Health Problems ,ICD-10 (WHO, 1993).

Patients with Schizophrenia are best managed with both pharmacologically and non-pharmacologically in the form of basic life training, psycho-education for both patients and families. Together with nondrug therapy, antipsychotic medications are the main stay of treatment options for patients with schizophrenia to enhance recovery in controlling symptoms, improving quality of life, regain basic life functioning and preventing relapse. However, most of patients with schizophrenia have poor adherence to medication, a main problem that affect the treatment outcome, mainly due to drug side effects. The outcome of medication therapy is usually obtained in a progressive manner taking weeks to months after treatment initiation though the effect is seen within hours or days of therapy initiation with optimum dosing of some antipsychotics (DiPiro, *et al.*, 2014; Kasper, *et al.*, 2015).

There are a number of well known established treatment guidelines to be used for schizophrenia management. These treatment guidelines suggest that in patients presenting with first episode schizophrenia, second generation antipsychotics (SGAs) are preferred over first generation antipsychotics (FGAs) due to their lower risk of neurologic side effects. If the first choice of medication therapy failed to control symptom or cannot be tolerated, alternative antipsychotics (SGA or FGA) should be tried up to optimum dose for adequate time lasting a minimum of four to six weeks. If the response with sequential monotherapy trials is not satisfactory, dose adjustment or a drug that is preferred in treatment resistant cases (clozapine) should be considered. Furthermore, in Patients with symptoms of suicidal ideation, frequent aggression or substance use; clozapine should be initiated immediately. If the patient shows partial response for clozapine, clozapine augmentation with other medications like mood stabilizers, anxiolytics, antidepressants, other antipsychotics etc. or electroconvulsive therapy (if the symptom persists) should be considered. If the options with clozapine treatment don't work, monotherapy trial with a drug that was not tried ever before should be considered before the initiation of combination therapy. Treatment guidelines suggest antipsychotic combination therapy only when all other monotherapy options failed to give adequate clinical response. Beyond these, if poor adherence contributes to inadequate clinical improvement, the long-acting injectable antipsychotics should be recommended (Expert, 1999; Lehman, 2004; Moore *et al.*, 2008; Kreyenbuhl *et al.*, 2010; IPAP, 2009; Hassan *et al.*, 2012; NICE, 2014).

1.2. Statement of the Problem

Basically monotherapy is the supported therapy over combination therapy and the later should be considered only as a last option when other treatment options failed to control schizophrenia symptoms. Nevertheless, antipsychotic combination therapy (ACT) is common in clinical practice with prevalence rates varying from 4% as reported in a study in Nigeria to 67.7% as per a study in Serbia (Adeponle *et al*.,2007; Divac *et al*., 2007). This treatment approach; however, have issues regarding increment of daily dose, increased side effects, drug-drug interactions, treatment nonadherence, difficulties in identifying cause and effect of multiple agents, and cost.

The practice of antipsychotic combination therapy has been associated with increment of total daily dose (Suzuki *et al*., 2004; Procyshyn *et al*., 2010), indirectly leading to dose related adverse events (Freudenreich & Goff, 2002; Yasuhiko, *et al.*, 2012). In addition, drug interactions can result in increase in drug concentrations that could lead to the occurrence of side effects (Freudenreich & Goff, 2002; Guy, *et al.*, 2009). ACT may also have an impact on patients' medication adherence. Following this, treatment discontinuation may happen that result in relapse of the disease condition leading to social and economical crisis (Freudenreich & Goff, 2002; Guy, *et al.,* 2009). ACT is also associated with cost, in general, i.e. direct medication cost and indirectly with other health care costs such as side effect management and relapse management which could be resulted from treatment discontinuation (Baandrup *et al*., 2011).

Mental illness is a burdensome condition in Ethiopia in terms of burden (FMOH, 2012). Amanuel Specialized Mental Hospital is the only tertiary psychiatry hospital that delivers solely mental health services, including schizophrenia, for patients from all regions of the country. Antipsychotic combination therapy in schizophrenia is common in many countries as mentioned earlier and this disease condition is also prevalent in Ethiopia. As a result, this study was conducted to assess the practice of antipsychotic combination therapy among patients with schizophrenia on follow-up. The results of this study could also serve as source of direction by identifying areas for intervention.

1.3. Literature Review

1.3.1. Prevalence of Antipsychotic Combination Therapy

Although antipsychotic monotherapy is preferred most of the time, ACT in schizophrenia is a common practice with varying prevalence rate. Higher prevalence rate of ACT (67.7%) was reported in a study carried out on inpatients in Serbia during three years study period. Combination of two drugs accounted for 63.3% of the participants and 4.1% of patients were in combination of three medications (Divac *et al*., 2007). Another study conducted on admitted patients for one month period in Spain reported 47.1% of ACT practice with quetiapine as the most frequently drug (56.8%) used in combinations (López de *et al*., 2012).

A two year study conducted in USA in two study sites to assess the prevalence, trends and factors of ACT among patients with schizophrenia reported 23% prevalence rate of antipsychotic combination therapy. The most frequent drug classes involved in combination therapy were SGA with FGA (15.7%) followed by SGA with SGA (3.9%) and FGA with FGA for 2.8% of combination (Ganguly *et al*., 2004). Similarly, another two year study carried out in Florida found 21% prevalence of antipsychotic combination therapy (Constantine *et al., 2010)*.

A cross-sectional study on 329 patients with schizophrenia in psychiatry hospitals in Oslo, Norway reported ACT on 30.7% of the study participants. The most frequent drug class combinations were SGAs with SGA (60.4%) followed by SGA with FGA (36.6%). Only 3.2% of patients used the combination of three antipsychotics (Bolstad, *et al*., 2011).

A multicenter study in four European countries involving UK, Italy, Netherlands and Germany to determine the extent of ACT among 375 patients with schizophrenia reported 13% prevalence of ACT (Barbui, *et al*., 2006). Similarly, an audit study conducted on outpatients on follow up in a hospital at Lancashire, UK reported lower (17.4%) prevalence of ACT (Ranceva *et al*., 2010).

A one year prospective study conducted in Canada to determine the frequency of long term antipsychotic combination treatment of community mental health patients found 31% prevalence of ACT among patients with schizophrenia (Procyshyn *et al*., 2010).

Similarly, one year prospective study conducted to determine the combination treatment rate of oral antipsychotics in patients taking long acting injectable antipsychotic from a Mental

Health Center in USA, reported 46% prevalence rate of combination treatment of oral agents with long acting injectable antipsychotic (Aggarwal *et al*., 2012).

Another one year prospective study conducted among patients with schizophrenia in Japan reported 56.8% prevalence rate of ACT (Ye *et al*., 2012). Relatively, a study conducted on 398 clinically stable outpatients with schizophrenia in china reported lower rate of ACT on 17.6% of the study participants (Xiang *et al*., 2007).

A recent retrospective study carried out on antipsychotic medication use among patients with schizophrenia on outpatient follow up in Palestine showed a 53.1 % prevalence rate of ACT. The most common drugs involved in ACT were chlorpromazine (77.9%), fluphenazine decanoate depot (44.1%) and haloperidol (41.2%). Whereas FGA with FGA (31.2%), three FGAs (9.6%) and SGA with FGA (6.8%) were the most frequently combination types in terms of drug classes (Ihbeasheh *et al*., 2014).

A study conducted in outpatient psychiatric practice in Northern Nigeria revealed low prevalence of antipsychotic combination (4.6%). All drugs involved in combination were within first generation (Adeponle *et al*.,2007). However; ACT rate was relatively higher in a study conducted in South Africa with prevalence rate of 27.8%. The most frequently used combination type was haloperidol and a depot preparation which accounted 54.2% of the ACT (Koen *et al*.,2008).

1.3.2. Reasons for Antipsychotic Combination Therapy

Although antipsychotic combination therapy is not based on clear evidence, most guidelines recommend at least two antipsychotic monotherapy trial alternatively each lasting at least four to six weeks before considering combination therapy in patients having poor response (Expert, 1999; Moore *et al*., 2008; IPAP, 2009; NICE, 2009).

The most common reasons for ACT are treatment resistant schizophrenia (Sernyak & Rosenheck, 2004; Krynbuh *et al*.,2007b), for quick recovery (Stahl, 1999), medication switching (Sernyak & Rosenheck, 2004), poor compliance to oral medications (Miller & Craig, 2002) and to minimize side effect from high dose single agent by prescribing two drugs both at lower dose (Freudenreich & Goff, 2002; Guy, *et al*., 2009).

A survey on clinicians within a state hospital in USA reported augmentation as the most common reason for the initiation of ACT. Nevertheless, a chart review didn't get documented

reasons for ACT in half of the patients. In addition, adequate monotherapy trial including clozapine was not done on majority of the patients prior to ACT initiation (Schumacher *et al*., 2003).

In a structured interview of clinicians for 40 treatment resistant patients with schizophrenia in UK found that inefficacy of monotherapy (40%); inefficacy of existing combination therapy (13%); for the purpose of medication switching (10%); severe side-effects with single agent (10%); poor compliance with oral medication (5%); temporarily for raising the dose of the first agent (5%) and patient request(5%) were the mentioned reasons for initiating ACT and for 13% of the patients the reason was not known (Hawa & Stubs, 2003).

A study in West Glasgow to estimate the community prevalence of ACT and high dose antipsychotic treatment in 135 patients via audit reason for combined antipsychotic therapy was described in 69% of patients on ACT. The most common reason was to improve symptom control. In five patients, there was no clear documented reason about combination treatment (Lovely & Ian, 2013).

1.3.3. Factors Associated with Antipsychotic Combination Therapy

Different studies tried to identify factors associated with ACT. These factors include: patients' socio-demographic characteristics, clinical characteristics, medication and some outcome variables.

Younger age is associated with ACT. This finding was supported in studies in USA (Morrato, *et al*., 2007; Kreyenbuhl *et al*., 2007b) and by two studies in Spain (Lerma-Carrillo, *et al*., 2008; Molina, *et al.*, 2009). However, a study in Estonia found older age to be associated with ACT (Lass *et al*., 2008).

Moreover, a study conducted in Italy reported females to be treated with more in antipsychotic combination than males (Biancosino *et al*., 2005). Whereas studies in USA and Spain reported that male sex was associated with higher ACT (Ganguly *et al*., 2004; Molina, *et al.*, 2009).

Regarding marital status, married patients had a less likelihood to receive ACT as per studies in USA (Covell *et al*., 2002; Kreyenbuhl *et al*., 2007b). ACT was also more common in unmarried patients as reported in studies in USA (Covell *et al*., 2002) and Italy (Santone, *et*

al., 2011). This finding was also supported in a multicenter study in Europe showing being separated or widowed had a twofold likelihood of receiving ACT (Barbui *et al.* 2006).

Patients living alone have four odds of ACT than others (Barbui *et al*. 2006). However, a study in Italy lacked significant association between living arrangement and ACT (Bianco *et al.,* 2005). Living in an area of low population density was associated with antipsychotic polytherapy (Magliano *et al.* 2004).

Unemployment has a positive association with ACT as per a cross-sectional study in Korea (Jinyoung, *et al.*, 2014). However, a study carried out in Palestine lacked the association of ACT with employment status (Ihbeasheh *et al*., 2014).

Moreover, ACT was more common in schizophrenia patients with longer illness duration as per studies across multicenter comparative studies in East Asia (Sim *et al*., 2004), Germany (Janssen *et al*.,, 2004), Belgium (De Hert *et a*l., 2006), four European Countries (Barbui, *et al*., 2006), Oslo (Bolstad, *et al*., 2011) and Palestine (Ihbeasheh *et al*.,2014) supported this evidence.

Patients who had frequent psychiatric related hospital admissions had a chance to be on ACT as indicated by studies in USA (Jaffe & Levine, 2003; Morrato, et al., 2007), Germany (Janssen *et al*., 2004), Italy (Magliano, *et al.*, 2004) and Palastine (Ihbeasheh *et al*., 2014), but opposite result was found in a study conducted in Serbia (Divac *et al*., 2007).

Antipsychotic combination therapy using combination of clozapine and respiridone was more effective in reducing symptoms than antipsychotic monotherapy using clozapine (Josiassen *et al*. 2005). Similarly, a study on amisulpride combined with clozapine for patients didn't have response to clozapine monotherapy found that clozapine combination resulted better symptoms reduction on Brief Psychiatric Rating Score (BPRS) (Agelink *et al*., 2004). On contrary, other studies showed there was no difference between antipsychotic combination and that of monotherapy in symptoms improvement on Positive and Negative Symptom Scale (PANSS) (Honer, *et al*., 2006; Freudenreich *et al*., 2007; Ihbeasheh *et al*., 2014). However, BPRS negative, positive and total score was higher in ACT group compared with AMT in a study conducted in Korea (Jinyoung, *et al.*, 2014).

ACT is related to increase in daily dose as reported by studies in USA (Kreyenbuhl *et al*,, 2007a), UK (Ranceva *et al*., 2010), Canada (Procyshyn *et al*., 2010), Italy (Ghio *et al*., 2011), Scotland (Lovely & Ian, 2013) and Palastine (Ihbeasheh *et al*., 2014).

Even though nonadherence in schizophrenia is a major problem at all, nonadherence or partial medication adherence was related to ACT as shown in studies in Switzerland (Simon *et al*., 2005) , California (Ahn, *et al.*, 2008) and North Eastern Nigeria (Ibrahim, *et al.,* 2015).

Anticholinergic use was higher in patients receiving ACT than in those treated with antipsychotic monotherapy (Kreyenbuhl *et al*., 2007b; Xiang *et al.,* 2007; Gio *et al.* 2011). In addition, co-treatment with other adjuvant medications like antidepressants (Kreyenbuhl *et al*., 2007b), anxiolytics (De Hert *et al*., 2006; Centorrino *et al*., 2008), and mood stabilizers (Ganguly *et al*., 2007) has also been associated with ACT.

Side effect burden was one implication for ACT even though some combination therapies had a lower side effect as compared with monotherapy with higher dose (Guy, *et al*., 2009). Side effect mean score was higher for ACT group compared with FGA monotherapy for Liverpool University Neuroleptics Side effect Rating Scale in European multicenter study (Barbui, *et al*., 2006). A study in Japan on effects of ACT on side-effects and concurrent use of medications in schizophrenia outpatients had showed higher number of side effects in polypharmacy than in monotherapy groups. With respect to side effects, dry mouth and sexual dysfunction had a significantly higher prevalence in ACT compared with monotherapy. The rate of concurrent use with anticholinergics was significantly higher in ACT than in monotherapy (Yasuhiko, *et al.*, 2012).

2. Objective of the Study

2.1. General Objective

To assess the practice of antipsychotic combination therapy among patients with schizophrenia on follow-up at Amanuel Specialized Mental Hospital

2.2. Specific Objectives

o   To determine the extent of antipsychotic combination therapy

o   To investigate the reasons for antipsychotic combination therapy

o   To determine the extent of antipsychotic combination therapy related side effect burdens

o   To determine the level of antipsychotic combination therapy related medication adherence

o   To identify factors associated with antipsychotic combination therapy

3. Methods

3.1. Study Setting

The study was conducted at Psychiatry clinics of Amanuel Specialized Mental Hospital (ASMH) in Addis Ababa. ASMH is the only specialty mental health hospital in the country, and was established in the 1930s. It is administered under the Federal Ministry of Health and provides mental health service for patients from all regions of the country. The hospital has a total of 280 beds. In 2013/14 budget year, around 111,025 patients visited the outpatients department for follow up. Nearly half of those who visited, 48,267($\approx$4023 patients/month or $\approx$183 patients/working day) had a diagnosis of schizophrenia.

3.2. Study Design and Period

A cross sectional study was conducted at psychiatry clinics providing follow-up care to patients with psychosis. The study was conducted through a two stage process over a month from August 10 to September 10, 2015. First, patients were interviewed using a pretested structured questionnaire. In the second stage, information on diagnosis and treatment was extracted from the medical records of patients who were interviewed face to face.

3.3. Sample Size and Sampling Methods

The minimum number of sample required for this study was determined by using Single population proportion formula considering the following assumptions:

$$n= \frac{(Z_{a/2})^2\, p\,(1-p)}{d^2}$$

Where

n= minimum sample size required for the study

Z= standard normal distribution (Z=1.96) with confidence interval of 95% and a =0.05

P= the prevalence of antipsychotic combination therapy in schizophrenia unknown in our country; hence, P= 50 %(0.5) was used.

d= Absolute precision or tolerable margin of error (d) =5%=0.05

$$n= \frac{(Za/2)^2\, p\,(1-p)}{d^2} = \frac{(1.96)^2\, 0.5\,(1-0.5)}{(0.05)^2} = 384$$

Then adding 10% contingency (384 x 0.1 = 38.4 $\approx$39) for non-response, the final sample size for this study was estimated to be 423 (384+39).

Systematic random sampling technique was maintained to recruit the study population. The sampling fraction (k) was calculated to be 4023/423 ≈10. A starting point was chosen randomly from numbers 1 to 10.Then, every 10th patient was interviewed and medical record was reviewed regularly in each follow-up day.

3.4. Source and Study Population

All patients with schizophrenia on follow-up at ASMH psychiatry clinic were used as a source population for the selection of patients to be involved in the study. Out of the source population, those patients who came for refill from August 10 to September 10, 2015 were considered as study population. From the study population, patients fulfilling the inclusion criteria were enrolled in the study.

3.5. Inclusion and Exclusion Criteria

Inclusion Criteria

✓ Schizophrenia patients diagnosed based on DSM-V
✓ Age ≥13 years (Since the hospital provides service for patients >12 years old)
✓ Patients who were on antipsychotics for at least two months before the initiation of the study (this is to exclude newly diagnosed patients and patients that were not stable since it takes up to eight weeks to go for maintenance phase treatment for these patients)

Exclusion Criteria

✓ If their families/care givers came to collect medications rather than the patients themselves
✓ Patients who had acute attack of the illness and would not be able to provide information

3.6. Data Collection and Analysis

3.6.1. Data Collection Instruments

Data was collected by a structured questionnaire, indicated in Annex I, from the patient after it was translated to Amharic version (Annex II) using standard procedure. The questionnaire for interview contained Socio-demographic characteristics, Morisky Medication Adherence Predictor Scale, Glasgow Antipsychotics Side Effect Scale and the Positive and Negative Syndrome Scale. In addition to the administration of these standard questionnaires, data was extracted from the patients' clinical records to obtain the following information: initial date

of registration to estimate duration of illness, number of psychiatric related hospital admissions, other co-morbid illnesses and medication profiles. The standardized tools used are detailed below, and are included in Annex I.

Morisky Medication Adherence Scale-8

Morisky Medication Adherence Scale is a tool used to assess the medication taking behavior of patients. It is used for different types of chronic illnesses even though it was validated for hypertension. Hence, in this study, it was used to assess the medication adherence level of patients with schizophrenia. It contains eight individual questions focusing on past medication use patterns with scoring "Yes" = 1 and "No" = 0 for the first seven items except item number five in which the values of "Yes" and "No" were reversed and question number 8, is a likert response with options "never"=0, "once in a while"=0.25, "sometimes"=0.5, "usually"=0.75, and "always"=1. The total score was finally computed by adding all and sub-divided to give a range of scores from low adherence (score>2), medium adherence (score=0.25-2) and high adherence (score=0) as shown in part II of Annex-I.

Glasgow Antipsychotic Side Effect Scale

Glasgow antipsychotic side effect scale was used to assess and compare the side effect burdens of patients on antipsychotics. In this study, it was used to compare the side effect burdens of patients on combination against those who were on antipsychotic monotherapy. GASS is a patient self report measurement scale consisting of twenty two questions that cover a wide range of antipsychotic related side effects (Waddel & Taylor, 2008) as shown in Annex I. Unlike other tools, GASS covers a wide range of antipsychotics side effects including: sedations and central nervous system side effects; cardiovascular side effects; extra-pyramidal side effects; anti-cholinergic side effects; gastrointestinal side effect; genitourinary side effects; screening for diabetes mellitus; prolactinaemic side effects and weight gain. Questions 19 to 38 related to how the patient has felt over the previous week and questions 39 and 40 related to how they have felt in the last three months. Questions 19-38 are likert scale from "Never" scored=0; "Once" scored =1; "A few times" scored =2; "Every day" scored =3. Questions 39 and 40 are "Yes" and "No" scored as 3 and 0 respectively. Finally, total score was computed by adding the score for all questions and rated as: "Absent/Mild side effects", "Moderate side effects" and "Severe side effects" if the scores are 0-12, 13-26 and above 26 respectively as shown in Annex III.

Positive and Negative Syndrome Scale

The Positive and Negative Syndrome Scale (PANSS) is a well validated instrument for measuring degree of psychopathology in those diagnosed with psychotic disorders (Kay *et al*, 1987) and has been in use in Ethiopia among patients with schizophrenia (Fekadu *et al*. 2013; Borba *et al* 2015).The PANSS consists of a structured interview conducted with specific and detailed way for each question, each rated from one (symptom absent) to seven (extreme).There are thirty questions divided across three subscales: Positive (7 questions), negative (7 questions), and general psychopathology (16 questions) as shown in Annex I&IV. PANNS measurement was undertaken at least for 30 minutes for each patient.

Chlorpromazine Dose Equivalent

Chlorpromazine dose equivalent is a measure of the relative antipsychotic potencies of antipsychotic medications. It is equivalent to the potency of antipsychotic medications expressed as equivalent dose for 100 mg chlorpromazine as indicated in Annex V. The daily dose of each antipsychotic medication that each patient was taking was converted to milligram equivalents of chlorpromazine according to conversion factors (Woods, 2003; Danivas & Venkatasubramanian, 2013; Schooler & Levine, 1976). For patients on combination therapy, each converted antipsychotic specific CPZeq amount is added to arrive at a total daily dose. A maintenance dose of total CPZeq in the range of 300–600 mg is considered as therapeutic dose (Kreyenbuhl *et al*., 2010).

3.6.2. Data Collectors Recruitment and Training

 Eight psychiatry nurses were recruited as data collectors after taking the required training. The training was given to them regarding the data collection method, the appropriate use of the data collection instruments and the confidentiality of the collected data. The data collectors were recruited based on their experience in psychiatry practice who were capable of PANSS rating, assessing the adherence of patients from patients self report, measurement of antipsychotics side effects and assessing of patients chart retrospectively for extracting the required information.

3.6.3. Data Quality Control

Pre-test of the questionnaire was performed on 5% (22 patients) of the sample before conducting the study. Then, the final tool was developed with some modifications after reviewing the results of the pre-test. Patients who participated in the pretest were excluded in the final analysis. The principal investigator reviewed and checked the data collected for completeness and the necessary feedbacks were provided back daily to the data collectors throughout the study period. The quality of data was also checked at data entry, analysis, and interpretation and representation phases.

3.6.4. Data Analysis and Interpretation

For analysis, coded variables were entered into Epi Info v-7 then exported to and analyzed using SPSS v-20. Descriptive statistics (frequency, percent, mean, standard deviation and range) were used to summarize data and evaluate distribution of responses. Association between continuous variables and ACT was carried out using independent sample mean t-test. Univariate binary logistic regression analysis was performed to calculate crude odds ratio (COR) for each variable and those variables with p-value < 0.2 during that analysis were selected for multivariate binary logistic regression analysis and the result was expressed as adjusted odds ratio (AOR). 95% confidence level was used to determine factors associated with ACT. A p-value of < 5% was considered as statistically significant.

3.7. Study Variables

Independent Variables

➢ Socio-demographic variables: age, sex, place of residence, marital status, educational level, family income, source of medication fee, living arrangement, substance use.
➢ Clinical and medication related variables: duration of illness, psychiatric hospital admission, co-morbid illnesses, and anticholinergic and adjuvant medication use.
➢ Outcome Variables: side effect burdens, adherence level

Dependent Variable:

➢ Presence of Antipsychotic combination therapy

3.8. Ethical Considerations

This study was approved by the Ethical Review Board of School of Pharmacy, College of Health Science Addis Ababa University. It was also approved by an internal research committee of the hospital. Prior to data collection, individual informed verbal consent was obtained for study participants who were eighteen years and above. Both verbal assent and consent were obtained from the study participant and their families/caregivers, respectively, for those study participants below eighteen years old. Each patient was informed about the objective of the study, procedures of selection and assurance of confidentiality and their names were not registered to minimize social desirability bias and enhance anonymity. Patients were not forced to participate and received any monetary incentive and it was solely voluntary based. The collected data was handled and secured with the principal investigator in every data collection day.

3.9. Operational Definitions

Antipsychotic Combination Therapy (ACT): Co-treatment with more than one type of antipsychotic for at least 60 days, before the initiation of the study, was considered as antipsychotic combination therapy (Expert, 1999; Kreyenbuhl *et al*., 2007a; NICE, 2009,). Sixty days were selected as a cutoff because most guidelines suggest antipsychotic combination therapy up to eight weeks for some patients (Expert, 1999; IPAP, 2009; NICE, 2009).

Antipsychotic Monotherapy Trial: Trial at least with two antipsychotics alternatively in patients who showed little or no response to initial antipsychotic treatment for at least 6 weeks period before initiating combination therapy (Expert, 1999; NICE, 2009; Suzuki *et al*., 2011).

Chlorpromazine Equivalent Dose: The equivalent dose of antipsychotics for 100 mg of chlorpromazine as indicated in Annex V.

Sub-therapeutic Dose: Total daily chlorpromazine equivalent dose less than 300 mg.

Therapeutic Dose: Total daily chlorpromazine equivalent dose in a range of 300-600 mg.

Supra-therapeutic Dose: Total daily chlorpromazine equivalent dose in a range of 600-1000 mg.

Supra-maximal Dose: Total daily chlorpromazine equivalent dose above 1000 mg.

High Adherence: Morisky medication adherence scale-8 score of "0".

Medium Adherence: Morisky medication adherence scale-8 score of "0.25-2".

Low Adherence: Morisky medication adherence scale-8 score greater than "2".

Absent/Mild Side effects: Overall total GASS score of 0-12.

Moderate Side effects: Overall total GASS score of 13-26.

Severe Side effects: Overall total GASS score over 26.

4. Results

4.1. Socio-demographic Characteristics

409 study participants were finally involved for data analysis and interpretation of the study while the remaining 3.4 % were excluded due to incomplete data. The mean (SD) age of the study participants was 34.8 (10.1) ranging from 15 to 71 years. Nearly, two-fifths of the study participants were between 25 and 34 years. Males were dominant in number (68.0%) and more than two-fifth of the study participants (42.5%) completed secondary education and majority of them (79.5%) were from urban area. Nearly three-quarter of the study participants got their medication free of charge and 43.5% of all have low family income. Over half of the participants (66.5%) didn't have active working status in line with that most of the study population (91%) were living with family/their supporters. Regarding active substance use; 19.1%, 13.2% and 18.8 % of the study population had alcohol drinking, cigarette smoking and khat chewing behavior respectively as shown in Table 1.

Table 1: Socio-demographic characteristics of patients with schizophrenia on follow-up at Amanuel Specialized Mental Hospital

Variables		Total (N=409)
		Frequency/%
Age (years)		
	15-24*	65 (15.9)
	25-34	152 (37.2)
	35-44	113 (27.6)
	45-54	56 (13.7)
	54-64	18 (4.4)
	65+	5 (1.2)
Sex	Male	278 (68)
	Female	131 (32)
Education Status	No formal education	55 (13.4)
	Primary	116 (28.4)
	Secondary	174 (42.5)
	Higher Education	64 (15.6)
Residence	Urban	325 (79.5)
	Rural	84 (20.5)
Marital Status	Unmarried	272 (66.5)
	Married	95 (23.5)
	Divorced	33 (8.1)
	Widowed	9 (2.2)
Source of Medication Fee	Free	303 (74.1)
	Payment	106 (25.9)
Family Income(ETB)	Charity	3 (0.7)
	Very Low (≤445)	115 (28.1)
	Low (446-1200)	178 (43.5)
	Average (1201-2500)	69 (16.9)
	Above Average (2501-3500)	44 (10.8)
Working status	Working	137 (33.5)
	Not working	272 (66.5)
Living Arrangement	With Family/Supporter	372 (91)
	Alone	34 (8.3)
	In Charity	3 (0.7)
Alcohol Use Currently	Yes	78 (19.1)
	No	332 (80.9)
Smoking currently	Yes	54 (13.2)
	No	355 (86.8)
Khat Use Currently	Yes	77 (18.8)
	No	332 (1.2)

[1]

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[1] * Based on Previous studies

4.2. Clinical Characteristics of the Study Participants

As it is shown in Table 2, the study participants had a mean duration of schizophrenia for 7.4 years (SD±6.2) ranging from six months to twenty eight years. A third of participants (33.7%) had 6 to 10 years of duration of illness. Regarding their Psychiatric hospital admission history, their mean admission history was 3.9 (SD±4.7) ranging from no admission to twenty four times and about half of the study participants did not have previous hospital admission. Only 25 patients had co-morbid mental illness including; major depressive disorder, seizure disorder and bipolar disorder.

Table 2: Clinical characteristics of patients with schizophrenia on follow-up at Amanuel Specialized Mental Hospital

Variables	Frequency /%
Duration of Illness in years *	
<1 year	23 (5.6)
1-5 year	119 (29.1)
6-10 year	138 (33.7)
>10 year	129 (31.5)
Psychiatric Hospital Admission *	
No admission	206 (50.4)
1-5 times	134 (32.8)
6-10 times	30 (7.3)
>10 times	39 (9.5)
Other Co-morbid Mental Illness	
Yes**	25 (6.1)
No	38 (93.9)

2

On the PANSS measure, there were statistical differences (after independent sample mean t-test) between the mean score of ACT and monotherapy groups. The mean score of PANSS positive, PANSS negative, PANSS general Psychopathology and PANSS total was slightly higher for patients on ACT than patients on monotherapy as shown in Table 3.

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*Based on previous studies

** Co morbid mental Illnesses: Major Depression Disorder, Seizure

PANSS: Positive and Negative Syndrome Scale

Table 3: Positive and negative syndrome scale rating score of patients with schizophrenia on follow-up at Amanuel Specialized Mental Hospital

Variables	All patients (N=409) M±SD	AMT(n=320) M±SD	ACT(n=89) M±SD	t-test (P-value)
PANSS Positive Score	9.8±3.82	9.33±3.37	11.55±4.77	P<0.001
PANSS Negative Score	10.34±4.08	9.43±3.23	13.60±5.06	P<0.001
PANSS General Psychopathology Score	21.76±6.70	20.71±5.83	25.55±8.11	P<0.001
PANSS Total Score	41.91±12.42	39.47±10.31	50.7±15.1	P<0.001

4.3. Current Drug Therapy Characteristics

This study showed that the extent of antipsychotic combination therapy was practiced in over a fifth of patients (21.8%) engaged in longer term care. Use of anticholinergic medications and other adjuvant medication accounted for 6.4% and 17.4% respectively. The mean total daily doses in milligram, which was in chlorpromazine equivalent dose form, was 439.16 (SD±512.04) varying from 20 mg to 3000 mg and more than half of them were on sub-therapeutic dose category as indicated in Table 4.

Table 4: Current drug therapy characteristics of patients with schizophrenia on follow-up at Amanuel Specialized Mental Hospital

Variables		Frequency (%)
Number of Antipsychotics	Single Antipsychotic	320 (78.2)
	≥2 Antipsychotics	89 (21.8)
Total Daily Dose in CPZeq¤ dose (mg)	Sub-therapeutic (<300)	236 (57.7)
	Therapeutic (300-600)	92 (22.5)
	Supra-therapeutic (600-1000)	33 (8.1)
	Supra-maximal (>1000)	48 (11.7)
Anticholinergic medication use	Yes*	26 (6.4)
	No	383 (93.6)
Adjuvant medication use	Yes "	71 (17.4)
	No	338 (82.6)

Cross tabulating the study populations (as AMT/ACT) with total daily dose category revealed that, three-fourth of patients who were on AMT were in sub-therapeutic dose (less than 300mg CPZeq dose). On the other hand, more than 80 % of patients on ACT were on supra-therapeutic and supra-maximal doses whereas there were only 2.5% of participants who received above the therapeutic dose in patients receiving monotherapy. There were no patients who had more than one gram daily dose on AMT group compared with those who were on ACT as indicated in Figure 1. In addition, the mean chlorpromazine equivalent dose of patients on ACT was 1218.8 mg (SD±567.6) ranging from 175mg to 3000 mg whereas it was 222.3 mg (SD±172.4) varying from 20mg to 1000 mg for those who were on antipsychotic monotherapy.
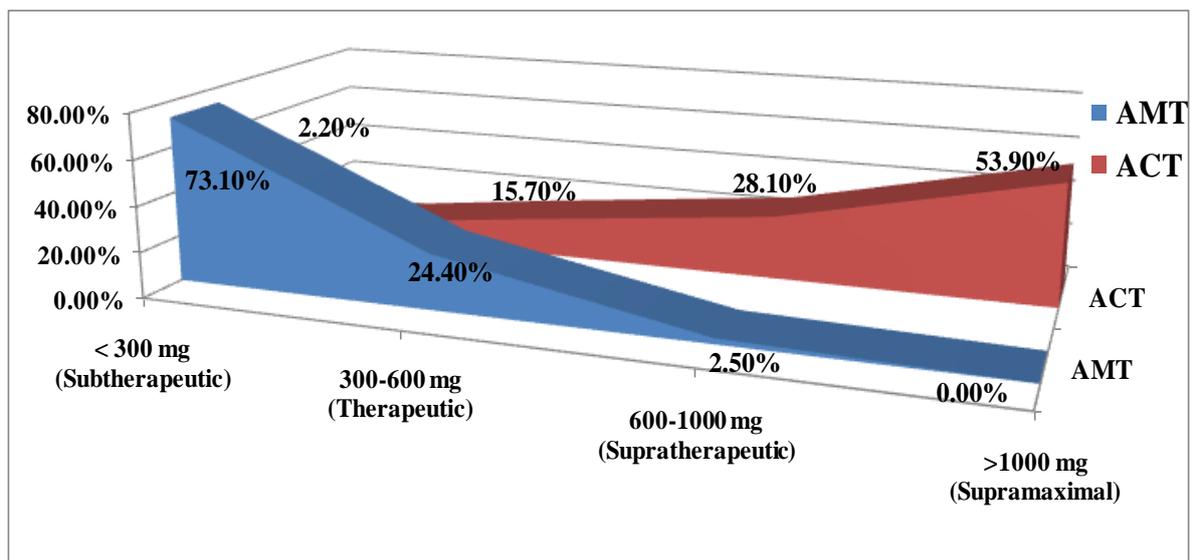
Figure 1: Impact of antipsychotic combination on the increment of total daily dose among patients with schizophrenia on follow-up at Amanuel Specialized Mental Hospital

As indicated in Figure 2, the most frequently drug classes involved in ACT were FGAs and about three fourth of patients on ACT were on the combination of two FGAs.

¤CPZeq dose: Chlorpromazine Equivalent dose
*Anticholinergic medication use: Trihexypenidyle (Benzhexole)
"Adjuvant Medications use: Sodium valporate,Amytriptyline,Flouxtiene,Propranolol,
AMT: Antipsychotic monotherapy
ACT: Antipsychotic combination therapy
M : Mean
SD: Standard deviation
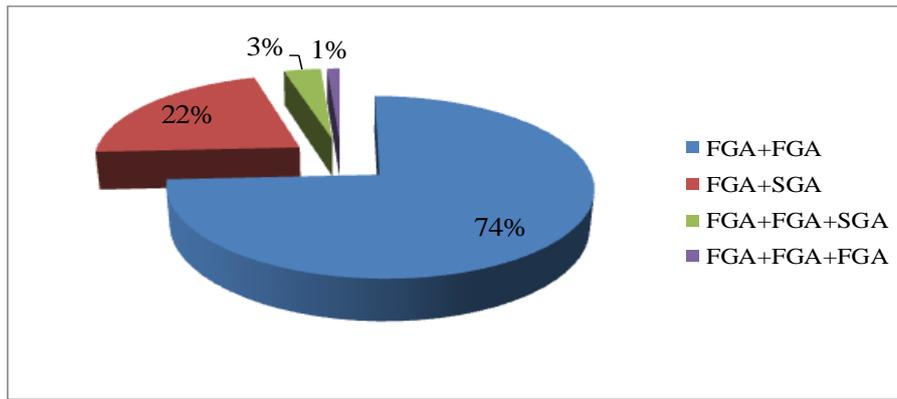
Figure 2: Class of drugs involved in antipsychotic combination therapy among patients with schizophrenia on follow-up at Amanuel Specialized Mental Hospital

On the other hand, the most frequent drug type of combination was chlorpromazine orally with fluphenazine decanoate depot intramuscularly followed by Risperidone orally with fluphenazine decanoate depot intramuscularly that accounted 65% and 10% of the combination type respectively as displayed in Figure 3.
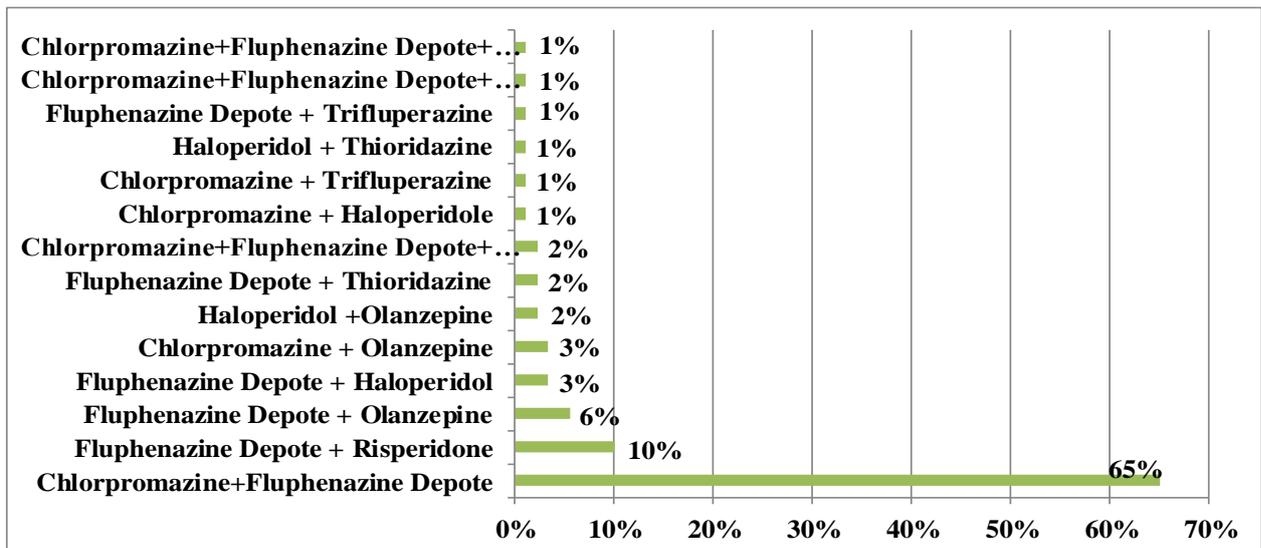
Figure 3: Type of drug combinations involved in antipsychotic combinations therapy among patients with schizophrenia on follow-up at Amanuel Specialized Mental Hospital

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FGA: First Generation Antipsychotic
SGA: Second Generation Antipsychotic

As indicated in Table 5, the top three drugs involved in antipsychotic combination were fluphenazine decanoate depot (88.2%), chlorpromazine orally (77.2%) and risperidone (14.6%) orally.

Table 5: Frequency of drugs involved in antipsychotic combination therapy among patients with schizophrenia on follow-up at Amanuel Specialized Mental Hospital

Drugs (n=89)	Frequency/%
Fluphenazine Depot	79 (88.8)
Chlorpromazine	66 (74.2)
Risperidone	13 (14.6)
Olanzepine	10 (11.2)
Haloperidole	8 (9)
Thioridazine	3 (3.4)
Trifluperazine	2 (2.2)

4.4. Antipsychotic Maintenance Dose and Monotherapy Trials Prior to Initiation of Antipsychotic Combination

Most of the patients on ACT (83.2%) were tried on monotherapy for greater than six weeks prior to ACT. However, more than half of the participants on ACT (53.9%) had only received a therapeutic dose trial of one class antipsychotic medication. The mean maintenance daily dose, immediately before combination, was 462.9 mg (SD±383.72) ranging from 50 to 2350 mg. Around two-fifth of patients (38.2%) were within therapeutic dose range immediately before combination. However, thirty two patients were in sub-therapeutic dose before they started to receive antipsychotic combination as indicated in Table 6.

Table 6: Maintenance dose and monotherapy trials prior to antipsychotic combination among patients with schizophrenia on follow-up at Amanuel Specialized Mental Hospital

Variables	Frequency (%)
Maintenance Daily CPZeq Dose in mg prior to ACT (n=89)	
Sub therapeutic (< 300 mg)	32 (36)
Therapeutic (300 mg - 600 mg)	34 (38.2)
Supra-therapeutic (600 mg - 1000 mg)	16 (18)
Supra-maximal (> 1000 mg)	7 (7.9)
Total	89 (100)
AMT trial period Prior ACT (n=89)	
< 6 weeks	15 (16.85)
> 6 Weeks	74 (83.15)
Total	89 (100)
Number of antipsychotics used for trial (n=89)	
Single drug only	48 (53.9)
Two drugs alternatively	24 (27)
Three/more drugs alternatively	17 (19.1)
Total	89 (100)

4.5. Reasons for Antipsychotic Combination Therapy

Reasons for ACT were extracted from the patients' medical chart. From that, inadequate response was the most common reason which accounted for more than half of the patients who were on ACT followed by patients' poor compliance to oral medication (16.8%). For thirteen patients the reasons for starting antipsychotic combination were not stated clearly in the patients' medical charts as indicated in Table 7.

Table 7: Reasons for antipsychotic combination therapy among patients with schizophrenia on follow-up at Amanuel Specialized Mental Hospital

Reasons for Combination		Frequency /%
Intolerance to side effect for high dose monotherapy (n=89)	Yes	5 (5.6)
	No	84 (94.4)
Smoking (n=89)	Yes	4 (4.5)
	No	85 (95.5)
Inadequate Response (n=89)	Yes	47 (52.8)
	No	42 (47.2)
Additive dosage effect (n-=89)	Yes	14 (15.7)
	No	75 (84.2)
patients' poor compliance to oral medication (n=89)	Yes	15 (16.8)
	No	74 (83.2)
Frequent Relapse (n=89)	Yes	13 (14.6)
	No	76 (85.4)
Not Justified (n=89)	Yes	13 (14.6)
	No	76 (83.6)

4.6. Extent of Antipsychotic Combination Therapy Related Side Effect Burdens

Based on Glasgow antipsychotic side effects rating scale, one in ten patients on antipsychotic combination experienced severe side effects. Where as one in hundred patients on monotherapy experienced severe side effects. Conversely, the probability of being free or developing mild side effects was more for patients on AMT (80%) than patients on combination therapy (53%) as indicated in Figure 4.
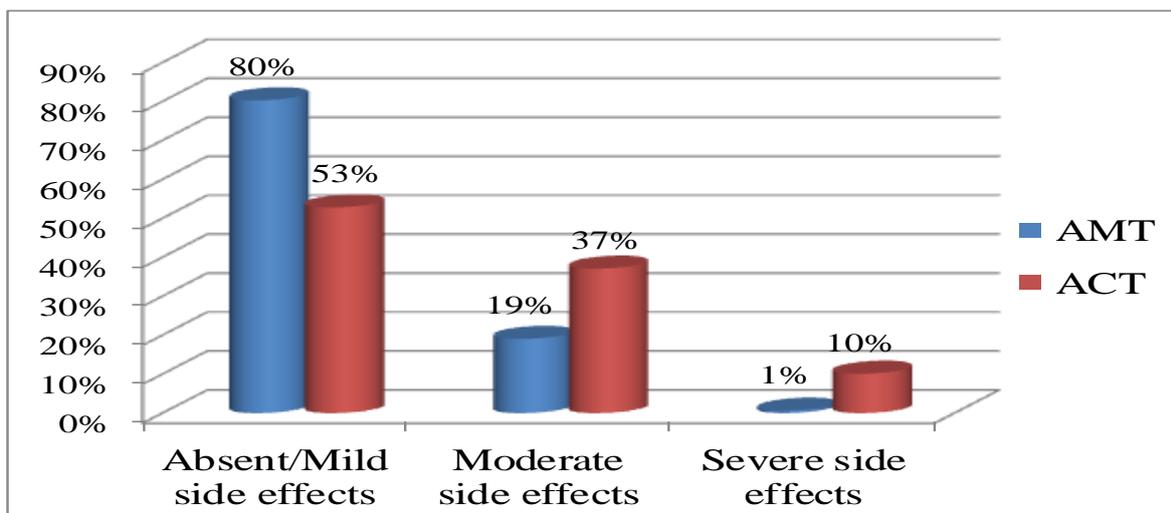
Figure 4: Antipsychotic combination therapy related side effect burdens among patients with schizophrenia on follow-up at Amanuel Specialized Mental Hospital

4.7. Level of Antipsychotic Combination Therapy Related Medication Adherence

From patients' self-response to the eight-item Morisky Medication Adherence Scale, majority of patients on combination therapy (70.79%) had low adherence level compared with those who were on monotherapy (32.18%). On the other hand, patients on monotherapy had more than two fold better high adherence (20.96% vs. 10.11%) and medium adherence (46.88% vs. 19.10%) as stated in Table 8.

Table 8: Level of medication adherence among patients with schizophrenia on follow-up at Amanuel Specialized Mental Hospital

Adherence Category	AMT Frequency/%	ACT Frequency/%	Total
High Adherence	67 (20.94%)	9 (10.11%)	76 (18.58%)
Medium Adherence	150 (46.88%)	17 (19.10%)	167 (40.83%)
Low Adherence	103 (32.18%)	63 (70.79%)	166 (40.59%)
Total	320 (100.0%)	89 (100.0%)	409 (100.0%)

4.8. Factors Associated with Antipsychotic Combination Therapy

To determine the association of independent variables on ACT, univariate logistic regression analysis was carried out. The univariate analysis was done by including all exploratory variables including socio-demographic factors, clinical factors and outcome factors. The variable group expected to have less likelihood for ACT, based on literatures, was taken as the reference group.

Upon univariate logistic regression analysis, socio-demographic characteristics including: age, sex, educational level, current substance use (smoking, alcohol and khat); clinical characteristics including: duration of illness, psychiatric related hospital admission rates, anticholinergic and other adjuvant medication use had a significant association with ACT. In addition, outcome factors including: side effect burdens and adherence level had significant association as displayed in Table 9.

Accordingly, the odds of ACT for age group of 25 to 34 years were about eight times (COR= 8.39, 95% CI: 3.42-20.61) more common compared to those between 15 to 24 years. Males had 3.42 times odds (COR=3.42, 95 % CI: 1.82-6.42) of ACT compared to females. On the other hand, the odds of ACT in patients with higher education level were 0.28 times (COR=0.28, 95% CI: 0.10-0.77) that of patients who had no formal education. Regarding substance use, the odds of ACT in patients who were current smokers, alcohol drinkers and khat chewers were three times (COR=3.18, 95% CI: 1.86-5.44), two times (COR=2.21, 95% CI: 1.19-4.10) and three times (COR=2.74, 95% CI: 1.60-4.7) more compared to patients who didn't have substance use behavior respectively.

The odds of ACT for patients who had six to ten years duration of illness as well as those who had more than ten years duration of illness were five times (COR=5.07, 95% CI:1.14-22.63) and thirteen times (COR=12.97, 95% CI:2.95-56.93) more compared to patients who had less than one year illness duration respectively. Similarly, The odds of ACT for patients who had six to ten times psychiatric related hospital admission history as well as those who had admission for more than ten times were three times (COR=2.61, 95% CI: 1.24-5.48) and fourteen times (COR=14, 95% CI: 6.04-30.64) more compared to patients who had no previous psychiatric related hospital admission respectively. The odds of ACT for patients who had other co-morbid mental illness was 0.30 times (COR=0.30, 95% CI: 0.07, 1.28) that of patients who didn't have as shown in Table 9.

Outcome factors and other adjuvant medication use had also significant association in univariate logistic regression analysis. The odds of ACT for patients who had severe side effects were twenty five times (COR=24.61, 95 % CI: 5.15-117.50) more common compared to patients who had no/mild side effects. The odds of ACT in patients who had low level of adherence were five times (COR=4.55, 95% CI: 2.12-9.77) more compared to patients who had high adherence. Similarly, the odds of ACT in patients who had anticholinergic prescription were six times (COR=5.80, 95% CI: 3.50-9.63) more common compared to patients who hadn't. On the other hand, the odds of ACT in patients who had other adjuvant prescription were 0.28 times (COR=0.28, 95% CI=0.07-1.22) that of patients who didn't have adjuvant prescription as displayed in Table 9.

Variables with p-value<0.2 in the univariate logistic regression analysis were taken to multivariate logistic regression analysis to see whether there is significant association or not by controlling confounding factors. During the multivariate logistic regression analysis; age, sex, duration of illness, number of psychiatric hospitalizations, side effect burdens and anticholinergic use were found to have significant association with ACT as shown in Table 9.

In line with this, the odds of ACT in patients with age group of 25 to 34 years were five times (AOR=4.74, 95 % CI: 1.33-16.9) more common compared to patients of 15 to 25 years old. Nevertheless, the odds of ACT in patients of 35 to 44 years old were 0.11 times (AOR=0.11, 95% CI: 0.02-0.7) that of patients of 15-24 years old. The odds of ACT for male patients were also four times (AOR=3.77, 95 % CI: 1.21-11.81) more common compared to female patients. The odds of ACT in patients who had greater than ten years duration of illness and more than ten times psychiatric related hospital admission were about ten times (AOR=9.86, 95 % CI: 1.40-69.14) and eight times (AOR=8.21, 95 % CI: 2.04-32.99) more compared to patients who had less than one year duration of illness and those who didn't have psychiatric hospital admission respectively as shown in Table 9.

The odds of ACT in patients who experienced severe side effect were sixteen times (AOR=16.12, 95% CI: 1.12-232.78) more common compared to patients who didn't experience side effect at all or who experienced mild side effects. Lastly, the odds of ACT in patients who had anticholinergic prescription were about seven times (AOR=6.82, 95% CI: 2.97-15.66) more common compared to patients who hadn't concomitant anticholinergic use as displayed in Table 9.

Table 9: Multivariate logistic regression analysis results of factors associated with antipsychotic combination therapy among patients with schizophrenia on follow-up at Amanuel Specialized Mental Hospital

Variables		Antipsychotic Combination		COR (95 % CI)	AOR(95% CI)
		Absent (%)	Present (%)		
Age Category	15-24	59 (18.4)	6 (6.7)	1.00	1.00
	25-34	82 (25.6)	70 (78.7)	8.39 (3.42, 20.61)*	4.74 (1.33, 16.9)*
	35-44	110 (34.4)	3 (3.4)	0.27 (0.07, 1.11)	0.11 (0.02, 0.70)*
	45-54	50 (15.6)	6 (6.7)	1.18 (0.36, 8.79)	0.35 (0.06, 2.01)
	54-64	15 (4.7)	3 (3.4)	1.97 (0.44, 8.79)	0.27 (0.02, 3.16)
	65+	4 (1.3)	1 (1.1)	2.46 (0.24, 25.69)	1.84 (0.04, 85.57)
Sex	Female	118 (36.9)	13 (14.6)	1.00	1.00
	Male	202 (63.1)	76 (85.4)	3.42 (1.82, 6.42)*	3.77 (1.21, 11.81)*
Education Status					
	None	40 (12.5)	15 (16.9)	1.00	1.00
	Primary	96 (30.0)	20 (22.5)	0.56 (0.26, 1.19)	0.71 (0.16, 3.14)
	Secondary	126 (39.4)	48 (53.9)	1.02 (0.52, 2.01)	1.81 (0.47, 6.96)
	Higher	58 (18.1)	6 (6.7)	0.28 (0.10, 0.77)*	0.47 (0.07, 3.06)
Medication fee	Free	231 (72.2)	72 (80.9)	1.00	1.00
	Payment	89 (27.8)	17 (19.1)	0.61 (0.34, 1.10)	1.14 (0.40, 3.27)
Smoking Currently	No	274 (85.6)	58 (65.2)	1.00	1.00
	Yes	46 (14.4)	31 (34.8)	3.18 (1.86, 5.44)*	0.78 (0.16, 2.66)
Drinking Alcohol Currently					
	No	285 (89.1)	69 (77.5)	1.00	1.00
	Yes	35 (10.9)	20 (22.5)	2.21(1.19, 4.10)*	1.24 (0.24, 6.44)
Khat Chewing Currently					
	No	272 (85)	60 (67.4)	1.00	1.00
	Yes	48 (15)	29 (32.6)	2.74 (1.60, 4.70)*	0.79 (0.18, 3.41)
Co morbid Mental Illness					
	No	297 (92.81)	87 (97.75)	1.00	1.00
	Yes	23 (7.19)	2 (2.25)	0.30 (0.07, 1.28)*	0.11 (0.01, 1.42)
Duration of Illness					
	< 1 Yr	32 (10)	2 (2.3)	1.00	1.00
	1-5 Yrs	148 (46.3)	14 (15.7)	1.51 (0.33, 6.99)	1.20 (0.19, 7.45)
	6-10Yrs	82 (25.6)	26 (29.2)	5.07 (1.14, 22.63)*	2.77 (0.44, 17.71)
	>10 Yrs	58 (18.1)	47 (52.8)	12.97 (2.95, 56.93)*	9.86 (1.40, 69.14)*
Psychiatric Admission					
	None	112 (35)	16 (18)	1.00	1.00
	1-5 times	140 (43.8)	20 (22.5)	1.00 (0.45, 2.02)	0.72 (0.25, 2.10)
	6-10 times	51 (15.9)	19 (21.3)	2.61 (1.24, 5.48)*	2.46 (0.79, 7.67)
	>10 times	17 (5.3)	34 (38.2)	14.00 (6.04, 30.64)*	8.21 (2.04, 32.99)*
Side Effect Burden					
	Absent/Mild	257 (80.3)	47 (52.8)	1.00	1.00
	Moderate	61 (19.1)	33 (37.1)	2.96 (1.75, 5.00)	1.79 (0.71, 4.47)
	Severe	2 (0.6)	9 (10.1)	24.61 (5.15, 117.50)*	16.12 (1.12, 232.78)*
Adherence level					
	High	67 (20.9)	9 (10.1)	1.00	1.00
	Medium	150 (46.9)	17 (19.1)	0.84 (0.36, 1.99)	0.35 (0.09, 1.39)
	Low	103 (32.2)	63 (70.8)	4.55 (2.12, 9.77)*	1.18 (0.32, 4.36)
Anticholinergic Use	No	239 (74.7)	30 (33.7)	1.00	1.00
	Yes	81 (25.3)	59 (66.3)	5.80 (3.50, 9.63)*	6.82 (2.97, 15.66)*
Adjuvant Medication	No	296 (92.5)	87 (97.8)	1.00	1.00
	Yes	24 (7.5)	2 (2.2)	0.28 (0.07, 1.22)*	0.4(0.04, 4.29)

* Significant association (p<0.05)

5. Discussion

Despite the recommendation of antipsychotic monotherapy, in schizophrenia management, antipsychotic combination is common in clinical practice with prevalence rates varying widely. This study showed that ACT was practiced in over a fifth of patients (21.8%) engaged in longer term care. This was comparable with the finding from Florida, USA (Constantine *et al., 2010)*. However, it was somewhat higher when compared with a multicenter study in four European countries (Barbui, *et al.*, 2006), Nigeria (Adeponle *et al.*, 2007), China (Xiang *et al.*, 2007) and Lancashire (Ranceva *et al.*, 2010). On the other hand, this finding was lower as compared with many other studies in USA (Ganguly *et al.*, 2004; Aggarwal *et al.*, 2012), Serbia (Divac *et al.*, 2007), South Africa (Koen *et al.*, 2008), Canada (Procyshyn *et al.*, 2010), Oslo (Bolstad, *et al.*, 2011), Spain (López *et al.*, 2012), Japan (*Ye et al.*, 2012) and Palestine (Ihbeasheh *et al.*, 2014) in which the prevalence rate was in the range of 23-67.7%. This variation in prevalence of ACT with those studies might be accounted by differences in the operational definition (ranging from 3 days to beyond 3 months), the study set-up, the population studied, the year when the study was conducted, the study method and the duration of the study period. In addition, the broad availability of second generation antipsychotic in most western studies could also contribute for higher rate than this study.

In this study, the most frequent drug classes involved in combination therapy were within first generation antipsychotics. The drugs were fluphenazine depot and chlorpromazine orally but this class of drugs might lead to the occurrence of neurologic side effects. This was in line with a study conducted in Northern Nigeria (Adeponle *et al.*, 2007) and Palestine (Ihbeasheh *et al.*, 2014). However most of other studies found more of the combination within SGAs and SGAs with FGAs (Gangul *et al.*, 2004; Bolstad, *et al.*, 2011; López *et al.*, 2012; Jinyoung *et al.*, 2014).This might be due to limited availability of SGAs (only risperidone and olanzapine were available) in Ethiopia. In addition, the only available depot preparation, currently in Ethiopia, was fluphenazine decanoate till the conduct of this study whereas there were many alternative SGA as well as FGA depot preparation in previous studies. However, the frequency of more than two antipsychotics combination was less compared to other studies.

Consistent relationship exists between ACT and greater total antipsychotic daily dose as it was supported in studies in USA (Kreyenbuhl *et al.*, 2007a), Italy (Ghio *et al.*, 2011), UK (Ranceva *et al.*, 2010), Canada (Procyshyn *et al.*, 2010), Scotland (Lovely & Ian, 2013) and Palestine (Ihbeasheh *et al.*, 2014). These findings were in line with the present study in which

more than 80 % of patients on combination therapy were in supra-therapeutic to supra-maximal dose range. This was attributed to fluphenazine depot, the most frequently used drug in ACT in this study, which has a high CPZeq conversion factor that had an impact in raising the total mean daily dose. On the other hand, most of the patients on monotherapy group were in sub-therapeutic dose range, less than 300 mg daily dose. This might be due to the fear of side effects so that prescribers started with low dose and titrated up or down. However, if titration couldn't be done as per schedule, it might lead to failure in controlling symptoms. This indirectly might lead to a fallacious conclusion of poor symptom control in later which might require antipsychotic combination therapy. This point could be supported by the evidence found in this study in that about 36 % of patients, who were in combined therapy, were tried below the recommended daily dose before going to antipsychotic combination therapy. However, caution has to be taken as chlorpromazine equivalent dose has limitation in estimating the equivalent dose of SGAs and might underestimate the daily doses by stating as sub-therapeutic. This is because some SGAs even might work best at lower dose though their chlorpromazine equivalent dose seemed lower being in sub-therapeutic dose range.

Possible reasons for antipsychotic combination were retrieved from patients' charts retrospectively and for more than eighty percent of patients on combination there was justifiable documentation of reason for combination. This was higher compared to previous studies (Lovely & Ian, 2013; Schumacher *et al*., 2003). More than half of patients on combination therapy had inadequate response for treatment. This might have been accounted from treatment patterns with sub-therapeutic dose. Further, patients in combination therapy might have more illness severity and also most of the patients had longer duration of illness. This was in accordance with previous studies (Miller & Craig, 2002; Hawa & Stubs, 2003; Freudenreich *et al*., 2007; Lovely & Ian, 2013). Patients' poor compliance to oral medications was the second reason for 16.8% of patients on combination which might be the need for injectable antipsychotic (Fluphenazine depote) that could improve patient compliance. This was also supported by previous studies (Hawa & Craig 2002; Miller & Stubs 2003).

Though monotherapy for greater than six weeks was tried for most of the patients, before combination, fifteen (16%) patients were tried only for less than six weeks. Thirty six percent of patients on combination were also tried below the recommended dose and more than half of those patients on combination were tried with single antipsychotic. This result was below the recommendation of most guidelines where adequate monotherapy trial with adequate

dose titration for adequate time is recommended before initiation of combination therapy (Expert, 1999; NICE, 2009; Moore *et al*., 2008; IPAP, 2009). This might be resulted from patients could be seen by a number of psychiatrists so that the required monotherapy trial couldn't be done. In addition, patients might have inadequate response showing frequent relapse, violation and attack that might lead the psychiatrist the call for additional drug therapy to control those symptoms early.

On the PANSS measures, there were statistical significant differences (after independent sample t-test; $p<0.001$ for all types of scores) between the mean score of patients on antipsychotic combination therapy and monotherapy. The PANSS mean scores were slightly higher for patients on antipsychotic combination therapy than patients on antipsychotic mono therapy. These results were only agree with one recent study in Korea (Jinyoung, *et al*., 2014) but in contrary with other previous studies which stated PANSS mean score was lower in ACT (Josiassen, *et al*., 2005; Agelink *et al*., 2004) and PANSS mean score was not different between the two groups (Honer, *et al*., 2006; Ihbeasheh *et al*., 2014). This difference in PANSS score is likely to be because the patients on ACT might be a more ill group.

In this study, wider gap was detected regarding sever side effect burden between patients on ACT and monotherapy. The ratio of developing severe side effect was 10:1 for patients on ACT compared to monotherapy. Relatively, closer gap was detected regarding moderate side effects (1.95:1 for ACT vs AMT) and absent/mild side effects (1.5:1 for AMT vs ACT) between the two groups. Severe side effects were experienced more on patients on ACT because nearly 80% of patients on ACT were on high and very high daily dose therapy. Even though most of the studies conducted were for specific side effect profile using other than the instrument this study used for assessing side effect burden, this finding was supported by different studies (Barbui, *et al*., 2006; Guy, *et al*., 2009; Yasuhiko, *et al*., 2012).

Even though nonadherence in schizophrenia is a major problem at all, nonadherence or partial medication adherence was related to ACT as shown in studies in Switzerland (Simon *et al*., 2005), California (Ahn, *et al*., 2008) and North Eastern Nigeria (Ibrahim, *et al.*, 2015). The present study was in agreement with these studies. Patients on monotherapy as compared with combination therapy had more than a twofold better high adherence (20.96% vs. 10.11%) and medium adherence (46.88 % vs. 19.10 %). However, patients on combination therapy had about twofold (70.79% vs 32.18%) increase in low adherence level. These variations could be due to patients who were poorly adherent to medication have been

started on fluphenazine decanoate depot and this led to combination therapy. However, majority of patients on combination were on supra-therapeutic and supra-maximal doses because the dose for fluphenazine is high. In relation to this, patients who were above therapeutic dose might experience side-effects that could affect adherence to medications. If patients are put on ACT, the overall dose from that combination should be lower than a single drug at high dose.

Multivariate logistic regression analysis showed that; age, sex, duration of illness, number of psychiatric related hospitalization admissions, side effect burdens and anticholinergic use were found to have significant association with ACT. Accordingly, the odds ACT in patients with age group of 25 to 34 years were five times more common compared to patients of 15 to 24 years old. This could happen because younger age was considered as associated with greater illness severity and poorer outcomes. In addition, these patient groups might be perceived as more dangerous than other patient population causing harm on family members or the society. To prevent that violent attack, combination of oral and long acting injectable antipsychotics could be offered to them to in case they discontinued their oral medication. This finding was in accordance with studies in USA (Kreyenbuhl *et al*., 2007b; Morrato, *et al*., 2007) and Spain (Lerma-Carrillo, *et al., 2008;* Molina, *et al*., 2009). However, patients of 35 to 44 years old had 0.11 odds of ACT compared to patients of 15-24 years old. This result was in line with a study in Estonia that reported inverse relation between age and ACT (Lass *et al*., 2008). The association with young age is more likely to be because this is the most common age of presentation and therefore, people tend to be more acutely unwell as mentioned earlier.

In this study, the odds of ACT in male patients were four times more common compared to females. The association of male sex with ACT might be due to greater illness severity, chronicity, or dangerousness in males. Males had an earlier onset, poorer premorbid functioning and more negative symptoms and cognitive deficits, with greater structural brain and neurophysiologic abnormalities. Females have more rapid and greater response to antipsychotics. Families of males are more critical, and expressed emotion has a greater negative impact on males. This finding was consistent with previous studies (Ganguly *et al*., 2004; Morrato *et al.*, 2007).

Patients who had more than ten years duration of illness had an increased odds of ACT compared to patients who had less than one year duration of illness. This finding was related to the chronicity of the illness for that ACT was prescribed for patients who had little or no response with standard antipsychotic monotherapy as investigated by other studies in East Asia (Sim *et al*., 2004), Germany (Janssen *et al*., 2004), Belgium (De Hert *et al*., 2006), European (Barbui, *et al*., 2006) and Palestine (Ihbeasheh *et al*., 2014).

Patients who had frequent psychiatric related hospital admissions had an increased odds of ACT as indicated by studies in USA (Morrato, *et al*., 2007), Germany (Janssen *et al*., 2004), Italy (Magliano, *et al*., 2004), Oslo (Bolstad, *et al*., 2011) and Palestine (Ihbeasheh *et al*., 2014). The present study is in agreement with these studies. Patients who had frequent psychiatric related hospital admission (more than ten times) had an increased odds of ACT compared to patients who didn't have admission history. This might be related to patients could have inadequate symptom control, which was a major reason for ACT in the present study, that might result in frequent relapse and requiring repeated hospital admission. To prevent this scenario, psychiatrist would tend to put patients on antipsychotic combination to have a better symptom control.

At last, the odds of ACT in patients who experienced severe side effect were sixteen times more compared to patients who didn't experience side effect at all or who experienced mild side effects. As explained earlier, this could happen in relation with high dose treatment pattern due to combination therapy in this study. However, the confidence interval was too wide to be certain in estimating the exact effect size. This could happen because the number of patients experiencing severe side effects was too small compared to patients with absent/minimal side effect (the reference group). This finding was supported by different studies (Barbui *et al.*, 2006; Guy *et al.,* 2009, Yasuhiko *et al*.,2012) as well as the evidence found in this study that the odds of ACT in patients who had concomitant anticholinergics use were about seven times more compared to patients who didn't have concomitant anticholinergic use pattern. This can be explained as anticholinergics like trihexyphenidyle are mostly prescribed in schizophrenia in case of the emerging extrapyramidal side effects following high dose therapy. This result is consistent with studies previous studies (Ganguly *et al.* 2004; Kreyenbuhl *et al.* 2007; Xiang *et al.* 2007; Gio *et al*. (2011).

6. Limitation of the Study

The first limitation of this study was regarding the cross sectional nature of the study which did not allow drawing any definite conclusion concerning causality between antipsychotic combination therapy and its associated factors. This is because it is weak in ascertaining of temporal relationship i.e. which event could preceded in differentiating which event is the cause and which is the effect. Most variables used in this study relied on information obtained from medical files which are subject to errors in that there might be some missing data. The other limitation is regarding chlorpromazine equivalent dose which might underestimate the doses of atypical antipsychotics though it works best for typical antipsychotics. Hence, caution has to be taken in interpreting the CPZeq dose category. The study was done at single facility as well as among outpatients only and hence attention should be taken in extrapolating the results. Despite these limitations, the study was able to give some insight on antipsychotic combination therapy on patients with schizophrenia.

7. Conclusion

Antipsychotic combination therapy among patients with schizophrenia on follow-up was practiced on a fifth of the study participants. The frequency of combining within first generation antipsychotics class was high. Fluphenazine depot was the most frequent drug used in ACT. The most possible mentioned reason was inadequate response to treatment followed by patients' poor compliance to oral medications. Most of patients on ACT had higher total daily dose measured in chlorpromazine equivalent dose. Patients on combination therapy experienced more side effects and at the same time had low adherence level. Younger ages (25-34 years), male sex, greater than ten years duration of illness, frequent hospital admissions, severe side effect burdens and anticholinergic use had positive association with ACT. On contrary, age group of 35-44 years had inverse relation with ACT.

8. Recommendations

From this study, ACT among patients with schizophrenia on follow-up was practiced on a fifth of patients though this practice has many concerns. In any case, based on the results of this study, it would be important to recommend that:

➢ Health care providers should give attention in close monitoring patients for drug side effects.

➢ Clear and complete recording of the reasons should be maintained by prescribers whenever antipsychotic combinion therapy is required.

➢ Fluphenazine depot should be considered for patients with poor adherent to oral medications as a monotherapy and should be avoided in combination therapy.

➢ Safer alternatives for chlorpromazine like promethazine should be considered as sleep aid if intended to use with depot combination rather than chlorpromazine.

➢ The health care providers of the hospital should work together with Pharmaceutical Funds and Supply Agency (PFSA) and FMOH in availing alternative SGAs that have minimal side effects, and that are used for treatment resistant cases (e.g. Clozapine).

➢ The Ethiopian Food Medicine and Health Authority Control Agency (FMHACA) should revise and develop explicit guideline for schizophrenia management like other international guidelines. The hospital should also develop its own guideline.

➢ Furthermore, more researches are required to characterize the benefits and risks of antipsychotic combinations using different study designs and clinical tools.

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Annexes

Annex I: Consent Form and Data Abstraction Formats

Department of Pharmacology and Clinical pharmacy, School of Pharmacy, CHS, AAU

A Study on Assessment of Antipsychotic Combination Therapy among Patients with Schizophrenia on Follow-up at Amanuel Specialized Mental Hospital

Consent Form

Hello, My name is_____. I am here today to collect data to " *Assess Antipsychotic Combination Therapy among Patients with Schizophrenia on Follow-up*." The study is being conducted by Mr. Chalelgn Kassaw from Addis Ababa University, School of Pharmacy, Department of clinical pharmacy and pharmacology, post graduate program. The objective of this study is to assess the practice of antipsychotic combination therapy among schizophrenic patients on follow-up specifically the side effect burden you encountered and your medication adherence level. Therefore, the study will identify and investigate the gaps and will suggest the possible recommendations. Hence, it may benefit you in improving the medical care service for betterment of your treatment outcome. It is only through chance that you became part of the study like others; otherwise, if you do not want to be part of the study, you can refuse to participate. In doing so, you will not going to lose any service that you are getting from this hospital. So that I request you to take part in this study as well as follow and respond genuinely. All information given by you will be kept strictly confidential. Your participation is voluntary and you are not obligated to participate in the study. If you feel discomfort with study, it is your right to drop it any time you want. If you have questions regarding this study or would like to be informed of the results after its completion, please feel free to contact the principal investigator.

Thank You!

Address of the principal investigator:

Chalelgn Kassaw   Cell phone: +251- 910061725   E-mail: chalkassa@gmail.com

Are you willing to participate in this study?

1. Yes - ………………………….. Continue

2. No - …………………………… Skip to the next participant

Part one: Structured Questionnaire for Interview

I. Socio-demographic characteristics

		MR.No. _____		
1.	**Age (Years):_____**	**2. Sex**: 1. Male ◯ 2. Female ◯		
3.	**Education Status**: 1. No formal education ◯ 2. Primary ◯ 3.Secondary ◯ 4. Higher ◯			
4.	**Residence:** 1. Urban ◯ 2. Rural ◯			
5.	**Marital Status:** 1. Unmarried ◯ 2. Married ◯ 3. Divorced ◯4. Widowed◯			
6.	**Source of medication fee:** 1. Free ◯ 2. Payment ◯			
7.	**Family Income (ETB):** 1. < 445 ◯ 2. 446-1200 ◯ 3. 1201-2500 ◯ 4. 2501-3500 ◯ 5. >3501 ◯			
8.	**Working status:** 1. Working ◯ 2. Not working ◯			
9.	**Living Arrangements:** 1. Alone ◯ 2. With Family/Support ◯ 3. In Charity◯			
10.	**Current Substance Use:**	Yes	No	
	Smoking	◯	◯	
	Alcohol	◯	◯	
	Khat	◯	◯	

II. Eight Item Morisky Medication Adherence Predictor Scale, MMAPS)

S.N	MAPS questions	Yes	No
11.	Do you sometimes forget to take your pills?		
12.	People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?		
13.	Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?		
14.	When you travel or leave home, do you sometimes forget to bring along your medicine?		
15.	Did you take all your medicine yesterday?		
16.	When you feel like your symptoms are under control, do you sometimes stop taking your medicine?		
17.	Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?		
18.	How often do you have difficulty remembering to take all your medicine? A) Never/rarely B) Once in a while C) Sometimes D) Usually E) All the time		

III. Glasgow Antipsychotic Side-effect Scale (GASS)

S.N	Over the past week:	Never	Once	A few times	Every day	If you feel distress tick this box
19.	I felt sleepy during the day					
20.	I felt drugged or like a zombie					
21.	I felt dizzy when I stood up and/or have fainted					
22.	I have felt my heart beating irregularly or unusually fast					
23.	My muscles have been tense or jerky					
24.	My hands or arms have been shaky					
25.	My legs have felt restless and/or I couldn't sit still					
26.	I have been drooling					
27.	My movements or walking have been slower than usual					
28.	I have had, or people have noticed uncontrollable movements of my face or body					
29	My vision has been blurry					
30.	My mouth has been dry					
31.	I have had difficulty passing urine					
32	I have felt like I am going to be sick or have vomited					
33.	I have wet the bed					
34.	I have been very thirsty and/or passing urine frequently					
35.	The areas around my nipples have been sore and swollen					
36.	I have noticed fluid coming from my nipples					
37.	I have had problems enjoying sex					
38	Men only: I have had problems getting an erection					
For the last **three months**		Yes	No	If you feel distress tick this box		
39	Women only: I have noticed a change in my periods					
40	Men and women: I have been gaining weight					

IV.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
G1	Somatic concern	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 judgement & 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 Two: Data Abstraction Format from Patients' Chart

I. Clinical Characteristics

1. Type of Diagnosis _____

2. Initial date of registration _____

3. Other co-morbid mental illness   _____

4. Other co-morbid chronic medical illness _____

5. Number of hospital Admission(s) since diagnosis _____

II. Medication Profile

(6).Current Medications		(7) Reason for combination (if any combination) (it is possible to cite more than 1 reason if available)	(8) Maintenance dose before Combination (If combination)	(9) Monotherapy Trial before Combination (If combination)
FGAs	Daily Dose (mg)	a. Intolerance to side effects from high dose		**Drug used** a. Single Drug only
1.Chloroprmazine		b. Inadequate response	1._____	b. Two drugs alternatively
2.Fluphenazine		c. Smoking	2._____	c. > or 3 drugs alternatively
3.Haloperidole		d. Additive dosage effect	3._____	
4.Thioridazine		e. Frequent relapse	4._____	**Trial Duration**
5.Trifluperazine		f. Poor compliance to PO medications	5._____	a.< 6weeks
SGAs				b.> or 6 weeks
1.Risperidone		g. Patient preference	1._____	
2.Olanzapine		h. Others _____ _____ i. Not justified	2._____	
Anticholinergics				
Benzhexole				
Others				
Other Adjuvants				

FGA/SGA: First/Second Generation Antipsychotics   mg: milligram

Annex II: Consent Form and Patient Interview Questionnaire (Amharic Version)

የአማርኛ መጠይቅ ቅፅ

የጥናቱ መረጃ ቅጽ   ቀን:-_____

ውድ የቃለ-መጠይቁ ተሳታፊ

ስሜ_____ ይባላል። "በአማኑኤል የአእምሮ ስፔሻላይዝድ ሆስፒታል "በስኪዞፍሪኒያ" በሽታ ታካሚዎች ዙርያ የ"ስኪዞፍሪኒያ" መድሃኒቶች በታዘዘው መሰረት በአግባቡ የአወሳሰድና እና ስለሚከሰቱ የጎንዮሽ ጉዳቶች " የተሰኘ የድህረ ምረቃ ጥናት አባል ነኝ። የዚህ ጥናት ዋና አላማው የ"ስኪዞፍሪኒያ" መድኃኒቶች እንዴት እንደሚጠቀሙት፣ በታዘዘው መሰረት በአግባቡ እንዴት መድኃኒትዎን እንደሚወሰዱት እና የሚከሰቱ የመድሃኒቶች የጎንዮሽ ጉዳት በመለየት፣ የመፍትሄ ሃሳቦችን ማቅረብ ነው።

በዚህ ጥናት ላይ የእርስዎ የ"ስኪዞፍሪኒያ"መድኃኒቶች በታዘዘው መሰረት በአግባቡ የአወሳሰድና የአጠቃቀም ከህሎት በድንብ እንዲሁም ስለሚከሰቱ የመድሃኒት የጎንዮሽ ጉዳቶች ጠቃሚ ይጠናል። በመሆኑም ዋና ዋና ክፍተቶችን ከጥናቱ በሚገኙ ግኝቶች የ"ስኪዞፍሪኒያ" ህክምና ዉጤትን በተወሰነ መልኩ ለማሻሻል እንደሚቻል በመገመት፣ እርስዎ የጥቅሙ ተካፋይ ይሆናሉ ብለን እናምናለን። ስለዚህ የእርስዎ ቅንና ሐቀኛ መረጃ ለጥናቱ እጅግ በጣም ወሳኝ ነው።

የተከበረ ጊዜዎ ስለሰጡን እጅግ በጣም እናመሰግንዋታለን።

በቃለ መጠይቅ ለመሳተፍ የፈቃደኝነት ቃል መቀቢያ ቅጽ

በዚህ ጥናት የእርስዎ መረጃ ሙሉ በሙሉ በሚስጥር የተጠበቀና ለምርምሩ አላማ ብቻ የሚዉል ነው። በተጨማሪም የእርስዎ ተሳታፊነት በፈቃደኝነት የተመሠረተ ነው። የጥናቱ አላምውን ተረድተውና ጊዜዎን ሰውተው፣ ከ 40-45 ደቂቃዎች ለሚፈጅ ቃለ-መጠይቅ እውተኛው መረጃ ለመስጠት ፍቃደኛ በመሆንዎ በቅድሚያ አመሰግናለሁ።

በየትኛው ጊዜ ጥያቄ ካለዎት ቻለልኝ ካሳው ብለው

በ ስ.ቁ. (+251) -910-06 - 17- 25 ወይም

በ ኢ-ሜይልchalkassa@gmail.com ይጠይቁን።

_____   _____
የቃለ መጠይቅ የቀረበለት ሰው ፊርማ   የቃለ መጠይቅ አቅራቢ ፊርማ

ቃለ- መጠይቅ ከታካሚው

ክፍል 1፡ አጠቃላይ መገለጫዎች

		የህክምና ካርድ ቁጥር_____			
1.	**ዕድሜ:_____**	2. **ፆታ**: 1. ወንድ ⃝ 2. ሴት ⃝			
3.	**የት/ርት ደረጃ**: 1. ያልተማረ/ች ⃝ 2. 1ኛ ደረጃ ⃝ 3.ሁለተኛ ደረጃ ⃝ 4. ቴክኒካ ሙያ/ኮሌጅ/ዩኒቨርሲቲ ⃝			
4.	**የመኖሪያ አድራሻ**: 1. ከተማ ⃝ 2. ገጠር ⃝			
5.	**የጋብቻ ሁኔታ**: 1. ያላገባ/ች ⃝ 2. ያገባ/ች ⃝ 3. የፈታ/ች ⃝ 4.የሞተችበት/የሞተባት ⃝			
6.	**መድሃኒት የሚያገኙበት ሁኔታ**: 1. በነጻ ⃝ 2. በግዢ ⃝			
7.	**የቤተሰብ ወርሃዊ ገቢ (በብር)**: 1. < 445 ⃝ 2. 446-1200 ⃝ 3. 1201-2500 ⃝ 4. 2501-3500 ⃝ 5. >3501 ⃝			
8.	**የስራ ሁኔታ**: 1. ስራ ያለው/ያለት የሚሰራ/የምትሰራ ⃝ 2. ስራ የሌለው/የሌለት የማይሰራ/የማትሰራ ⃝			
9.	**የኑሮ ሁኔታ**: 1. ብቻውን/ብቻዋን የምትኖር ⃝ 2. ከቤተሰብ/ከረዳት ጋር ⃝ 3.በበጎአድራጎት ድርጅት ስር ⃝			
10.	የሚከተሉትን ይጠቀማሉ?		አዎ	አልጠቀምም	
		ሲጋራ	⃝	⃝	
		አልኮል	⃝	⃝	
		ጫት	⃝	⃝	

ክፍል 2፡ ሞሪስኪ" መድኃኒትን በታዘዘው መሰረት በአግባቡ ስለመውሰድ" መለኪያ- 8

ተ.ቁ	ጥያቄዎች	አዎ	አይደለም
11	አንዳንድ ጊዜ መድኃኒትዎን ረስተው ሳይወስዱ ቀርተው ያውቃሉ?		
12	ሰዎች አንዳንድ ጊዜ ከመርሳት ውጪ ባሉት የተለያዩ ምክንያቶች መድኃኒታቸውን ሳይወስዱ ይቀራሉ:: ባለፉት ሁለት ሳምንታት፣ መድኃኒትዎን ሳይወስዱ የቀሩበት ቀናቶች ነበሩ'?		
13	ሐኪምዎን ሳይነግሩ፣ መድኃኒትዎን እያወሰዱ ህመምዎ ሲባሰ፣ መድኃኒትዎን አቁርጠው ያውቃሉ?		
14	በጉዞ ምክንያት ወይም ከቤትዎ አርቀው ሲሄዙ፣ አንዳንድ ጊዜ መድኃኒትዎን (ወደጉዞው) ረስተውት ሳይወስዱት ያውቃሉ?		
15	በትላንትናው ዕለት ሁሉንም መድኃኒትዎን ወስደውታል?		
16	ህመምዎ ሲሻልዎት (የህመምዎ ስሜቶች ሲጠፉ) አንዳንድ ጊዜ መድኃኒትዎን አቁርጠው ያውቃሉ?		
17	በየቀኑ መድኃኒት መውሰድ፣ ለአንድ አንዳሰዎች ምቾት አይሰጣቸውም:: እርስዎ በየቀኑ እንድሁም አንድም ሰዓት ሳያዘሉ መድኃኒትዎን መውሰድዎ፣ የመሰላቸት ስሜት ተሰምቶት ያውቃል?		
18	መድኃኒትዎን አስታውሰው ለመውሰድ ምንያክል ይቸገራሉ?		

⃝ ጭራሽ አይቸግረኝም	⃝ ከስለታት አንድ ጊዜ ይቸግረኛል	⃝ አንዳንድ ጊዜ ይቸግረኛል	⃝ አብዛኛው ጊዜ ይቸግረኛል	⃝ ሁል ጊዜ ይቸግረኛል

ክፍል 3፡ ግላሰገው የስኪዚዮፍሪኒያ "መድሃኒቶች የጎንዮሽ ጉዳት ደረጃ መለኪያ

ተ.ቁ	ላለፈው አንድ ሳምንት፡	በጭራሽ	አንድ ጊዜ ብቻ	ከአንድ ጊዜ በላይ	ዘወትር በየቀኑ	የማይመለከተው ከሆን እዚህ ላይ ምልክት ያድርጉ
19	ቀን ላይ የእንቅልፍ ስሜት ይሰማኛል					
20	በደመነፍስ የምንቀሳቀስ ይመስለኛል					
21	ከተቀመጥኩበት ስነሳ ያዞረኛል/ራሴን ስቼ እስከመውደቅ ደረጃ					
22	የልብ ምቴ ይዘባል/በፍጥነት ይመታል					
23	ጡንቻዎቼ ይወጠሩና ያስቸግሩኛል					
24	እጆቼ ይንቀጠቀጣሉ					
25	እግሮቼን እረፍት እስካጣ ድረስ አንቀሳቅሳለሁ፤መቀመጥ አልችልም					
26	ላሁጭ ያስቸግረኛል					
27	እንቅስቃሴዬ ወይም ስራመድ ከበፊቱ በተለየ መለኩ የዘገየ ነው					
28	ከቁጥጥር ዉጭ የሆነ የሰውነት/የፊት እንቅስቃሴ/መንዘፍዘፍ ያጋጥመኛል ወይም ሰው እንዳለኝ ይነግሩኛል					
29	የደበዘዘ የአይን እይታ አጋጥሞኛል					
30	አፌ ይደርቃል					
31	ሽንት መሽናት ያቅተኛል					
32	የሚመያኝ/ የሚያስታውከኝ ይመስለኛል					
33	በእንቅልፌ አልጋ ላይ መሽናት አጋጥሞኛል					
34	ውሃ ቶሎቶሎ ይጠማኛል፤ሽንቴ ቶሎቶሎ ይመጣብኛል					
35	ጡቶቼ አካባቢ የማበጥና የህመም ስሜት ይሰማኛል					
36	በጡቶቼ ጫፍ ፈሳሽ ወጥቶ ያውቃል					
37	በግብረ ስጋ ግንኙነት ጊዜ ደስታ ማጣት					
38	(ለወንዶች ብቻ): የብልት አለመቆም ችግር አጋጥሞኝ ያውቃል					
ላለፉት ሶስት (3) ወራት		**አዎ**	**አላጋጠመኝም**			
39	(ለሴቶች ብቻ): የወር አበባ መዛባት አጋጥሞኛል					
40	(ለወንድም፤ ለሴትም): ክብደቴ ከበፊቱ ጨምሯኣል					

Annex III: Glasgow Antipsychotic Side-effect Scale (GASS) Scoring Guide

On the questionnaire questions 19 – 38 relate to how the patient has felt over the previous week and questions 39 and 40 relate to how they have felt in the last three months.

For questions 19-38:

Answers	Score
Never	0
Once	1
A few times	2
Every day	3

For questions 39&40:

Answers	Score
Yes	3
No	0

Add together the points for all of the questions to get an overall total and compare with the table below.

Over all total	Side-effects rating
0-12	Absent/Mild side-effects
13-26	Moderate side-effects
Above 26	Severe side-effects

 The column relating to the distress experienced by a particular side-effect is not scored, but is intended to help us to assess the patients views of the problem e.g. if a patient is classed as having only mild side-effects but has indicated that they find them distressing, they may need additional help with managing them or a change of treatment.

NB. (Q19&Q20)=Sedations and central nervous system side effects
      (Q21&Q22)= Cardiovascular side effects   (Q23-Q28) = Extrapyramidal side effects
      (Q29-Q31)= Anti-cholinergic side effects   (Q32) =Gastrointestinal side effect;
      (Q33) =Genitourinary side effects   (Q34) = Screening for diabetes mellitus
      (Q35-Q39)=Prolactinaemic side effects   (Q40) = Weight gain

Annex IV: Positive and Negative Syndrome Scale Scoring Guide

1. **Absent**: If the item is absent, it is scored 1

2. **Minimal:** A rating of 2 (minimal) denotes questionable or subtle or suspected pathology, or it also may allude to the extreme end of the normal range .

3. **Mild:** A rating of 3 (mild) is indicative of a symptom whose presence is clearly established but not pronounced and interferes little in day-to-day functioning.

4. **Moderate:** A rating of 4 (moderate) characterises a symptom which, though representing a serious problem, either occurs only occasionally or intrudes on daily life only to a moderate extent.

5. **Moderate Severe:** A rating of 5 (moderate severe) indicates marked manifestations that distinctly impact on one's functioning but are not all-consuming and usually can be contained at will.

6. **Severe:** A rating of 6 (severe) represents gross pathology that is present very frequently, proves highly disruptive to one's life, and often calls for direct supervision.

7. **Extreme:** A rating of 7 (extreme) refers to the most serious level of psychopathology, whereby the manifestations drastically interfere in most or all major life functions, typically necessitating close supervision and assistance in many areas.

Annex V: Chlorpromazine Dose Equivalencies of Antipsychotics

S.N	Generic Name	Equivalent dose for 100 mg Chlorpromazine
1	Haloperidol	2 mg per day
2	Risperidone (oral)	2 mg per day
3	Trifluoperazine	5 mg per day
4	Olanzapine	5 mg per day
5	Chlorpromazine	100 mg per day
6	Thioridazine	100 mg per day
7	Fluphenazine (depot)	2.5 mg per 21 days

Source: (Woods, 2003; Xiang *et al*., 2008; Danivas & Venkatasubramanian, 2013; Schooler & Levine, 1976)

NB. This list is based on currently available drugs in Ethiopia

For fluphenazine depot the manufacturers' recommended equivalent for the depot to oral conversion is used for the same drug and then converted to oral chlorpromazine equivalents. For fluphenazine the manufacturer recommends 12.5 mg depot/3 weeks as equivalent to 10 mg/d orally. This estimate is supported by a dose comparison study (12.5 mg depot/3 week equivalent to approximately 9 mg/d orally) (Schooler & Levine, 1976)