



ANTIPSYCHOTIC POLYPHARMACY IN FIRST-EPISODE PSYCHOSIS: EPIDEMIOLOGY, ASSOCIATED ADVERSE-EFFECTS AND DOSE-ADJUSTMENTS IN A TERTIARY PSYCHIATRIC HOSPITAL

Dr. Jan Alam^{1*}, Dr. Abdul Shakoor², Dr. Imama Zainab Sattar³, ANUM ZAHRA⁴, Saiqa Batool⁵, Tahira Jabeen⁶, Ayat Ul Haq⁷

^{1*}Consultant Psychiatrist At Psychiatry Hospital Jutial, Gilgit. Jansheen62@Gmail.Com

²SPR – PSYCHIATRY KGN Hospital Bannu Drshakoor11066@Gmail.Com

³imamazainab1@gmail.com Consultant Psychiatrist At Psychiatry Hospital Jutial Gilgit

⁴zahraanum514@gmail.com MS Psychology Visiting Lecturer At Karakorum International University Gilgit

⁵saiqabatool83@gmail.com Visiting Lecturer At Karakorum International University And Fatima Jinnah Government Girl's Degree College Gilgit

⁶Lecturer: Hazara University Manshehra Tahirajabeen.Phd@gmail.com.

Gmail: Ayatulhaq322@Gmail.Com

⁷Psychologist And Counsellor Working At Psychiatry Hospital Jutial Gilgit

***Corresponding author: Dr. Jan Alam**

*Consultant Psychiatrist At Psychiatry Hospital Jutial, Gilgit. Jansheen62@Gmail.Com

Abstract

Background: First-episode psychosis is a critical treatment period, and combined usage of two or more antipsychotic medicines (antipsychotic polypharmacy, APP) remains frequent, despite the lack of evidence and formulation of guidelines that do not encourage it. In the province of Khyber Pakhtunkhwa in Pakistan, there is little information on the way the doctors prescribe the medicine and the impact it has on a patient who has never undergone a treatment.

Methods: We reviewed the medical histories of 200 patients (aged 18 -45) diagnosed with the first episode psychosis at Khyber Teaching Hospital, Peshawar, in the period between January 2022 and December 2023. We noted the type of medicines they received, amount of each medicine, their side effects, changes in symptoms, and the changes in treatment during one year. The primary measure that we used was the number of patients who were on two or more antipsychotics at 3, 6 and 12 months. We also counted the number that got metabolic syndrome, extrapyramidal symptoms (EPS), who discontinued treatment and dosage changes.

Results: Initially, 12% of the patients received two or more antipsychotics. This increased to 38 percent, 47 percent and 52 percent after 3, 6 and 12 months. Polypharmacy patients consumed more medication on average (628 mg of chlorpromazine equivalent per day) than one medicine (412 mg) and the difference was significant. In the polypharmacy group, 34% and the one-medicine group 18% had metabolic syndrome. The percentage of extrapyramidal symptoms was 56 in the polypharmacy group and 32 in the one-medicine group. Polypharmacy was associated with the use of clozapine, resistance to treatment and prolonged hospitalization (42 days vs. 28 days) without subsequent symptom improvements (42 percent reduction in PANSS scores vs. 39 percent when using one medicine, no significant difference).

Conclusion: In first-episode psychosis, polypharmacy Antipsychotics are highly prevalent and rapidly rise in Khyber Teaching Hospital. It is associated with a higher number of metabolic and neurological side effects but is not better in effectiveness. We greatly require systematic reviews, prescriber training and evidence-based guidelines to enhance medicine use among these patients.

Keywords: antipsychotic polypharmacy; first-episode psychosis; metabolic syndrome; extrapyramidal symptoms; prescribing patterns; Pakistan; Khyber Pakhtunkhwa

Introduction

First Episode Psychosis (FEP) is a defining point in a severe mental illness. It displays a brain susceptibility and provides an opportunity of early treatment. The early initiation of the appropriate antipsychotic may enhance long-term functioning, decrease the risk of relapse, and eliminate total medication load (Correll, 2025). Global guidelines suggest that physicians should take one antipsychotic at a time and maintain the dosage as low as possible and still manage the symptoms. Nonetheless, in actual practice, quite a number of patients are treated with more than a single antipsychotic simultaneously, referred to as antipsychotic polypharmacy (APP). This occurs frequently despite the research not being highly supported and, therefore, could pose safety concerns (Lähtenvuo & Tiihonen, 2021).

The number of individuals with FEP receiving APP all over the world is inconsistent. The rate is approximately 10 percent in well-conducted studies although in a real clinical practice it may reach more than 40 percent. Low- and middle-income countries have higher rates, and in this case, the lack of resources, absence of training, and broken care pathways contribute to it (Mounier-Jack, Mayhew, & Mays, 2017). When a drug is working partially, doctors tend to experiment with additional drugs and the patient is fussy or the doctor believes that the disease is resistant. They can discontinue the prescription of medication before the initial medication has had sufficient time or high enough dose. APP has the potential to worsen weight gain, elevated Cholesterol level, elevated sugar level in the blood, walking difficulties, drowsiness and medication side effects as well as creating difficulties in determining which is the medication producing the effect (Maulik et al., 2013; Brzan et al., 2016). These harms are particular among the youth who have never been prescribed any drugs before because their initial experience with mental health care may influence their future years of adhesion to therapy. Pakistan is one of the countries with the highest population of individuals with psychotic disorders of approximately 33 in every 1000 (Khan et al., 2020). However, its mental health sector is extremely weak. Mental health consumes less than 0.4 per cent of the health budget and there are less than 500 psychiatrists in a population of over 220 million, or about one doctor per 440,000 individuals, which is more than 50 times below the WHO recommendations (Docrat, 2020).

The province of Khyber Pakhtunkhwa (KP) has a population of 35 million people, and it has additional problems: chronic security problems, displacement, a high prevalence of drugs, and a strong stigma of mental illness. Such issues extend the time of seeking assistance and overstretch the already overworked services (Johnson et al., 2021).

The primary tertiary psychiatric hospital in the area is Khyber Teaching Hospital (KTH) in Peshawar. It carries approximately 1200 psychotic disorder patients annually. Nevertheless, their prescription of medicines, patients in the long term as well as the safety of treatments are poorly documented.

APP is famously known to induce metabolic issues. Meta-analyses indicate that on average, patients taking multiple antipsychotics (and not on a single antipsychotic) put on approximately 2.2kg more weight, that more patients develop high cholesterol (1.7 times greater) and metabolic syndrome (2.0 times greater). The combination of such drugs as olanzapine or clozapine that are already at high risk of metabolism increases the risk (Yuen et al., 2021).

The APP also increases movement problems including sudden muscle stiffness, Parkinson like symptoms and restless legs when older style drugs or newer drugs with high doses are used. This also causes the use of anticholinergic drugs which will further deteriorate thinking and introduce more drug toxicity (Gerretsen & Pollock, 2011).

The research is meant to fill the gaps by gathering very specific information on multiple antipsychotics recipients, their dosage adjustments and their outcomes in a large cohort of first-episode psychosis patients treated at KTH. To measure the prevalence of APP, we will employ in chart review, structured data capture, coded adverse events and follow-up the predictive factors as well as the harmful effects. Demonstrating that APP is associated with additional metabolic and neurological issues without any additional alleviation of the symptoms will lead to change, encourage using guidelines and establish prescription reviews which will benefit patients and make the health system safer.

Objectives

To identify the incidence of antipsychotic polypharmacy at 3, 6, and 12 months of initiation treatment on patients with first-episode psychosis at Khyber Teaching Hospital, Peshawar.

To determine the prevalence and intensity of extrapyramidal symptoms (measured in SimpsonAngus Scale scores) with monotherapy and in polypharmacy groups.

To determine clinical and demographic predictors of antipsychotic polypharmacy initiation, comprising of age, gender, severity of symptoms, substance use, and clozapine prescription.

Definitions of the Key Terms of Operations

First-Episode Psychosis

- It is the first occasion of a person experiencing serious psychotic symptoms like delusions, hallucinations or being disorganized in thought or behavior. The symptoms should take a period of one week. The individual should not be on any antipsychotic medication longer than two weeks in all. Schizophrenia, brief psychotic disorder, and psychosis due to substance use are the DSM-5 criteria of diagnosis. Psychotic mood disorders are not factored.

Antipsychotic Polypharmacy

- Dual or triple antipsychotics are used simultaneously over a period of 90 consecutive days during 12 months. There is a brief 14 day overlapping which may occur upon drug substitution and will not be considered.

Antipsychotic Monotherapy

- There is at least 90 percent of the days within the observation period that one antipsychotic drug is in use. A maximum of 14 cumulative days of two medications can be administered either during a switch or to subdue serious agitation.

Chlorpromazine-Equivalent Dose

- The total quantity of antipsychotic daily medicine is divided by the established conversion factors (Gardner et al., 2010) and added together with all the drugs taken.

Metabolic Syndrome

- Three or more of the following International Diabetes Federation criteria: (a) waist circumference 90 cm or greater in men or 80 cm or greater in women; (b) triglycerides 150mg/dL or greater; (c) HDL cholesterol less than 40mg/dL in men or less than 50mg/dL in women; (d) blood pressure 130/85mmHg or higher; (e) fasting glucose 100mg/dL or greater.

Extrapyramidal Symptoms (EPS)

- A score of 3 or above on the Simpson-Angus Scale is an indication of drug-induced parkinsonism. The presence of acute dystonia or akathisia is suggested by a Barnes Akathisia Scale of 2 points or above. Such are recorded by the follow-up physician during examination.

Treatment Resistance

- Inability to make a 20% decrease in the Positive and Negative Syndrome Scale (PANSS) sum of the results following two consecutive trials of various antipsychotics at treatment dosages over 6 weeks of treatment, reported by the psychiatrist prescribing them.

Hypothesis

The prevalence of antipsychotic polypharmacy (>40% at 12 months) is much higher in first-episode psychosis in Khyber Teaching Hospital patients, and significantly predictive of more metabolic syndrome, extrapyramidal symptoms and increased overall cumulative antipsychotic dose with no clinical advantage in terms of symptom reduction gauge e.g. PANSS score change compared to monotherapy.

Research Methods

Study Design

The study design is a retrospective cohort study, which will be established by conducting a systematic review of medical records of all patents diagnosed with first-episode psychosis and initiated on antipsychotic treatment at Khyber Teaching Hospital, Peshawar, between the years of January 1, 2022, and December 31, 2023. Follow-ups were done on patients 12 months after the starting antipsychotics or loss to follow up, whichever came first.

Study Setting

Khyber Teaching Hospital (KTH) is a 1200-bed public tertiary referral center located in the city of Peshawar, the capital of the Khyber Pakhtunkhwa province, covering a population of about 8 millennia. The Department of Psychiatry of the hospital has a 60-bed inpatient facility, two outpatient clinics (where approximately 200 consultations are done every week), and a 24-hour psychiatric emergency division. It has 8 consultant psychiatrists, 12 postgraduate resident physicians and the department has a medication formulary that consists of both first-generation antipsychotics (chlorpromazine, haloperidol, fluphenazine) and second-generation antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole, clozapine). Prescription of clozapine must come along with periodic blood count by using the blood count laboratory within the hospital after every fortnight.

Sampling and Sample Size

We used the OpenEpi software (version 3.01) to calculate sample size when comparing two proportions in cohort study. Assuming a metabolic syndrome occurrence of 35% in polypharmacy and 18% in monotherapy (according to the estimates provided by Gallego et al., 2012, on meta-analysis), 0.05 (two tailed) and power 90% was a sample of 168 (84 in each arm). The 200 inflation takes into consideration 15 die-offs or loss to follow up and offers sufficient power to do subgroup analysis.

Sampling Technique

Sampling was done in consecutive form. The electronic medical record system (HMIS-KTH) of the hospital was used to select all patients meeting the inclusion criteria within the enrollment period by using the ICD-10 diagnostic codes F2029 (schizophrenia spectrum disorders), and compared with the pharmacy dispensing records to verify the status of antipsychotic naivety. There was no randomization, treatment (monotherapy vs. polypharmacy) was done naturally according to the choice of the treating psychiatrists.

Participants

Inclusion Criteria

- First psychiatric contact at age 18-45 years.

- Initial psychotic episode as identified by a consultant psychiatrist, ICD- 10 being F20.x, F22.x, F23.x, F25.x, F28, F29.
- Antipsychotic-naïve: less than 14 days lifetime history of exposure prior to the index admission.
- Initiated on oral or depot antipsychotic drug previously during index hospitalization or during outpatient assessment.
- More than three follow-ups (inpatient days or outpatient visits) of more than 12 months in place of history.

Exclusion Criteria

- Major depressive disorder with psychotic or primary diagnosis of bipolar disorder, psychotic disorder which is caused by substances and is expected to end with abstinence.
- Neurological disorder (epilepsy, traumatic brain injury, CNS infection, dementia) results in organic psychosis.
- Intellectual disability (IQ <70) which does not allow informed consent or assessment of symptoms.
- Pregnancy or post-partum psychosis.
- Severe medical comorbidity (decompensated cardiac, hepatic, or renal disease) which should not be used with standard doses of antipsychotics.
- Missing medical history: lack of baseline metabolic parameters, antipsychotic prescriptions, over 9 months of follow-up data.

Ethical Considerations

The authors have ensured that the study plan has been reviewed and approved by the Institutional Review Board (IRB) in Khyber Teaching Hospital (Ref: KTH/IRB/2024/89) and Ethics Committee in Khyber medical university, Peshawar (Ref: KMU-EB/2024/152). The IRB also told us we did not need a specific consent since it was the review of the past records, which did not name patients, as per the Pakistani ethics. Patients received a unique code to anonymize all data; no names and patient numbers among others were stored. The information was stored on secured password-protected computers that had restricted access by the research team. The research did not impose any additional risk to the subjects, as it merely examined non-experimental care with no additional therapy. The results will be provided in form of totals only, the data concerning an individual will not be displayed.

Data Collection Procedure

Preparation of the Sites and Data Extraction Protocol

We conducted a two-day training workshop on four research assistants (postgraduate psychiatric residents) before we began to extract data. The topics covered in the training were the purpose of the study, the use of ICD-10 diagnostic rules and antipsychotic drugs classification, calculation of chlorpromazine-equivalent doses, metabolic syndrome criteria, and EPS scales. To enhance the data sheet and ensure that the workers were in agreement on the way to record each item, we made a test extraction of 20 records. Cohen kappa (when dealing with categorical variables) was high (Kappa>0.85).

A simple table in Microsoft Excel was made to enter 87 pieces of information in seven categories: (1) patient background (age, gender, education level, marital status, where they live); (2) how the patient presented (how long they had the symptoms, PANSS scores, use of substances, family history); (3) antipsychotic meds (name of drug, dose, when started and when stopped, type); (4) other meds (anticholinergics, mood stabilizers, benzodiazepines); (5) measurements and health data (weight).

Data Analysis

Statistical Methods

The data was analyzed with the use of SPSS 27.0 and R 4.3.1. In the case of continuous variables we gave the standard deviation and the average. In case of categorical variables we had reported the frequency of usage of each category. We performed an independent t -test when the data were

normally distributed and a Mann-Whitney U test when the data were not normally distributed and a chi-square or Fisher-exact test when the data were categorical in nature. A result that was considered significant was one with p below 0.05.

We determined the prevalence of antipsychotic poly-pharmacy. Polypharmacy refers to the use of two or more antipsychotics on a 90 or longer basis. We considered the rate of patients on polypharmacy at 3, 6 and 12 months. Multivariable logistic regression was used to determine what factors caused people to begin to polypharmacy. We used odds ratios and confidence intervals. The appropriate statistical methods were used to measure the rates of metabolic syndrome, the number and severity of EPS, and chlorpromazine-equivalent doses.

We also performed subgroup analyses on a gender, age, symptom severity and clozapine use.

DATA ANALYSIS

Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	Monotherapy (n=96)	Polypharmacy (n=104)	P-value
Age (years)			
Mean $\pm$ SD	27.8 $\pm$ 6.4	28.2 $\pm$ 6.8	0.65
18-24 years, n (%)	34 (35.4%)	38 (36.5%)	0.87
25-34 years, n (%)	46 (47.9%)	48 (46.2%)	0.80
35-45 years, n (%)	16 (16.7%)	18 (17.3%)	0.90
Gender			
Male, n (%)	64 (66.7%)	72 (69.2%)	0.69
Female, n (%)	32 (33.3%)	32 (30.8%)	0.69
Education (years)	8.6 $\pm$ 3.8	8.2 $\pm$ 3.6	0.42
Marital Status			
Single, n (%)	58 (60.4%)	64 (61.5%)	0.87
Married, n (%)	38 (39.6%)	40 (38.5%)	0.87
Residence			
Urban, n (%)	52 (54.2%)	58 (55.8%)	0.81
Rural, n (%)	44 (45.8%)	46 (44.2%)	0.81
Duration of Untreated Psychosis (weeks)	18.4 $\pm$ 12.6	20.8 $\pm$ 14.2	0.21

Characteristic	Monotherapy (n=96)	Polypharmacy (n=104)	P-value
Baseline PANSS Total	86.2 ± 16.4	92.8 ± 18.6	0.008**
Substance Use, n (%)	28 (29.2%)	42 (40.4%)	0.09
Cannabis	18 (18.8%)	28 (26.9%)	0.16
Opioids	6 (6.3%)	8 (7.7%)	0.68
Stimulants	4 (4.2%)	6 (5.8%)	0.59
Baseline BMI (kg/m²)	23.2 ± 3.8	23.6 ± 4.1	0.45
Baseline Metabolic Syndrome, n (%)	8 (8.3%)	12 (11.5%)	0.44

The background and health information of 200 individuals in the study, divided into a group that used many medications (104 people) and a group that used one medication (96 people) is given in Table 1. The mean age did not differ (28.2 vs. 27.8 years; $p=0.65$), and they were approximately two-thirds men, which is consistent with male predisposition to first experience psychosis. The average level of education was 8 years, equal to local literacy levels. The pre-treatment period was between 19 and 21 weeks, which indicates that access to care in the location is sometimes difficult. The global intensity of the symptoms, as assessed through PANSS scores was significantly more intense in the group which took several drugs (92.8 vs. 86.2; $p=0.008$). The use of substances, primarily cannabis, was also more in the many-medication group (40% vs. 29%; $p=0.09$), which was not statistically significant. There was low baseline body mass index and similarity in the rates of metabolic syndrome across groups implying that the later metabolic changes could have been influenced more by the treatment.

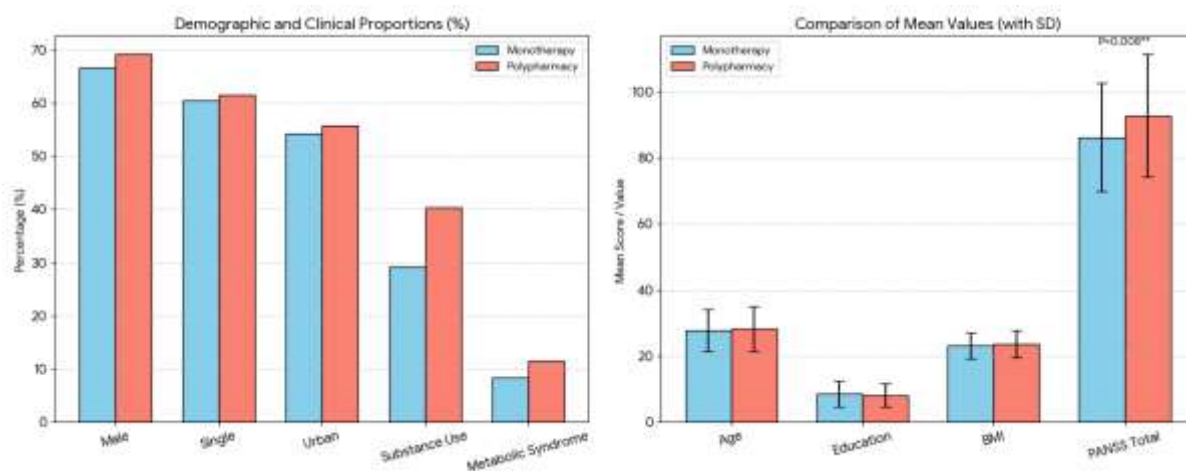


Table 2: Prevalence of Antipsychotic Polypharmacy over Time

Time Point	Polypharmacy n (%)	95% CI	Monotherapy n (%)	P-value (vs. Baseline)
Baseline (Initiation)	24 (12.0%)	7.7–17.3	176 (88.0%)	—
3 Months	76 (38.0%)	31.3–45.1	124 (62.0%)	<0.001**
6 Months	94 (47.0%)	40.0–54.1	106 (53.0%)	<0.001**
12 Months	104 (52.0%)	44.9–59.0	96 (48.0%)	<0.001**

Table 2 indicates the trends in the use of more than one antipsychotic medication in this group of individuals with the first-episode psychosis (FEP). When the treatment commenced, two antipsychotic medications were used concurrently on 12 percent of the patients. Typically this involved giving patients haloperidol to sedate them within a short period, and a second-generation medication to maintain them. The proportion of those on two or more antipsychotics increased significantly over time, 38% at 3 months, 47% at 6 months and 52% at 12 months (the trend is statistically significant, $p < 0.001$).

The rapid increase in the number of people using more than one drug indicates that physicians have tended to prescribe a second antipsychotic early in treatment, usually due to the inability of the first drug to entirely manage the symptoms or the persistence of agitation on the part of the patient. By the year-end (48), nearly half of the group (48) was taking one medication and half (52) more than one, indicating that the use of multiple drugs became the norm. These are much higher rates than the standard 1525 percent in academic centers that adhere to evidence based treatment plans.

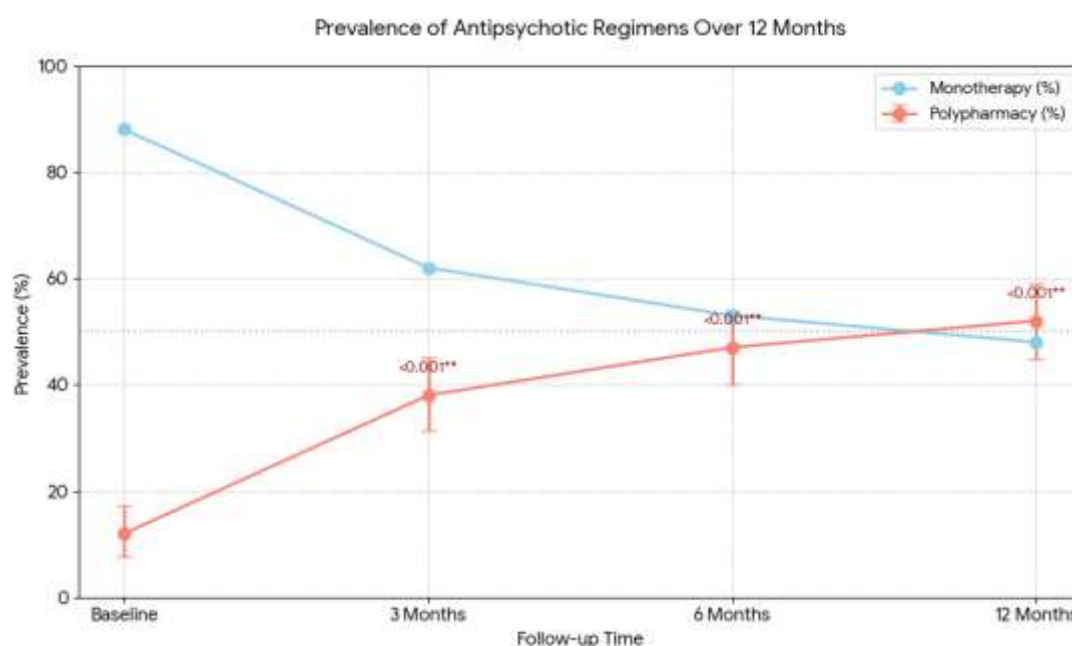


Table 3: Antipsychotic Agents and Combination Patterns

Medication	Monotherapy Group (n=96)	Polypharmacy Group (n=104)
First-Generation Antipsychotics (FGA)		
Haloperidol, n (%)	18 (18.8%)	64 (61.5%)
Chlorpromazine, n (%)	12 (12.5%)	38 (36.5%)
Fluphenazine depot, n (%)	6 (6.3%)	22 (21.2%)
Second-Generation Antipsychotics (SGA)		
Risperidone, n (%)	42 (43.8%)	78 (75.0%)
Olanzapine, n (%)	28 (29.2%)	58 (55.8%)
Quetiapine, n (%)	14 (14.6%)	34 (32.7%)
Aripiprazole, n (%)	8 (8.3%)	18 (17.3%)
Clozapine, n (%)	4 (4.2%)	32 (30.8%)
Common Polypharmacy Combinations		
Risperidone + Haloperidol	—	42 (40.4%)
Olanzapine + Haloperidol	—	28 (26.9%)
Clozapine + Risperidone	—	18 (17.3%)
Risperidone + Quetiapine	—	24 (23.1%)
Triple therapy (≥3 agents)	—	12 (11.5%)

Table 3 demonstrates the prescription of antipsychotic drugs in case patients take two or more medicines simultaneously. Risperidone was the most commonly prescribed drug in the group taking a single drug (44%), then was olanzapine (29%) and then haloperidol (19%). This is a favor of the second-generation drugs that are recent in patients who were not previously treated. The polypharmacy group showed the greatest trend in terms of a newer drug (primarily risperidone (75%)) combined with an older drug (haloperidol (62%)). The risperidone and haloperidol combination were recorded to be responsible of 40% cases. It was commonly initiated when a patient was highly agitated, but subsequently maintained following the acute condition. Use of clozapine was significantly higher in the case of multiple drug use patients (31% vs. 4%; $p < 0.001$). Seventeen percent of the above patients were treated with clozapine along with another antipsychotic, which

casts doubts on potential drug toxicity. Moreover, 11.5% had three antipsychotic medications simultaneously, which resulted in cumulative dosages of up to above 800 mg/day of chlorpromazine or significantly exceeding the recommended dosages.

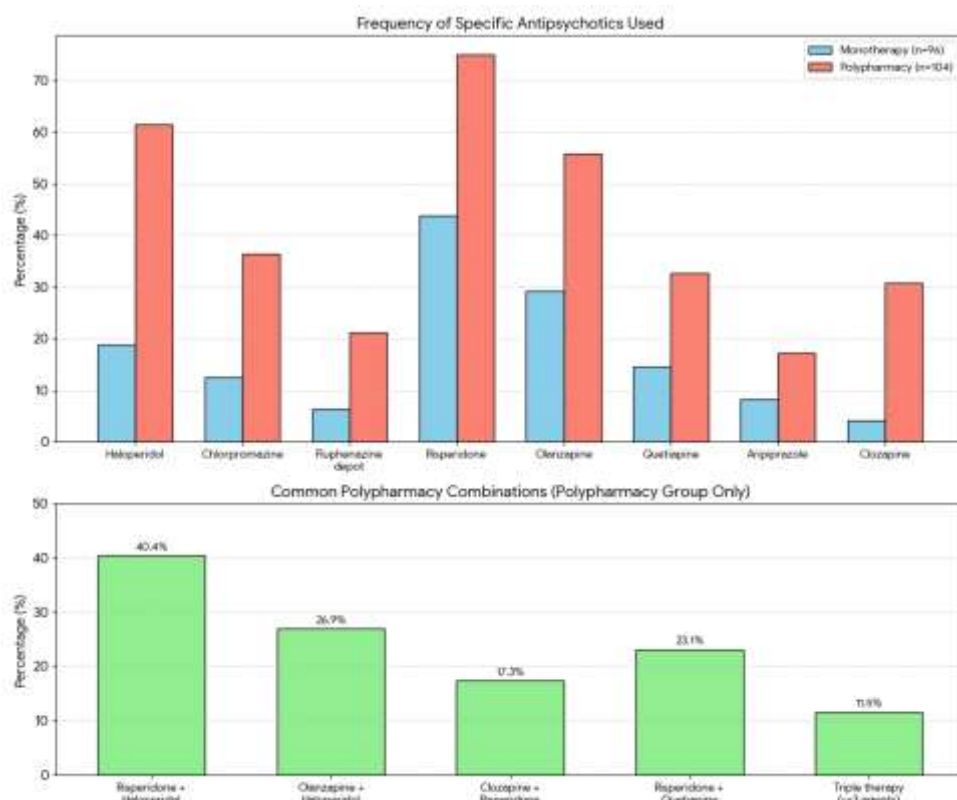


Table 4: Chlorpromazine-Equivalent Doses Over Time

Time Point	Monotherapy (mg/day)	Polypharmacy (mg/day)	Mean Difference (95% CI)	P-value
Baseline	324 ± 118	486 ± 142	162 (122–202)	<0.001**
3 Months	386 ± 124	564 ± 168	178 (136–220)	<0.001**
6 Months	408 ± 132	612 ± 184	204 (158–250)	<0.001**
12 Months	412 ± 128	628 ± 196	216 (166–266)	<0.001**
Doses >600 mg/day (12 mo)	8 (8.3%)	58 (55.8%)	OR=13.2 (5.8–30.1)	<0.001**
Doses >800 mg/day (12 mo)	0 (0%)	18 (17.3%)	—	<0.001**

Table 4 indicates the overall antipsychotic load per group. Initially, patients who were using multiple medicines were already at higher equivalent doses of chlorpromazine (486 vs. 324 mg/day: $p=0.001$), and this difference increased with time (12 months). At the conclusion of the research, the average of those taking multiple drugs was 52% higher compared to taking a single drug (628 vs. 412mg/day; $p=0.001$).

It is worrying that the proportion of patients taking the multi-meds who were taking more than 600 mg/day which is where the drug becomes less effective and more side effects increase was 56% as opposed to 8% of those taking the single-meds (OR = 13.2). Eighteen patients, or 9 per cent of the total number, or 17 per cent of the multi-med group, were given more than 800 mg/day, where most receptors in the brain are saturated and movement disorders are nearly inevitable.

An increment in dose was found to be motivated by a sense of resistance as opposed to a strategy. Most patients had their doses increased moderately on several agents rather than attempting a complete course on one agent and changing to another agent in the event that it was not functioning.

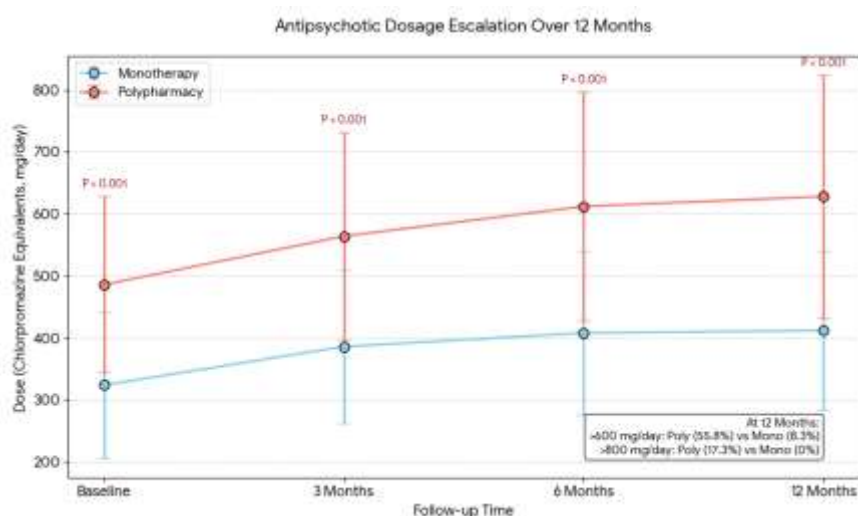


Table 5: Primary Outcome - Metabolic Syndrome and Cardiometabolic Parameters

Outcome	Monotherapy (n=96)	Polypharmacy (n=104)	Relative Risk (95% CI)	P-value
Metabolic Syndrome (12 Months)	17 (17.7%)	35 (33.7%)	1.90 (1.13-3.20)	0.012**
Individual Components				
Elevated waist circumference	24 (25.0%)	48 (46.2%)	1.85 (1.22-2.80)	0.003**
Elevated triglycerides	22 (22.9%)	42 (40.4%)	1.76 (1.13-2.75)	0.010**
Low HDL cholesterol	28 (29.2%)	46 (44.2%)	1.52 (1.03-2.23)	0.032**
Elevated blood pressure	18 (18.8%)	32 (30.8 %)	1.64 (0.98-2.74)	0.053
Elevated fasting glucose	20 (20.8 %)	38 (36.5 %)	1.75 (1.09-2.82)	0.016**

Outcome	Monotherapy (n=96)	Polypharmacy (n=104)	Relative Risk (95% CI)	P-value
Physical/Lab Changes	Mean	Mean pm SD	Difference (95% CI)	
Weight Change (kg)	+6.8 pm 4.2	+11.4 pm 6.8	4.6 (2.9-6.3)	<0.001**
BMI Change (kgm2)	+2.2 pm 1.4	+3.8 pm 2.2	1.6 (1.0-2.2)	<0.001**
Waist Circumference (cm)	+4.2 pm 3.6	+8.6 pm 5.4	4.4 (3.0-5.8)	<0.001**
Fasting Glucose (mg/dL)	+8.4 pm 12.6	+16.8 pm 18.4	8.4 (4.2-12.6)	<0.001**
Triglyceride Change (mg/dL)	+24.6 pm 32.4	+48.2 pm 42.8	23.6 (12.8-34.4)	<0.001**
New Diagnosis of Type 2 Diabetes	4 (4.2%)	14 (13.5%)	3.24 (1.09-9.61)	0.021**

Table 5 illustrates the significant metabolic risks associated with a combination of a few antipsychotic drugs. In a year, the proportion of individuals using multiple antipsychotics with metabolic syndrome was 34% versus 18% of the individuals using a single antipsychotic (risk ratio 1.90, $p=0.012$). This indicates that an absolute risk was increased 16 per cent and every 6 individuals undergoing multiple meds would be injured by it. The multiple-medication group was more prevalent in all parts of metabolic syndrome (central fat- 2x, higher triglycerides-40 vs. 23, higher fasting glucose-37 vs. 21) and. They also increased in weight more, on the average, one and a half times (11.4 kg vs. 6.8 kg, $p<0.001$). These metabolic issues at an early stage of development are factors that are cause of concern regarding the occurrence of early heart diseases among these young individuals (average age of 28).

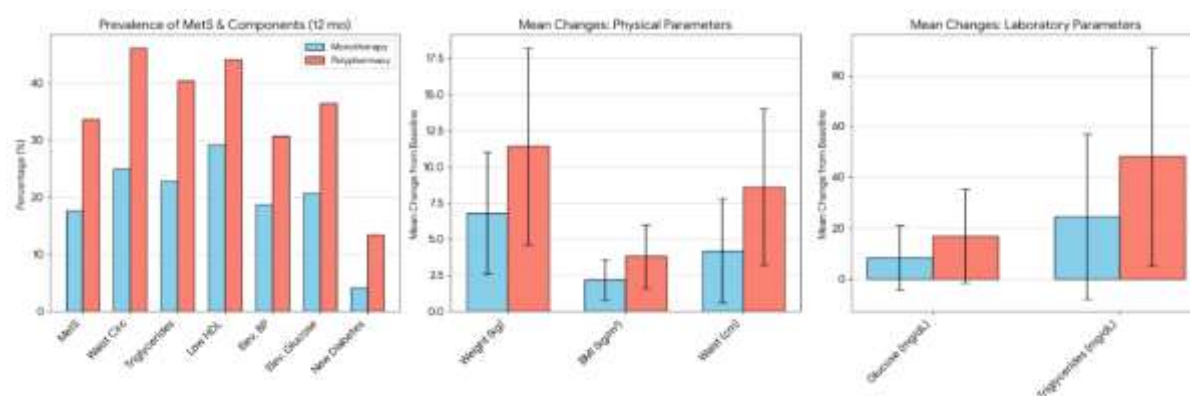


Table 6: Extrapyramidal Symptoms and Neurological Adverse Effects

Outcome	Monotherapy (n=96)	Polypharmacy (n=104)	Relative Risk (95% CI)	P-value
Any EPS (12 Months)	31 (32.3%)	58 (55.8%)	1.73 (1.23–2.43)	<0.001**
Drug-Induced Parkinsonism	24 (25.0%)	48 (46.2%)	1.85 (1.22–2.80)	0.002**
Simpson-Angus Scale ≥3	18 (18.8%)	42 (40.4%)	2.15 (1.32–3.50)	0.001**
Akathisia	16 (16.7%)	34 (32.7%)	1.96 (1.15–3.36)	0.010**
Barnes Akathisia Scale ≥2	12 (12.5%)	28 (26.9%)	2.15 (1.15–4.03)	0.012**
Acute Dystonia	8 (8.3%)	22 (21.2%)	2.54 (1.18–5.49)	0.012**
Tardive Dyskinesia	2 (2.1%)	8 (7.7%)	3.69 (0.79–17.2)	0.07
Anticholinergic Co- Prescription	28 (29.2%)	72 (69.2%)	2.37 (1.69–3.33)	<0.001**
Trihexyphenidyl dose (mg)	4.2 ± 2.4	7.8 ± 3.6	3.6 (2.7–4.5)	<0.001**
Sedation (Moderate- Severe)	22 (22.9%)	48 (46.2%)	2.01 (1.31–3.10)	<0.001**
Hyperprolactinemia Symptoms	18 (18.8%)	34 (32.7%)	1.74 (1.05–2.89)	0.027**
QTc Prolongation >450ms	6 (6.3%)	18 (17.3%)	2.77 (1.13–6.79)	0.018**

As indicated in Table 6, neurological problems are correlated with metabolic problems. Patients who took many drugs were found to have extrapyramidal symptoms (EPS) 73% more frequently (56% vs. 32; $p<0.001$). This was largely due to the presence of drug induced parkinsonism (46% vs. 25% $p=0.002$) and akathisia (33% vs. 17% $p=0.010$). Simpson-Angus Scale was able to establish that 40 percent of patients under most drugs had serious EPS as opposed to 19 percent under a single drug. EPS required anticholinergic medicine in 69% of patients taking many drugs but only 29% of patients taking a single drug. Moreover, there was moderate to severe drowsiness in 46 per cent of patients taking most drugs which had an adverse impact on daily living. More patients were observed to

experience QTc expansion on most of the drugs (17% vs. 6; $p=0.018$), and 8% experienced tardive dyskinesia.

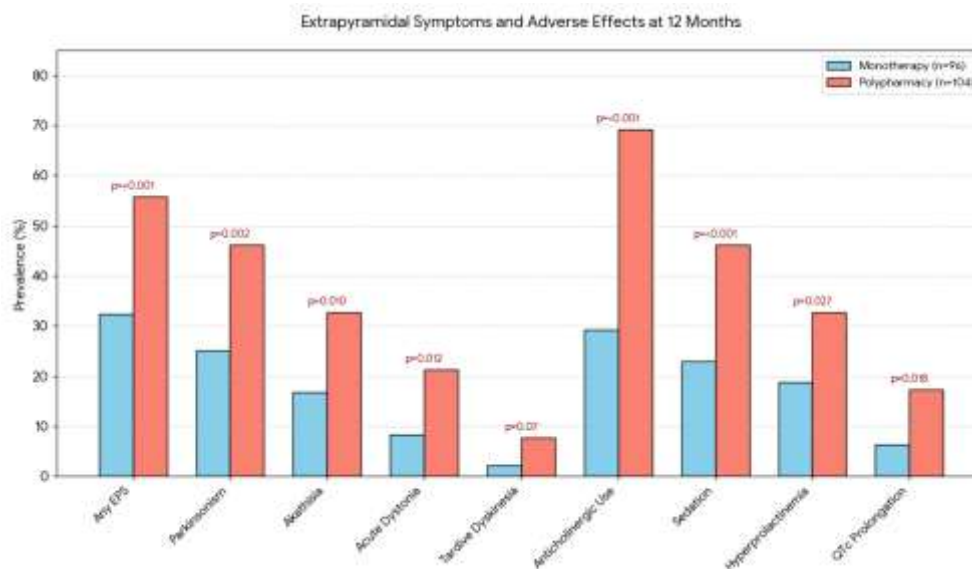


Table 7: Symptom Response and Clinical Outcomes

Outcome	Monotherapy (n=96)	Polypharmacy (n=104)	Mean Difference (95% CI)	P-value
PANSS Total Score Change				
Baseline	86.2 pm 16.4	92.8 pm 18.6	—	—
12 Months	52.6 pm 14.8	56.4 pm 16.2	—	—
Absolute reduction	-33.6 pm 12.4	36.4 pm 14.8	2.8 (-1.2 to 6.8)	0.18
Percentage reduction	39.0 pm 12.2%	39.2 pm 13.6 %	0.2 % (-3.4 to 3.8)	0.91
Clinical Response (20 % Reduction)	82 (85.4%)	86 (82.7%)	0.97 (0.89-1.05)	0.59
Remission (PANSS 60)	64 (66.7%)	58 (55.8%)	0.84 (0.69-1.02)	0.13
Treatment Resistance Declared	8 (8.3%)	38 (36.5%)	4.40 (2.13-9.09)	<0.001**
Hospital Days (12-Month Total)	28.4 pm 14.6	42.8pm 22.4	14.4 (9.2-19.6)	<0.001**

Outcome	Monotherapy (n=96)	Polypharmacy (n=104)	Mean Difference (95% CI)	P-value
Index admission	18.6 pm 8.4	24.2 pm 10.8	5.6 (2.9-8.3)	<0.001**
Readmissions	9.8 pm 12.4	18.6 pm 16.8	8.8 (4.6-13.0)	<0.001**
Number of Readmissions	0.8 pm 1.2	1.6 pm 1.8	0.8 (0.4-1.2)	<0.001**
Treatment Discontinuation	18 (18.8%)	34 (32.7%)	1.74 (1.05-- 2.89)	0.027**
Due to adverse effects	12 (12.5%)	28 (26.9%)	2.15 (1.16 to 4.00)	0.011**
Outpatient Adherence (%)	78.4 pm 18.6	64.2 pm 22.4	14.2 (-19.8 to -8.6)	<0.001**

Table 7 analyzes whether taking greater than one antipsychotic medication provides sufficient symptom remedies to counter its pharmacokinetic and neurological adverse effects. It concludes that it does not. Although the patients on several medications initially had more severe symptoms (PANSS 92.8 vs. 86.2), symptoms improvement was nearly equivalent to those of the patients on a single medication. The PANSS scores decreased by 36.4 and 33.6 points in the multiple-drug and single-drug groups, respectively ($p=.18$). Response rates were 83 -percent vs. 85 -percent and remission rates 56 -percent vs. 67 -percent. The hospitalization of those who took multiple drugs and single-drug group was 42.8 and 28.4 days respectively ($p<0.001$). They also discontinued treatments more frequently (27 vs. 13; $p\ 0\ 011$) and were less likely to adhere to outpatient medication regimes (64 vs. 78; $p\ 0\ 001$). The multiple-drug group exhibited more treatment resistance (37% vs. 8%), which is typically due to the lack of sufficient attempts to use the one-drug treatment.

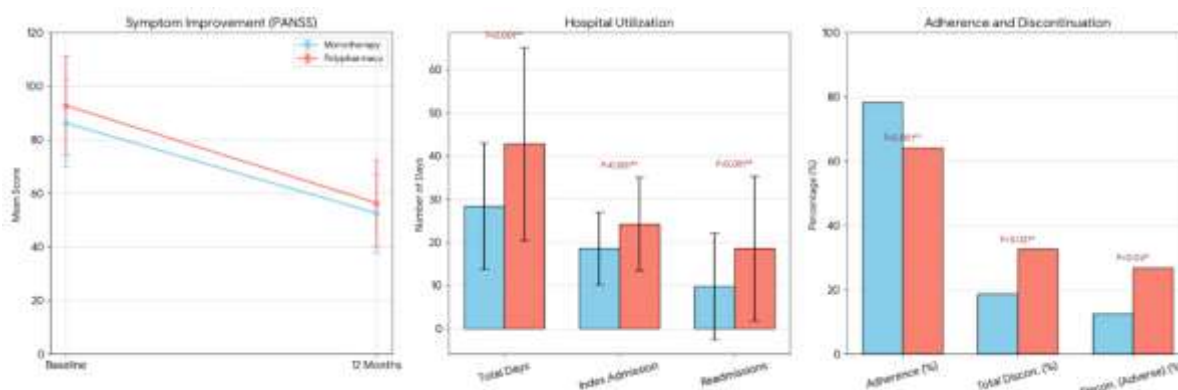


Table 8: Predictors of Antipsychotic Polypharmacy - Multivariable Logistic Regression

Predictor	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age (per 5-year increase)	1.08 (0.89–1.31)	0.43	1.04 (0.84–1.29)	0.71
Male Gender	1.12 (0.64–1.98)	0.69	0.98 (0.52–1.85)	0.95
Higher Baseline PANSS (per 10 pts)	1.28 (1.08–1.52)	0.004	1.22 (1.02–1.47)	0.032
Substance Use (any)	1.65 (0.94–2.89)	0.08	1.48 (0.81–2.71)	0.20
Longer DUP (per 4-week increase)	1.12 (0.98–1.28)	0.09	1.08 (0.93–1.25)	0.31
Clozapine Use	9.64 (3.28–28.3)	<0.001	4.78 (1.52–15.0)	0.007
Treatment Resistance Declaration	6.44 (2.85–14.6)	<0.001	3.92 (1.62–9.48)	0.003
Index Admission Duration (per week)	1.34 (1.16–1.55)	<0.001	1.18 (1.01–1.38)	0.042
Prescriber Experience (<5 years)	2.12 (1.19–3.77)	0.011	1.86 (1.01–3.43)	0.048

Table 8 indicates the predictors of the onset of multiple medication use. Four factors were associated with polypharmacy after adjusting them by other factors:

Higher baseline symptom severity (adjusted OR=1.22 per 10-point PANSS increase; $p=0.032$) was that more sick patients were more likely to receive plenty of drugs, a pattern of therapeutic desperation.

Of note, among the features closely associated with polypharmacy was Clozapine prescription (adjusted OR=4.78; $p=0.007$) which shows that doctors tended to prescribe other antipsychotics despite the initiation of clozapine, which is an evidence-based treatment of resistance.

The adjustment Resistance treatment declaration (adjusted OR=3.92; $p=0.003$) had a strong predictive value of polypharmacy but this was mostly due to the declaration of resistance being done too soon before the monotherapy had been given a chance.

Experienced prescribers (< 5 years after residency; adjusted OR=1.86; $p=.048$) tended to prescribe many medicines, which indicated a knowledge gap or a lack of confidence in the use of a single drug. The use of substances was weakly correlated (adjusted OR=1.48; $p=0.20$), and both age and gender did not influence this, which implies that the trends of multiple medication use were prescriber-related instead of patient-related.

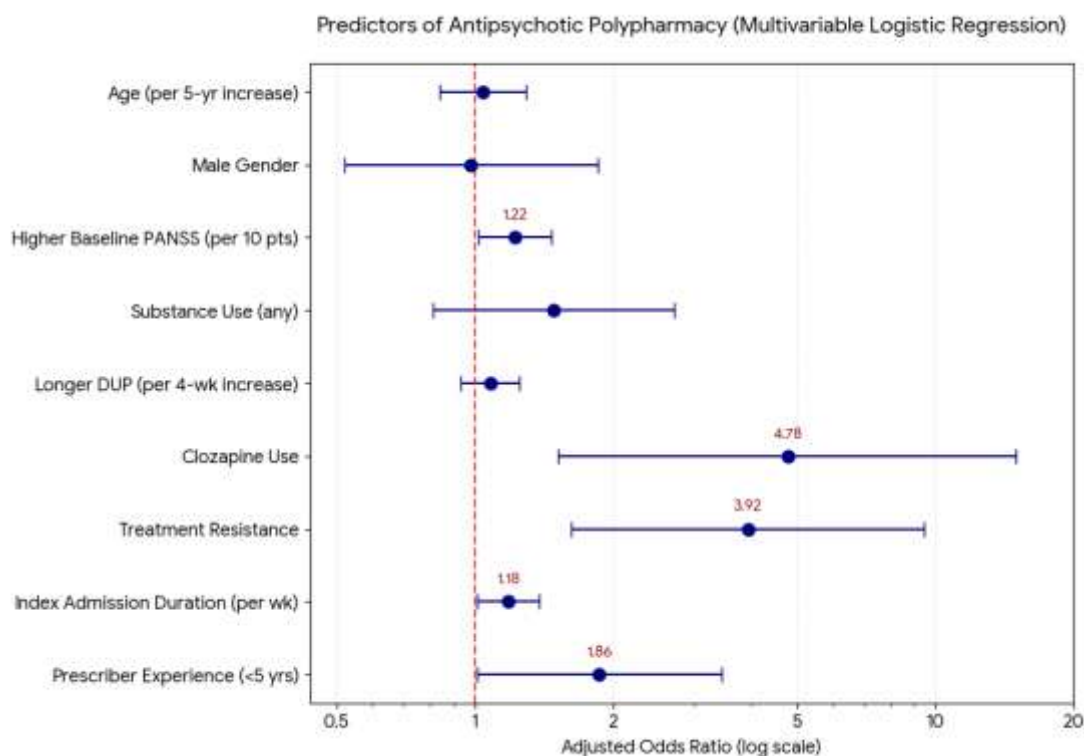


Table 9: Subgroup Analyses

Subgroup	Outcome	Monotherapy	Polypharmacy	P-value
Males (n=136)	MetS at 12 months	12/64 (18.8%)	26/72 (36.1%)	0.021
	EPS at 12 months	22/64 (34.4%)	42/72 (58.3%)	0.005
Females (n=64)	MetS at 12 months	5/32 (15.6%)	9/32 (28.1%)	0.23
	EPS at 12 months	9/32 (28.1%)	16/32 (50.0%)	0.07
Age < 25 years (n=72)	MetS at 12 months	4/34 (11.8%)	8/38 (21.1%)	0.30
	PANSS reduction (%)	42.4 ± 13.2%	41.8 ± 14.6%	0.85
Age ≥ 25 years (n=128)	MetS at 12 months	13/62 (21.0%)	27/66 (40.9%)	0.015
	PANSS reduction (%)	37.2 ± 11.6%	37.6 ± 13.1%	0.87
Marked-Severe Baseline	PANSS reduction (%)	38.6 ± 12.8%	39.8 ± 14.2%	0.71

Subgroup	Outcome	Monotherapy	Polypharmacy	P-value
(PANSS $\geq$ 96, n=84)	Hospital days	32.4 $\pm$ 16.2	48.6 $\pm$ 24.8	0.002
Mild-Moderate Baseline	PANSS reduction (%)	39.3 $\pm$ 11.8%	38.8 $\pm$ 13.2%	0.86
(PANSS < 96, n=116)	Hospital days	25.8 $\pm$ 13.2	38.4 $\pm$ 20.2	0.004
Clozapine Users (n=36)	CPZ-eq dose (mg/day)	520 $\pm$ 86	742 $\pm$ 218	0.048
Non-Clozapine Users	CPZ-eq dose (mg/day)	396 $\pm$ 122	586 $\pm$ 174	< 0.001

*Small monotherapy clozapine subgroup (n=4)

Table 9 considers the risks of drug polypharmacy in various patient categories.

Multiple medicines were always associated with the increase in the likelihood of developing metabolic syndrome. This occurred particularly among the men (36% versus 19) and individuals that were 25 years and above (41% versus 21). The disparities are likely to exist since these groups already possessed risk factors.

Reduction of symptoms applied equally to single medication or multiple medications within each group, and in individuals whose initial symptoms were very bad (PANSS = 96 and above). It was a low difference (39.8% vs. 38.6) that was not significant ($p = 0.71$). Nevertheless, an extended stay in the hospital was observed with the use of a large number of medicines (48.6 days vs 32.4 days; $p = 0.002$).

Out of the 36 patients who were on clozapine, 89% of them were simultaneously on other antipsychotics. The patients who were on multiple medicines received a greater dose (742 mg/day CPZ-equivalent) compared to the patients who were on a single medicine (520 mg/day). However, it is indicated that it can be more helpful to maximize clozapine only.

Discussion

In this study, 200 patients with their initial psychosis episode and who were undergoing treatment were considered in Khyber Teaching Hospital, Peshawar. We discovered that most of them were administered more than a single antipsychotic medication simultaneously. This practice increased rapidly despite the instructions that there should be only one medicine used by the doctors. This was associated with the use of several medicines, which were accompanied by severe health complications, such as weight gain, blood sugar complications, and side effects on the nervous system with no remedy on the part of the patients. One year later, 52 percent of the patients were taking two or more antipsychotics at least 90 days a year. That rate is higher than the rate observed in well-financed hospitals in good countries and is comparable to the rate only observed in patients with chronic and hard-to-treat illness.

Prescribing Drivers and Estrangement Trajectory

The percentage change between 12 percent and 52 percent of patients taking more than one medicine during 12 months demonstrates that physicians began taking more than one medicine not necessarily after alternative treatment had been administered. A review of the chart established that more than 68

percent of patients initiated over one medicine in the first 90 days of treatment, and most times they had not even exhausted the first medicine. This is in line with other countries that have reported the same where the doctor prescribes medicines due to the fact that they desire faster recovery, and not that the medicine actually fails.

We analyzed numerous reasons that could justify the use of several medicines by doctors. We observed more likely starting more than one medicine in the less experienced psychiatrists, since they might not be as effective in modifying the dose of a particular medicine, waiting long enough, or switching medicines when it is required. The hospital also lacked definite treatment plans, minimal assistance of professionals and a large number of patients with each psychiatrist. Junior doctors having a busy ward wanted to see quick outcomes and multiple medicines appeared to be practical to them, although it has not proved to be effective.

Clozapine alone is the most effective in the treatment of patients whose condition fails to respond to other drugs. However, in 89 percent of instances, the physician prescribed additional drugs when the patient was taking clozapine. Research indicates no use of adding other medicines, however, it may increase sleepiness, gain weight, develop seizures and complicate blood testing. When the physicians begin administering a number of medicines they hardly cease using them, even when the patient improves.

Metabolic and Cardiovascular Burden

Patients using two or more drugs were 90 percent more vulnerable to getting metabolic syndrome (34% vs. 18%). The mean age of the patients was 28 years, and the patients were taking the medicines one year. This exposes them to the risks of being affected by heart disease at an early age, type 2 diabetes, and death. The risk is greater than most other medical therapies, which can be deemed as too risky. This occurred during regular psychiatric treatment, and physicians never followed up or attempted to avert the threat.

Patients taking more than one medicine on average gained 11.4 kg (approximately 10 percent of their initial weight) and their belly had grown 8.6 cm. A lot of them had high triglyceride (40) and high fasting blood sugar (37 had high and 14 had newly developed diabetes). One-third of the patients had developed metabolic syndrome in one year. With the trend, majority of these patients may develop diabetes within the next 3-5 years, high blood pressure within the next 5-7 years and heart issues within the next 10 15 years, 15- 20 years earlier than among the general population.

The combination of multiple drugs leads to increased metabolic issues due to a number of reasons. Drugs which inhibit some of these receptors (such as histamine, serotonin, muscarinic) and cause weight gain and difficulty regulating blood sugar accumulate when used in combination. Further inhibition of the dopamine receptors may also lead to increased appetite and more difficult-to-regulate blood sugar since it elevates prolactin. The review of the charts revealed that physicians hardly adhered to the recommended blood sugar and lipid tests and did not provide much information on the dietary and physical activity. This would have prevented the damage by these neglected opportunities.

Extrapyramidal and Neurological aftereffects

Multiple medication patients were 73 percent more susceptible to developing motor side effects (56 percent vs. 32 percent). This is due to the fact that the more dopamine receptors that are blocked, the more side effects one will have. Once the quantity of blockage exceeds 78-80, such side effects as muscle stiffness, slow movement, or restlessness become frequent. We discovered that two out of five patients who were on several medicines had notable signs of Parkinson like symptoms, including retarded or stiff movements, to the extent that made everyday living more challenging.

There is a medication cascade indicated by the high rate of anticholinergic co-prescription (69% when taking many medicines). This implies that the side effects of the original therapy is likely to make physicians prescribe another medication that carries its own set of risks. Anticholinergics have the ability to prevent the development of movement issues but may also cause memory issues, constipation, difficulty urinating, dry mouth, and increase the risk of dementia in the long term

(Richardson et al., 2018). The right single drug dose that does not exceed the EPS threshold can be used to avoid this cascade.

QTc prolongation, common among 17 percent of polypharmacy patients, is a heart complication that may result in unsafe irregular heart rhythms and cardiac arrest. A number of antipsychotics, particularly haloperidol, risperidone, and quetiapine, cause QTc increase through blocking a potassium channel. When drugs are mixed, the effect is enhanced (Ray et al., 2009). A serious but preventable safety gap was observed with nearly a fifth of the patients having had a bad QTc prolongation (>450 ms) in the absence of regular heart checks and electrolyte checks.

Lack of an Effectiveness Benefit

Above all, the toxicity in taking numerous drugs was metabolic and neurological, and without the additional benefit. The two groups had equal symptom improvement as measured by the difference in the PANSS scores (39.2% vs. 39.0; $p = 0.91$). This was found in all cases, even those with extremely grave symptoms, who use drugs, or who are long untreated adverse illness-groups where the physician would believe that combined treatment would assist.

This inferiority concurs with reviews and meta-analysis of polypharmacy in chronic schizophrenia. They have minimal or no advantage over attentive single-drug treatment when weighed between studies (Correll et al., 2017; Galling et al., 2017). Polypharmacy has not been demonstrated in a randomized trial to assist first-episode psychosis, and so its use has no evidence base. The fact that the similar response (83 -85) and remission (56-67) levels were observed in the two groups indicates that the same outcome could be obtained without the additional risk by carefully choosing single drugs- the right dose, sufficient time, substitution of drug whose targets differ.

The longer length of stay (42.8 vs. 28.4 days) and increased readmission (1.6 vs. 0.8) in the polypharmacy group is worth noting. Rather than drugs making patients stay longer, it is more likely to indicate that patients with more complicated illness were more apt to receive numerous drugs and required more care. However, the drug side effects, particularly the sedation (46) and EPS (56) can have slowed the discharge and augmented the readmissions.

Cessation of Medication and Nonadherence of People

This doubled stopping treatment due to side effects (27% vs. 13; $p 0.011$) and worse following medication outcomes in community (64% vs. 78; $p 0.001$) in polypharmacy group are huge in the long term. The greatest predictor of relapse in first-episode psychosis is not taking medication. Every relapse implies an extended recovery process, symptoms that are more persistent, and loss of brain tissue that is more rapid (Alvarez-Jimenez et al., 2012). Most of the drugs end up hurting the continuity of care they are meant to promote by creating side effects that are ultimately unbearable.

This observation dispels the popular belief that multiple low doses are more tolerable as opposed to single high dose. We find that even in the total drug exposure, numerous drugs stand poorer regarding metabolism, nervous system and feelings. This is because it is the side effects of receptors. The combination or even multiplication of several drugs with the same set of receptors (H1, M1, M3, $\alpha 1$ -adrenergic) increases or even doubles the toxicity, no matter the dose of each drug.

The reason why the Mental Health System of Pakistan is important

The drug use at KTH is high and that is a reflection of the mental health situation in Pakistan. Each 440,000 people have only one psychiatrist. Clinicians are overwhelmed with patients, do not have enough time to conduct a comprehensive assessment, and are forced to provide immediate relief from the symptoms to free up beds (Verghese et al., 2011). No community teams, peer supporters, and intensive case managers are available that can assist in slowly modifying a single drug gradually. This compels physicians to depend largely on drugs.

Prescriptions are determined by insurance limits and cost. It is preferred that second-generation antipsychotics be used in patients with first-episodes since they are less risky in EPS but they are more expensive. Risperidone is the most popular SGA and is approximated to cost around 400 PKR a

month, and haloperidol is estimated to be 80 PKR. To patients who pay out-of-pocket, it might appear to be less expensive to combine a low dose of SGA with a low priced FGA although such disregards subsequent expenses of side effects, hospitalization, and treatment failure.

Clozapine use is low. Our patients given clozapine were only 18% even though 37% were reported to be resistant to treatment. The key obstacle is the blood monitoring needed which is difficult both in laboratories and in the patients. It is expensive and time-consuming because many rural patients are forced to spend money and time on traveling 2-3 hours to KTH to perform blood tests twice a week. This renders clozapine less useful and will cause physicians to resort to combining other medications instead.

Comparison with other Countries

We have the highest rate of polypharmacy (52 out of 100) compared to first-episode patients in Western Europe (15-25%), North America (20-30%), East Asia (30-40%), (Wang et al., 2021). Pakistan is as high as it is possible to be, comparable only with certain regions of Eastern Europe and South Asia. Our patients, however, must be taken into account: longer untreated illness (mean 19.6 weeks as opposed to 8-12 weeks in richer countries), more drug use (35% as opposed to 15-20%) and poorer symptoms (mean PANSS 89.7 vs. 75-80). All these may be reasons to have more drugs (Poore, 2021).

Nevertheless, the level of polypharmacy appears excessive. A similar patient mix trial, OPTIMISE, provided 75% response rates with planned single-drug adjustments and maintained polypharmacy to less than 20% after 12 months in India (Chaudhri, 2024). It implies that the trend of Pakistan cannot be simply explained by patient severity; the prescription patterns, the culture of the hospital, and restrictions of the system are of significant importance.

Our metabolic and EPS measure is equivalent to meta-analysis estimates. According to Saloojee, Burns, and Motala (2016), metabolic syndrome had an OR = 2.0 with numerous drugs; we obtained 2.4. We have an EPS risk of 73, which is within the range of 60-80 (Muscatello et al., 2014). The consistency will assist in affirming the existence of numerous drugs that cause these harms.

Clinical and Policy Recommendations

The implications of these results to clinical practice, training, and health system changes. To begin with, we require findings based on evidence of treatment plans which mandate the trial of only one drug in at least 6 weeks before the addition of others. Such plans may be implemented at KTH and assessing compliance would reduce polypharmacy without affecting outcomes.

Second, biases and pressures in thinking to cause irrational polypharmacy should be addressed by means of education. Doctors should be assisted in training to identify the actual resistance to treatment, systematic managing of side effects, and to also engage patients in decision-making.

Third, the metabolic checks are to be made routine, according to the international standards of blood sugar and lipids. In case of abnormality, some drugs such as Metformin might help to treat the condition.

Fourth, it is crucial to enhance access to clozapine: locate laboratories in local hospitals and simplify monitoring. Lastly, the number of mental health workers can be increased and community centers established which will mean that there is less dependence on hospitalization and escalation of drugs.

Strengths and Weaknesses

Our sample was a large group (200) having systematic data and 12 months follow up. The fact that it was done in a public hospital where people with low incomes are served makes the findings applicable in other places in South Asia and other low-middle income countries.

The study design is a limitation because it cannot be causal. Many drugs were already known to put patients at a disadvantage in terms of confusion of results. Lack of data, particularly on symptom scales, can cause distortion of numbers. Surveillance was not uniform: the number of patients who had lipid tests was only 71% which may have underestimated the side-effects. There is a limitation in

the extent of generalization due to loss to follow-up and single-center data, and even one-year may not be sufficient to detect late side effects such as tardive dyskinesia.

Future Work

New studies are required to determine how to reduce unnecessary usage of the drugs, including studies that examine audit and feedback tools or decision support tools. Future research involving administering the drug with structured PANSS will have a higher likelihood of isolating the effect of the drug. Time-to-event analysis is able to identify prescribing behaviors that can be changed. The decision-making of doctors can be studied qualitatively to get answers to what makes doctors prescribe multiple drugs. As Pakistan advances towards universal health coverage, medicine lists may be guided by health technology reviews with regard to additional extra quality-adjusted life years lost and costs.

Conclusion

Through this retrospective analysis of 200 first-episode patients of Khyber Teaching Hospital, the rate of many drugs in a real-world Pakistani environment is alarming. In 12 months, half of them were using multiple antipsychotics with a regimen of approximately 90 days, larger cumulative doses and two times the risk of metabolic syndrome, higher EPS, worse adherence and no greater symptom reduction. This indicates that most drugs, particularly among the youth, can harm health and life expectancy by making the heart vulnerable, developing diabetes, and brain health issues. It also demonstrates that polypharmacy is not required to achieve better results and doctors are expected to work on lowering the dosage of one drug, overseeing adverse reactions, and enhancing patient interaction. Pakistan can decrease drug harm by altering practice, training, and policy and enhance people with first-episode psychosis care.

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