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ახალგაზრდა მკვლევარები

Vol. 3 Issue 3, 2025

https://doi.org/10.52340/jr.2025.03.03.17

Prevalence and Correlates of Drug-induced Extrapyramidal Symptoms in patients with Schizophrenia

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Abstract

Background: Extrapyramidal symptoms (EPS) are prevalent side effects of antipsychotic medications in patients with schizophrenia. Identifying the demographic and clinical factors associated with EPS is essential for optimizing treatment strategies, and patient outcomes. **Methods:** A retrospective chart review was conducted among patients with schizophrenia receiving antipsychotic medications, focusing on EPS distributed into Parkinsonism, Acute Dystonia, Akathisia, and Tardive Dyskinesia. A total of 115 records were included in the analysis. Baseline disparities were evaluated using appropriate statistical tests. Factor Analysis, ANOVA, and partial correlation network analysis were employed to find out key contributors to EPS in schizophrenia patients. A multinomial logistic regression analysis was employed to examine the association of age, gender, and built type.

Results: The prevalence of extrapyramidal symptoms (EPS) was 38.3 percent, with Parkinsonism being most common (30.8%), followed by Tardive Dyskinesia (4.3%), Acute Dystonia (2.6%), and Akathisia (1.7%). EPS were more frequent in females, especially Parkinsonism and Tardive Dyskinesia. First-generation antipsychotics showed a higher EPS prevalence (66 %) compared to second-generation antipsychotics (34%). Significant differences in treatment duration and chlorpromazine equivalent dose were observed between EPS and non-EPS groups ($p < 0.05$). ANOVA showed a significant effect of symptom type on age ($p = 0.014$). Factor analysis (KMO 0.565, Bartlett $p < 0.001$) identified prescription pattern and body type as major contributors. Partial correlation analysis showed positive associations between body mass index, chlorpromazine dose, and treatment duration. Logistic

regression revealed significant associations of Tardive Dyskinesia with age, Akathisia with athletic and pyknic body types ($p < 0.001$), and Dystonia with male gender and both body types ($p < 0.001$).

Conclusion: Female gender, asthenic body type, longer treatment duration, and higher chlorpromazine equivalent daily dose were significant predictors of EPS. Lower BMI was associated with Parkinsonism, suggesting a role of metabolic factors. EPS also correlated with increased healthcare utilization.

Keywords: Extrapyramidal Symptoms (EPS), Movement Disorders, Schizophrenia.

Background

Antipsychotic medications are crucial in managing acute and chronic psychiatric disorders, including schizophrenia, bipolar mood disorders, and related conditions [1]. Antipsychotic medications, both typical and atypical, are commonly used to treat schizophrenia by binding to dopamine receptors in the central nervous system and blocking dopamine. This leads to a decrease in dopamine levels in the basal ganglia, which can contribute to the development of EPS [2]. Extrapyramidal symptoms (EPS) are movement disorders caused by dopamine-receptor-blocking medications, pose difficulties for psychiatrist in managing patients effectively [3].

Risk factors for EPS are multifaceted, including demographics such as gender, age, antipsychotic type, D2 receptor antagonism effect, duration of drug treatment, illness, substance addiction, and genetic diversity [4]. Treatment of EPS generally involves lowering the dose of the antipsychotic medication or trying a different dose. In some cases, specific drugs may be used to target and alleviate the symptoms [5]. These medications are categorized into two classes: first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) [6]. Empirical evidence indicates a high prevalence of antipsychotic-induced movement disorders among patients on extended FGAs. SGAs, despite showing reduced susceptibility to inducing EPS compared to FGAs, still pose challenges, and patients experience movement disorders even with these newer pharmacological agents [7].

EPS not only carries a stigma but also causes subjective distress among patients, hindering adherence to medication regimens and complicating the diagnostic process [8]. Acute EPS emerges shortly after initiating antipsychotic therapy, while tardive symptoms develops over an extended period of sustained antipsychotic use [9]. Extrapyramidal symptoms (EPS) remain a significant challenge in managing schizophrenia and other psychiatric disorders treated with antipsychotic medications [10]. The psychiatrist face challenges in adjusting dosages to find the optimal balance between effectiveness and minimal side effects. Extrapyramidal symptoms remain a significant challenge in managing schizophrenia and other psychiatric disorders treated with antipsychotic medications [11]. Limited research exists on factors influencing EPS, including gender differences, body type, family history, and their impact on healthcare utilization. This study aims to evaluate EPS prevalence, identify risk factors, analyze gender differences, explore variable interrelationships, and assess healthcare utilization impacts.

Material and Methods

Participant Selection Method

The participant selection method for this study involved a convenience sampling approach, targeting a cohort of 115 patients diagnosed with schizophrenia for 32 months at Department of Psychiatry, a tertiary care center between January 2021 and September 2023. Exclusion criteria were applied to maintain the integrity of the data as shown in **Figure 1**. This study received ethical approval from the Institutional Review Board (IRB) (Approval. No. ****/IEC/4081) ensuring that the research adhered to the established ethical guidelines and standards.

Data Collection

Data collection for each patient was conducted through a retrospective chart review method. From the hospital database, patients diagnosed with schizophrenia were identified, resulting in approximately 331 records extracted in PDF format. Data extraction was facilitated using pyMuPDF package, which enabled the identification of patients, extraction of keywords, and exportation of data to excel format [12]. The collected data encompassed sociodemographic details, including age, locality, family history, gender, marital status, and employment status. Clinical variables such as appetite, body build, smoking status, comorbidities, and medication details, including the number and type of antipsychotics First-Generation Antipsychotics (FGA) and Second-Generation Antipsychotics (SGA), chlorpromazine equivalent daily dose of antipsychotics, mental health diagnosis, and duration of treatment were also recorded. The data was divided into two groups: EPS and Non-EPS. The EPS group had both schizophrenia and extrapyramidal symptoms, while the Non-EPS group does not have EPS. Clinicians conducted comprehensive evaluations of EPS and meticulously documented the patient's symptoms. Subsequently, these symptoms were classified into four distinct subtypes: Acute dystonia, Akathisia, Parkinsonism, and Tardive dyskinesia based on the observed symptoms. A total of 115 patient's records were included in the final analysis, ensuring a thorough examination of the relevant data points for meaningful insights into the prevalence and factors associated with EPS in schizophrenia.

Inclusion and Exclusion Criteria

The study inclusion criteria encompassed patients aged 18 to 70 years diagnosed with schizophrenia by qualified mental health professionals, actively prescribed antipsychotic medications as part of their treatment regimen. Furthermore, patients with changes in diagnosis were excluded from the study to maintain the homogeneity of the study population.

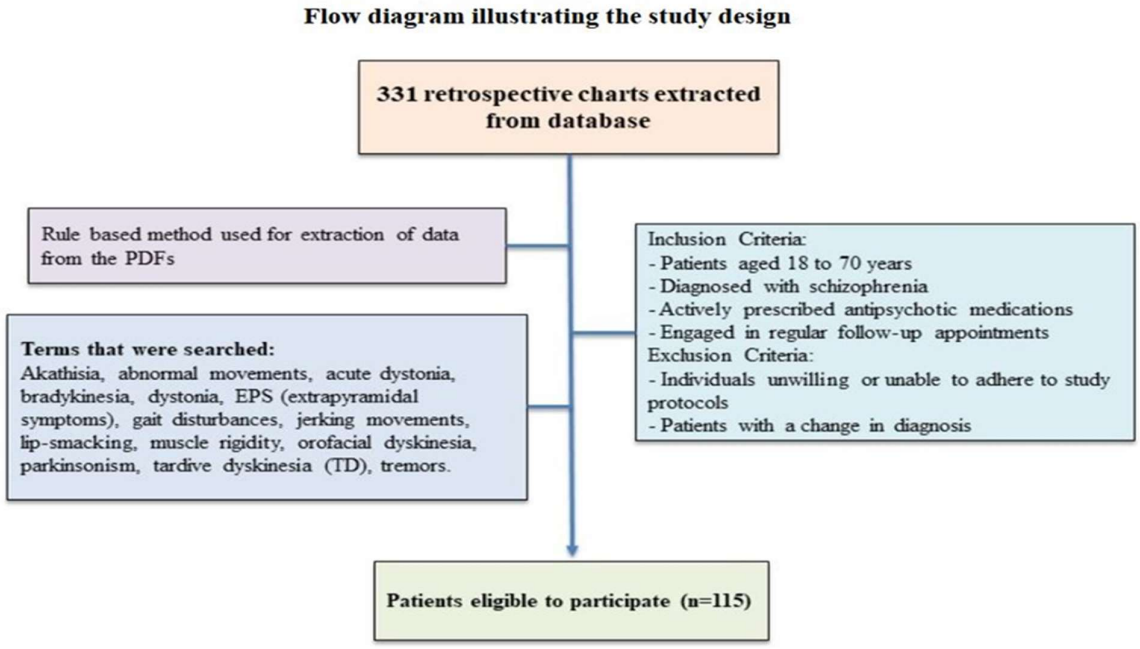


Figure 1. *Flow diagram illustrating the study design.*

115 patients followed up to examine the prevalence of extrapyramidal Symptoms (EPS) throughout the study duration. A rule-based method was used to extract data using keywords related to extrapyramidal symptoms.

Statistical analysis

To assess disparities in baseline characteristics between the EPS and Non-EPS groups, we employed the Wilcoxon rank-sum test for continuous variables and the Chi-square test for categorical variables. The prevalence of EPS was determined and the distribution of sociodemographic and clinical variables. Factor analysis was performed to identify key factors, and partial correlation network was computed to examine associations between continuous variables. The precision of edge-weights within the network was evaluated through non-parametric bootstrapping, employing 2500 bootstraps, utilizing the bootnet package [13]. ANOVA was conducted to examine differences in age across four EPS types. A multinomial logistic regression analysis conducted to find the association of age, gender, and built type. The statistical analysis was carried out using R software (version 4.3.1).

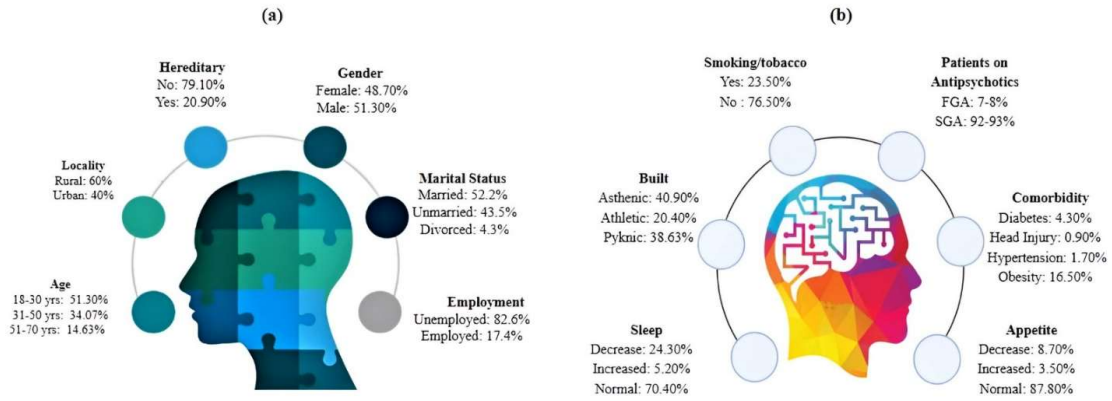
Results

The demographic characteristics and clinical profiles of the study participants

The majority of participants in the study were from rural areas (60.00%), male (51.30%), and married (52.20%).The majority of participants were unemployed (82.60%) and had no history of smoking or

tobacco use (76.50%). Obesity was the most common comorbidity (16.50%). The built type was distributed as 40.90% asthenic, 20.40% athletic, and 38.63% pyknic. Concerning antipsychotic medications, 93.00% were on Second-Generation Antipsychotics (SGAs), and 7.00% were on First-Generation Antipsychotics (FGAs) as shown in **Figure 2.**

Figure 2*. Distribution of sociodemographic and clinical variables in the study in terms of percentage (a) Distribution of key socio-demographics factors such as Age, Locality, Heredity, Gender, Marital Status, Employment status (b) The clinical variables such as smoking habits, appetite, sleep, comorbidity, built, type of antipsychotics among study participants.*



Prevalence of EPS and incidence rate of antipsychotic medications

Out of the initial 155 patients enrolled in the study, 115 individuals met all the inclusion criteria. This study comprised 56 females and 59 males, all of them were undergoing antipsychotic treatment. The overall estimated prevalence of EPS within the entire study is 38.3%, with Parkinsonism being the predominant symptom. Parkinsonism was the most common (30.8%), followed by Tardive Dyskinesia (4.3%), Acute Dystonia (2.6%), and Akathisia (1.7%). Our analysis revealed that Parkinsonism and Tardive Dyskinesia are more prevalent among females as compared to males within the study population. The prevalence of EPS was analyzed based on treatment with First-Generation Antipsychotics (FGAs) and Second-Generation Antipsychotics (SGAs), revealing significant differences between the two classes of medications. There is a significant difference between FGAs and SGAs treatment in Parkinsonism. However, no significant differences were noted in other EPS groups based on the antipsychotic treatment, as indicated in **Table 1**. The FGAs exhibit a higher prevalence of EPS at 66%, compared to SGAs, which account for 34% as shown in **Figure 3**. The study found that 43% of asthenic patients (characterized by a slender and lightly muscled physique) in the EPS group exhibited extrapyramidal symptoms.

TABLE 1. PREVALENCE OF NON-EPS AND EPS ACCORDING TO ANTIPSYCHOTIC TREATMENT.

	Non-EPS	*Parkinsonism*	*Other EPS*
Total Patients	*71*	*36*	*8*
Subjects treated with FGA	*2*	*3*	*4*
Subjects treated with SGA	*69*	*33*	*4*
Chi-Square test	*35.05*	*12.32*	*1.70*
p-value	*<.001**	*<.001**	*0.19*

$p < 0.05$ significant; Non-significant ($p \geq 0.05$) values are shown without superscripts. EPS: Extrapyramidal symptoms; FGA: First Generation Antipsychotics; SGA: Second Generation Antipsychotics.

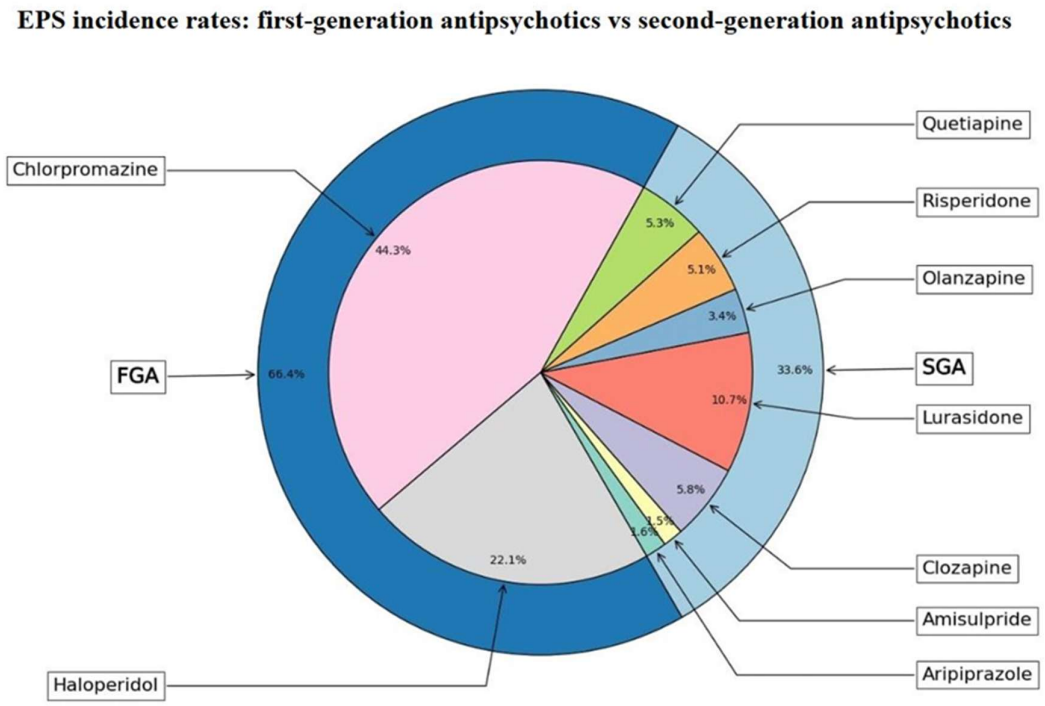


Figure 3. EPS incidence rates between first generation antipsychotics and second generation antipsychotics.

The chart compares Extrapyramidal Symptoms (EPS) incidences between First-Generation Antipsychotics (FGA) and Second-Generation Antipsychotics (SGA). FGAs account for 66.4% of EPS cases, predominantly from Chlorpromazine (44.3%) and Haloperidol (22.1%). SGAs contribute 33.6%

of EPS, with the highest incidences from Lurasidone (10.7%) and Clozapine (5.8%), followed by smaller contributions from other SGAs like Risperidone and Olanzapine.

Wilcoxon rank-sum test, ANOVA and Factor Analysis

A Wilcoxon rank-sum test as performed in **Table 2** revealing significant results in the duration of treatment and the daily dose equivalence of chlorpromazine between EPS and Non-EPS groups [14]. ANOVA was conducted to examine differences in age across four EPS symptom types (Parkinsonism, Tardive Dyskinesia, Dystonia, and Akathisia) as shown in **Figure 4(a)**.The results revealed a statistically significant effect of symptom type on age, $F(3, 40) = 3.97$, $p = .014$. The effect size was large, $\eta^2 = 0.23$, 95% CI [0.03, 1.00], indicating that approximately 23% of the variance in age was explained by symptom type**.** We also performed a Principal Axis Factoring analysis with Varimax rotation and Kaiser Normalization[15], which led to the discovery of three factors. The Kaiser-Meyer-Olkin (KMO) Measure of Sampling Adequacy showed a value of 0.565, suggesting a moderate level of adequacy in the sample. Additionally, Bartlett's Test of sphericity demonstrated a significant outcome, with an approximate Chi-Square value of 206.757 ($df = 78$, $p < 0.001$). These factors, identified through factor analysis, hold promise as potential contributors to the extrapyramidal symptoms. The Factor analysis yielded the identification of three discernible factors: number of FGA & SGA prescribed and built type.

Table 2. *Wilcox rank sum test for non-EPS and EPS according to Age, BMI, Chlorpromazine Equivalent Daily Dose, and Duration of Treatment.*

	Total (n =115)	*EPS (n= 44)*	*Non-EPS (n=71)*	*Wilcoxon (W)*	*p value*
Age, mean (SD) years	*33.86(12.4)*	*34(11.8)*	*33.73(12.8)*	*1516.5*	*0.795*
BMI, mean (SD) kg/m²	*23.30(5.14)*	*23.90(5.20)*	*22.90(5.10)*	*1362*	*0.340*
Net EQ dose, mean (SD) mg/day	*226.12(154.4)*	*224.4(183.9)*	*227.15(134.4)*	*1352.5*	***0.043****
Duration of treatment, mean (SD) years	*7.40(7.07)*	*6.80(6.76)*	*7.73(7.28)*	*1675.5*	*0.514*
No. of SGA, mean (SD)	*1.03(0.34)*	*0.95(0.37)*	*1.08(0.32)*	*1752*	***0.045****
No. of FGA, mean (SD)	*0.06(0.25)*	*0.13(0.34)*	*0.028(0.16)*	*1393*	***0.027****

**$p < 0.05$ significant; Non-significant ($p \geq 0.05$) values are shown without superscripts.*

EPS: Extrapyramidal symptoms; FGA: First Generation Antipsychotics; Net EQ dose: Chlorpromazine Equivalent Daily Dose; SD: Standard deviation; SGA: Second Generation Antipsychotics; W: Wilcoxon statistic.

Network Analysis

The Partial correlation network among the continuous variables e.g. BMI, age, duration of treatment in years and chlorpromazine equivalent daily dose as shown in **Figure 4(b)**. The network is composed of nodes, representing the observed variables, and edges, representing the connections among them. Each connection in the network represents a partial correlation coefficient. The thickness of an edge graphically represents the magnitude of the association. Light connections represent weak coefficients. The Partial correlation network, incorporating continuous variables such as BMI, age, duration of treatment, and chlorpromazine equivalent daily dose, furnishes a visual representation of their intricate interrelationships. The results indicate positive association between Body Mass Index (BMI), chlorpromazine equivalent daily dose, and the duration of treatment.

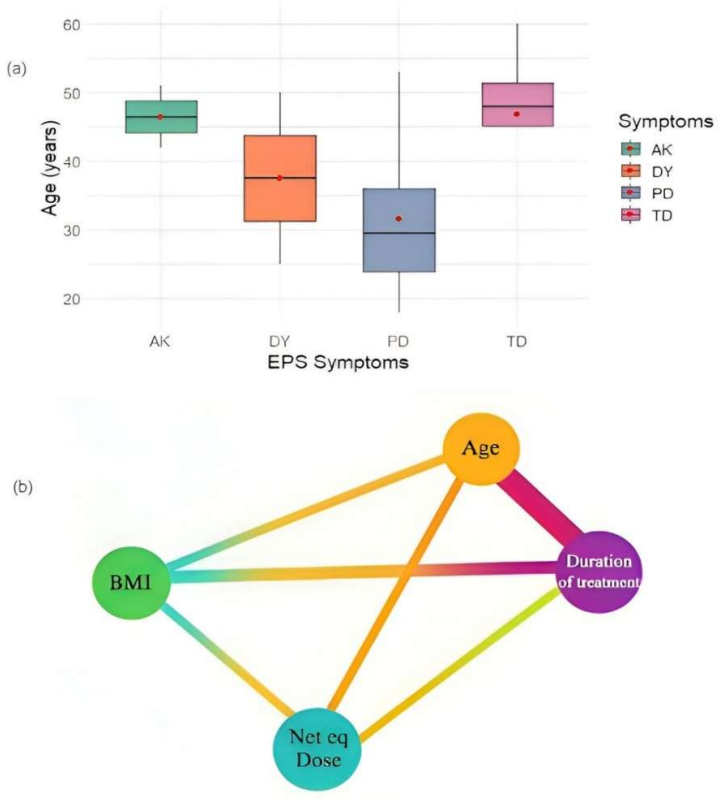


Figure 4. The age distribution of EPS patients and partial correlation network.

Boxplots illustrating the age distribution of patients exhibiting extrapyramidal symptoms (EPS), namely Akathisia (AK), Dystonia (DY), Parkinsonism (PD), and Tardive Dyskinesia (TD). Red dots indicate the mean age for each symptom group. The figure demonstrates that patients with Tardive Dyskinesia and Akathisia tend to be older, whereas those with Parkinsonism generally present at a

younger age group. These patterns may reflect age-related susceptibility or differential emergence of EPS subtypes in response to antipsychotic treatment. (b) Enhanced Partial Correlation Network depicting relationships among BMI, Age, Duration of Treatment (in years), and Chlorpromazine Equivalent Daily Dose (Net EQ). Each node represents a variable, and edges denote partial correlations between them, with thickness indicating the strength of association. The network reveals that BMI is positively associated with both Net EQ dose and treatment duration, reflecting meaningful clinical connections among these parameters.

Multinomial Logistic Regression

A multinomial logistic regression analysis[16] was conducted to examine the association of age, gender, and built type with the likelihood of exhibiting different extrapyramidal symptoms, using Parkinsonism (PD) as the reference category as shown in **Table 3**. In the comparison between Tardive Dyskinesia (TD) and Parkinsonism, age emerged as a significant predictor ($p = .043$), indicating that the likelihood of TD increased with advancing age. Gender ($p = .275$), athletic body type ($p = .762$), and pyknic body type ($p = .571$) were not significantly associated with TD. In the model comparing Akathisia (AK) to Parkinsonism, both athletic and pyknic body types showed strong and statistically significant associations with increased odds of Akathisia ($p < .001$ for both). Neither age ($p = .898$) nor gender ($p = .349$) demonstrated a significant effect in this comparison. For the contrast between Dystonia (DYS) and Parkinsonism, male gender was strongly associated with higher odds of Dystonia ($p < .001$). Both athletic ($p < .001$) and pyknic ($p < .001$) body types were also significantly associated with increased odds, while age was not a significant predictor ($p = 0.339$).These findings are visually supported by the predicted probability plots presented in **Figure 5**, which illustrate the interaction of age, gender, and body type with EPS.

Table 3*. Multinomial Logistic Regression Predicting Extrapyramidal Symptoms.*

Comparison	*Predictor*	*β*	*z*	*p*	*OR*
TD vs PD	*Age*	1.35×10^{-1}	*2.02*	***0.04****	*1.14*
	Gender (Male)	*1.62*	*1.09*	*0.27*	*5.04*
	Athletic	-4.23×10^{-1}	-3.03×10^{-1}	*0.76*	6.55×10^{-1}
	Pyknic	-8.38×10^{-1}	-5.66×10^{-1}	*0.57*	4.32×10^{-1}
AK vs PD	*Age*	1.00×10^{-2}	1.28×10^{-1}	*0.89*	*1.01*

Comparison	*Predictor*	*β*	*z*	*p*	*OR*
	Gender (Male)	*1.70*	*9.37×10^{-1}*	*0.34*	*5.50*
	Athletic	*3.70×10^{1}*	*2.52×10^{1}*	***<.001****	*1.21×10^{16}*
	Pyknic	*3.86×10^{1}*	*2.92×10^{1}*	***<.001****	*5.82×10^{16}*
DYS vs PD	*Age*	*1.17*	*9.55×10^{-1}*	*0.33*	*3.22*
	Gender (Male)	*5.21×10^{1}*	*1.81×10^{3}*	***<.001****	*4.18×10^{22}*
	Athletic	*9.22×10^{-1}*	*3.94×10^{12}*	***<.001****	*2.51*
	Pyknic	*3.77×10^{1}*	*1.31×10^{3}*	***<.001****	*2.38×10^{1}*

**p < 0.05; Non-significant (p ≥ 0.05) values are shown without superscripts.*

TD: Tardive Dyskinesia; AK: Akathisia; DYS: Dystonia; PD: Parkinsonism; β: Regression Coefficient; z: z-statistic; p: p-value; OR: Odds Ratio.

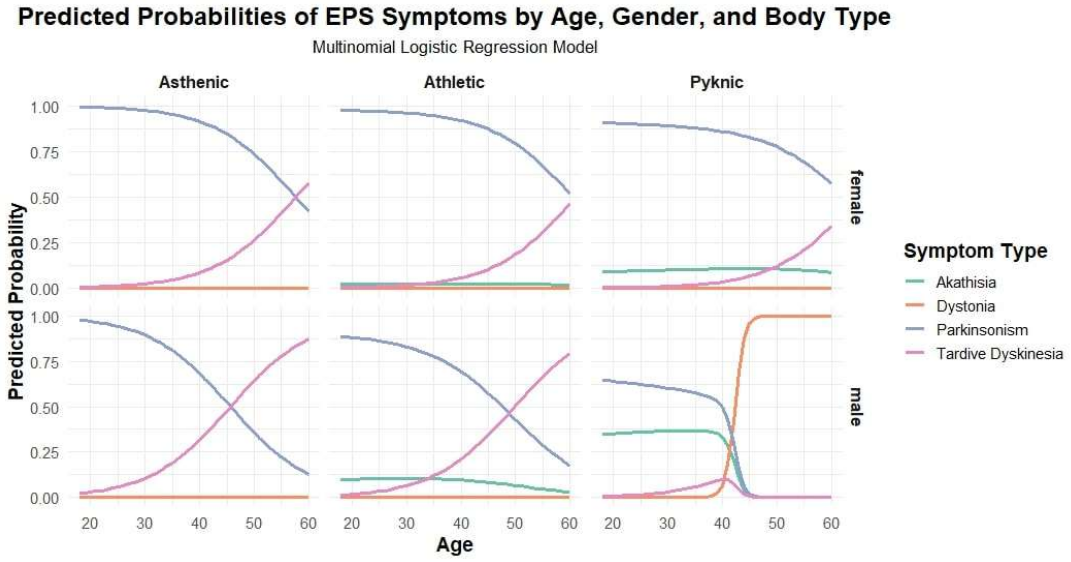


Figure 5. The predicted probabilities from a multinomial logistic regression model.

This figure presents predicted probabilities from a multinomial logistic regression model analysing the distribution of four EPS subtypes: Parkinsonism, Tardive Dyskinesia (TD), Dystonia, and Akathisia—across age, gender (rows), and body type (columns: Asthenic, Athletic, Pyknic). The blue curve (Parkinsonism) dominates in younger ages, especially before age 40, while the magenta curve (TD)

increases steadily with age across all body types and genders. A clear crossover between PD and TD is observed, particularly in males. In Pyknic males, the orange curve (Dystonia) shows a sharp midlife spike, highlighting a body-type-specific risk not seen in females or other body types. The green curve (akathisia) remains low across all subgroups, suggesting minimal influence from demographic or somatotype factors in this cohort.

Discussion

The findings of our study provide valuable insights into the demographic and clinical factors related to the prevalence of EPS in patients undergoing antipsychotic treatment for schizophrenia. In a cross-sectional study further supports our findings, revealing a comparable prevalence of EPS among patients with schizophrenia spectrum disorders regardless of antipsychotic class, challenging the notion of atypical antipsychotics carrying a lower risk of EPS [17]. A study on the prevalence of extrapyramidal symptoms in in-patients with severe mental illnesses emphasizes the multifaceted nature of EPS with older age, medical comorbidities, and medical treatments playing significant roles [18]. Elderly females are more likely to develop extrapyramidal symptoms (EPS), such as drug-induced Parkinsonism and tardive dyskinesia (TD), compared to males, particularly in older age [19]. This increased susceptibility is attributed to several factors, including hormonal changes post-menopause, where the decline in estrogen reduces its protective effect on the dopaminergic system [20]. These findings emphasize the need for tailored patient-provider discussions and interventions to address medication-induced movement disorders across different age demographics.

Our study identified a higher incidence of EPS among patients prescribed First-Generation Antipsychotics (FGAs), emphasizing the need for clinicians to carefully weigh the medication-related risks while making treatment decisions. The study contributes to the existing body of literature by identifying number of FGA and SGA as risk factors for EPS with schizophrenia [21]. Underweight is significantly associated with greater rates of bradykinesia and muscle rigidity, and a lower rate of gait disturbance in Asian patients with schizophrenia [22]. In our study, we observed a notable association between Parkinsonism and low BMI in patients. It is plausible that individuals with a leaner physique may possess altered metabolic pathways or pharmacokinetic profiles that render them more susceptible to the neurologic effects of antipsychotic medications [23]. We also observed that patients with EPS had a significantly higher average number of healthcare visits per patient compared to those without EPS. We found that EPS were associated with an elevated risk of hospitalization and greater healthcare expenditures among individuals diagnosed with schizophrenia [24].

While our study offers valuable insights into the demographic and clinical factors of EPS in patients diagnosed from schizophrenia, it is crucial to acknowledge certain limitations. A larger and more diverse sample would enhance the external validity of the study, providing a broader understanding of the factors contributing to EPS across various populations. The exclusive data collection from one center may introduce regional biases, restricting the broader applicability of the results. Replicating

this study across multiple centers and diverse geographical locations would yield a more comprehensive understanding of the impact of demographic and clinical factors on EPS prevalence. The relatively small sample sizes within certain EPS categories may have reduced the statistical power to detect true associations. Future research should include longitudinal studies to track EPS progression over time, assess treatment impact, and develop targeted interventions. Collaborative efforts across healthcare institutions will be essential for improving patient outcomes and refining treatment guidelines for schizophrenia-related movement.

Conclusion

The overall prevalence of EPS was found to be 38.3%, with Parkinsonism being the most commonly observed symptom. A significant difference in EPS was noted between patients treated with first-generation antipsychotics (FGAs) and those on second-generation antipsychotics (SGAs), with a higher prevalence in the FGA group. Women exhibited a higher prevalence of these symptoms, likely due to differences in drug metabolism and hormonal influences. Body type also emerged as an important factor, with asthenic individuals showing a higher risk of EPS. Statistical analysis revealed that both the duration of treatment and the daily dose (in chlorpromazine equivalents) were significantly associated with EPS. The ANOVA test confirmed a significant variation in age across different EPS types, while factor analysis pointed to underlying factors such as medication type and body type contributing to symptom patterns. The partial correlation network analysis highlighted a positive associations among BMI, treatment duration, and the dosage, suggesting that these variables may interact to influence EPS outcomes. EPS was linked to increased healthcare visits, higher hospitalization rates, and greater healthcare expenditures, emphasizing its clinical and economic burden. In conclusion, the findings underscore the need for clinicians to consider patient-specific characteristics such as age, gender, body type, treatment duration, and medication type when prescribing antipsychotics. Tailoring treatment based on these factors may help reduce the risk of EPS and improve patient outcomes. Continued research is needed to further understand the mechanisms underlying these associations and to develop preventive strategies for managing EPS in psychiatric care.

List of Abbreviations

- **AK** – Akathisia
- **ANOVA** – Analysis of Variance
- **BMI** – Body Mass Index
- **CI** – Confidence Interval
- **DYS** – Dystonia
- **EPS** – Extrapyramidal Symptoms
- **FGA** – First Generation Antipsychotics

- **IRB** – Institutional Review Board
- **KMO** – Kaiser-Meyer-Olkin
- **Net EQ dose** – Chlorpromazine Equivalent Daily Dose
- **OR** – Odds Ratio
- **PD** – Parkinsonism
- **SD** – Standard Deviation
- **SGA** – Second Generation Antipsychotics
- **TD** – Tardive Dyskinesia
- **z** – z-score (standardized test statistic)
- **β** – Beta coefficient (regression weight)
- **χ^2** – Chi-square test statistic

Acknowledgment

We extend our sincere gratitude to the Indian Institutes of Technology (IIT) and the All-India Institute of Medical Sciences (AIIMS) Jodhpur for their invaluable support and collaborative efforts throughout this study. We are also grateful for the infrastructure and ethical oversight provided by both institutions, which ensured the ethical conduct of our study. Our heartfelt appreciation goes out to all those who contributed to the success of this study at IIT, AIIMS Jodhpur, and beyond.

Conflicts of Interest

There are no conflicts of interest to declare.

Author Contributions

Conceptualization: Dr. Navratan Suthar; Data curation: Monika Sharma; Methodology: all authors; Project administration: all authors; Supervision: Dr. Pankaj Yadav, Dr. Navratan Suthar; Writing of the original draft: Monika Sharma, Dr. Navratan Suthar; Writing, review, and editing: all authors.

Declarations

Human Ethics

This study received ethical approval from the Institutional Review Board (IRB) of the Institute (Approval No. IEC/4081), ensuring that the research was conducted in compliance with recognized ethical standards.

Consent to participate

Written informed consent was obtained from all participants before their inclusion in the study. Participants were clearly informed about the objectives, procedures, potential risks and benefits of the study. They were informed that their participation was voluntary, with the right to withdraw at any

stage without any consequences. All procedures used in this research followed the guidelines laid forth in the Helsinki Declaration by the World Medical Association.

Funding

This study did not receive any financial support from funding agencies.

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