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ORIGINAL ARTICLE

Clinical characteristics and treatment outcomes of patients with newly diagnosed schizophrenia: A 4-year single-center experience in Saudi Arabia

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Abstract

Objectives: Understanding how local "psychiatry clinic" characteristics shape research findings is essential for applying research into evolution, outcomes, and costs of mental health. However, a paucity of "psychiatry clinics" details has implications for the interpretation and utilization of this research.

Methods: We reviewed data of 746 patients with new-onset schizophrenia on antipsychotic monotherapy seen over four years in an "adult psychiatry clinic" at Jazan Health, Saudi Arabia. Protocol-driven interviews and investigations were recorded prospectively and extracted from the medical records for the study. Summary statistics and logistic regression analyses were applied to assess patients' characteristics and outcomes.

Results: The median patient age was 32 (IQR 27-39) years. Of patients, 589 (79.0%) were male, and 679 (91.0%) had a low-level education. The median follow-up duration was 51.4 (IQR 27.4-96.3) weeks. The most used initial antipsychotic drugs were olanzapine (48.8%), haloperidol (13.9%), and aripiprazole (11.3%). The numbers of patients who retained the initial drug at 24 and 52 weeks were 539 (72.3%) and 325 (43.6%), respectively. The initial drug was changed in 246 (33.0%) patients. The median time to initial drug change was 43.9 (IQR 14.8-85.0) weeks. The logistic regression demonstrated that male sex ($P < 0.004$), young adult age group ($P < 0.027$), predominant positive symptoms ($P < 0.021$), treatment with haloperidol ($P < 0.024$), and khat use ($P < 0.006$) were significant factors for drug change.

Conclusions: This clinical records study demonstrated substantial individual variations in characteristics and in responding to initial antipsychotic medication. Insight into these findings will facilitate the planning for comprehensive research programs.

KEYWORDS
antipsychotic drugs, newly diagnosed, outcomes, schizophrenia

1 | INTRODUCTION

Despite its relatively low prevalence, schizophrenia is associated with significant health, social, and economic concerns.[1-3] Patients who have been diagnosed with schizophrenia should be urgently referred for psychiatric evaluation.[4,5] "Adult psychiatry clinic" at Jazan Health, Saudi Arabia, have been established with the intention of providing patients with a rapid specialist assessment in order to obtain an early diagnosis and facilitate the management of mental health conditions, including schizophrenia. This clinic aims to achieve short time periods between the index presentation (the potential first psychotic episode) and clinic consultation with an experienced psychiatrist, usually with protocol-driven clinical diagnostic interviews and investigations. The clinic also has substantial potential to facilitate efficient and comprehensive research programs. An understanding of how this local clinic characteristics shape research findings is essential for interpreting and utilizing research as well as for the planning of practice and education in the area. However, a paucity of data addressing the design, demographics, findings, and other details of these clinics all over the country has been noted.[6] Without these details, research outcomes may be misinterpreted, with little insight into why study results differ between clinic sites. This study reviewed data for a large cohort of patients with new-onset schizophrenia seen over four years in an established independent "adult psychiatry clinic" at Jazan Health, Saudi Arabia. This clinic is situated in a major public mental health hospital and operates with similar levels of expertise as to other clinics in the country using comparable protocols. We aimed to describe the findings for patients who presented to this clinic and obtained a new diagnosis of schizophrenia. We examined clinical presentation, assessments undertaken, investigation results, and drug treatment outcomes. The findings from this clinic will be instructive for interpretation and utilization of future research and planning of patient care in this area.

2 | METHODS

2.1 | Study design, patients, and routine adult psychiatry clinic protocol

Included in this study were patients ≥18 years of age at presentation to the "adult psychiatry clinic," who received a new diagnosis of schizophrenia and who had at least a 12-week follow-up between January 1, 2013, and December 31, 2016. Criteria for schizophrenia include signs and symptoms of at least six months duration, including at least one month of active-phase positive and negative symptoms.[4] Delusions, hallucinations, disorganized speech, and disorganized behavior are examples of positive symptoms. Negative symptoms include a decrease in the range and intensity of expressed emotions (ie, affective flattening) and a diminished initiation of goal-directed activities (ie, avolition). The term newly diagnosed was defined as having no previous diagnosis of schizophrenia and no history of antipsychotic medication use three months before their first presentation to the "adult psychiatry clinic." The "adult psychiatry clinic" is situated in a major public mental health hospital and operates with high levels of expertise and within the government-funded healthcare system. The hospital serves geographically large areas of Jazan, a region located on the southwestern edge of Saudi Arabia, near Yemen. Referrals come from the community via General Practitioners, the hospital emergency departments, or surrounding hospitals.

Routinely, each patient is assessed thoroughly by a consultant psychiatrist. This includes a detailed description of events of interest as well as associated symptoms. Screening tests to detect the presence of amphetamines, khat, and cannabis are routinely requested. Diagnosis of schizophrenia is often established at the first appointment according to the International Classification of Diseases, 10th Revision. Study data were obtained via an audit of the records of the "adult psychiatry clinic." For this study, the clinical information and investigations were reviewed thoroughly by three psychiatrists (see Acknowledgments), and the following data were extracted: sex, age, detailed description of symptoms, clinical presentation, investigations, antipsychotic drug treatment, drug combination with CNS stimulants or depressants, and screening tests for substance use including amphetamines, khat, and cannabis.

2.2 | Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences software (SPSS version 20.0, IBM, USA). Analyses used non-parametric measures as data were generally not normally distributed (Kolmogorov-Smirnov test). These included summary statistics, Pearson chi-square test for categorical measures, and Mann-Whitney U test for age variable. A logistic regression model was carried out to assess the effect of sex, age, education level, predominant schizophrenia symptoms, the initial antipsychotic drug prescribed, and substance use (amphetamine, khat, and cannabinoid) on the likelihood of drug change. Results were considered statistically significant at the 5% level (two-sided).

3 | RESULTS

Patients' characteristics are presented in Table 1. There were 746 clinic attendees who met the inclusion criteria. The median age at first attendance was 32 (IQR 27-39; range 18-65) years. In total, 589 (79.0%) were male, and 679 (91.0%) had education below the secondary level. The median follow-up duration was 51.4 (IQR 27.4-96.3; range 12-209) weeks. The most used initial antipsychotic drug was olanzapine (48.8%), followed by haloperidol (13.9%), aripiprazole (11.3%), and risperidone (10.6%). The number of patients who retained the initial antipsychotic drug at 12, 24, and 52 weeks was 675 (90.5%), 539 (72.3%), and 325 (43.6%), respectively. Using the Pearson chi-square test, high-level education was the only factor associated with ≥52 weeks drug retention ($\chi^2(3) = 11.164$, $P < 0.011$).

The initial antipsychotic drug was changed in 246 (33.0%) patients. The median time to initial drug change was 43.9 (IQR 14.8-85.0; range 1.0-214.9) weeks. Reasons for initial drug change were lack of efficacy in controlling symptoms of schizophrenia (includes non-adherence to medications) in 134 (54.5%) patients, adverse drug effects in 43 (17.5%), both causes in 52 (21.1%), and unspecified in 10 (4.1%). Pearson chi-square test revealed a significant correlation between drug change and several independent variables including male sex ($P < 0.00$), young adult age group ($P < 0.017$), high-level education ($P < 0.014$), and presentation with positive symptoms ($P < 0.00$). A logistic regression model was carried out to assess the effect of sex, age, education level, predominant schizophrenia symptoms, the initial antipsychotic drug prescribed, and substance use (amphetamine, khat, and cannabinoid) on the likelihood of drug change. The overall model was statistically significant when compared to the null model ($\chi2(19) = 112.76$, $P < .001$), explained 19.5% of the variation of drug change (Nagelkerke R2), and correctly predicted 70.8% of cases. Male sex ($P < 0.004$), young adult age group ($P < 0.027$), predominant positive symptoms ($P < 0.021$), the initial antipsychotic drug prescribed particularly haloperidol, paliperidone, and quetiapine ($P < .024$), and khat use ($P < .006$) were significant. The odds of drug change were 2.

TABLE 1 Patients' characteristics

Category	Frequency	Percent
Sex		
Male	589	79
Female	157	21
Age group		
18-24	116	15.5
25-34	342	45.8
35-49	236	31.6
50-65	52	7
Education		
0-6 years	272	36.5
7-9 years	413	55.4
10-15 years	57	7.6
≥16 years	4	0.5
Predominant symptoms		
Positive	649	87
Negative	97	13
Substance use		
Cannabis	77	10.3
Amphetamine	218	29.2
Khat	168	22.5
Total	746	100

4 | DISCUSSION

This article retrospectively studied a consecutive series of patients who attended an "adult psychiatry clinic" over four years for clinical assessment of a potential first psychotic episode. Included were all patients with newly diagnosed schizophrenia on antipsychotic monotherapy (N = 746). Of these, 246 (33.0%) patients failed to respond to the initial antipsychotic medication. Failure was defined as the need to change the initial antipsychotic medication due to lack of efficacy in controlling the symptoms of schizophrenia and/or intolerable adverse effects. In this study, failure to respond to the initial drug was most likely due to lack of efficacy despite the fact that antipsychotics were given in their maximum therapeutic doses (Table 2). Poor adherence to medications, therefore, cannot be excluded.

Failure to control schizophrenia symptoms can be associated with relapse, exacerbations, and premature discontinuation of the treatment and often prompts physicians to change the initial antipsychotic drug. Patients who fail to respond to medications also have a higher risk of hospitalization, and this could result in a tremendous increase in the treatment cost.[7,8] Finding appropriate treatment strategies and clinical recommendations for those most at-risk is an enormous challenge due to the substantial variations in patients' characteristics and outcomes. Here, we applied a logistic regression analysis to assess patient factors that were

TABLE 2 Initial drug prescribed and frequency of change

Drug	Frequency	Percent	Median dose (range) mg/day	Frequency (%) of drug change
Amisulpride	4	0.5	400 (200-800)	0
Aripiprazole	84	11.3	15 (10-30)	15 (17.9%)
Clozapine	2	0.3	300 (150-600)	0
Haloperidol	104	13.9	10 (5-20)	52 (50.0%)
Olanzapine	364	48.8	10 (10-30)	110 (30.2%)
Paliperidone	41	5.5	6 (3-12)	18 (43.9%)
Quetiapine	61	8.2	400 (300-800)	25 (41.0%)
Risperidone	79	10.6	4 (2-8)	25 (31.6%)
Trifluoperazine	7	0.9	1 (1-2)	1 (14.3%)
Total	746	100		

associated with a higher risk of drug change, and we found that male sex, young adult age group, predominant positive symptoms, the initial antipsychotic drug prescribed, and khat use were significant (Table 3).

Among complex genetic disorders, schizophrenia has one of the highest heritabilities.[9] Symptoms such as hallucinations and delusions usually begin between ages 16 and 30 and tend to emerge earlier in males than females. The median age of the patients who attended our "adult psychiatry clinic" was 32 (IQR 27-39); this suggests that even if the diagnosis has been recent, the onset of schizophrenia symptoms could have been much earlier. Moreover, schizophrenia affects males and females equally, but the attendees were mostly males (79%). This might be explained by the fact that mental health conditions in the Saudi community are still considered as a stigma, particularly for women, and hence 80% of Saudis with severe mental health disorders do not seek any treatment, even when available (The Saudi National Health and Stress Survey; unpublished technical report 2019).[6] The logistic regression model demonstrated that the odds of drug change for males and young adult patients was almost two times the odds for females and those in the older age groups. The study also showed that schizophrenia is more prevalent among less educated people (0-6 and 7-9 years; 91.9%), but the drug change was significant among those with high-level education (≥16 years), although we had only four patients in this age group.

An antipsychotic monotherapy should be initiated as soon as possible after schizophrenia is diagnosed.[4,5] The antipsychotics improve the positive and negative symptoms of schizophrenia by impacting the brain's neurotransmitter system, specifically, the D2 dopamine and 5-HT2A serotonin receptors. However, it has been documented that 30% of patients with predominant "positive symptoms" do not respond to medications.[10] Moreover, the first-generation (or typical) antipsychotics, which commonly cause extrapyramidal symptoms, do not have a therapeutic impact on schizophrenia's "negative symptoms." Second-generation (or atypical) antipsychotics are more effective for negative symptoms but commonly cause metabolic changes and increase the risk of cardiovascular diseases. This study showed a two times higher risk of treatment failure with the initial antipsychotic medication in patients with predominant "positive symptoms." There was also a significant association between the initial antipsychotic medication as a whole and the risk of drug change. In the detailed results, the odds of drug change in patients receiving haloperidol were almost five times the odds for those receiving the reference drug in the model (trifluoperazine). Reasons for switching haloperidol included lack of efficacy (53.8%), adverse effects (11.5%), and both (34.6%). Patients receiving olanzapine, paliperidone, or quetiapine were also found to have a two to three times higher risk of drug change.

The study also found that khat use was a significant factor for the drug change in patients with newly diagnosed schizophrenia. Khat, Catha edulis (Vahl) Forssk. ex Endl., is a plant medicine used by many people in the Eastern Mediterranean Region.[11] In Jazan, which lies in the southwest region of Saudi Arabia, khat use has been a traditional practice, and the current patterns of use are becoming more excessive.[12] Khat is consumed by chewing and continuously produces pharmacokinetic properties.[13,14] The fresh leaves and twigs of the khat shrub contain high concentrations of cathinone, an amphetamine analog that produces euphoric effects.[13,14] Increased energy, empathy, openness, and libido are other desired effects reported by khat users.[15,16] Although limited use may not be accompanied by serious consequences, prolonged exposure could lead to dependence, psychosis, and mood disturbances.[17-20] The World Health Organization reported that khat causes psychological but not physical dependence among

TABLE 3 Factors associated with drug change

	Univariate logistic regression			
	OR	95% CI		
Category		Lower	Upper	*P*-value
Sex				
Male	2.164	1.283	3.647	0.004
Female	1			
Age group				0.089
18-24	2.648	1.116	6.281	0.027
25-34	1.801	0.811	4.002	0.149
35-49	1.534	0.690	3.412	0.294
50-65	1			
Education				0.703
0-6 years	1			
7-9 years	1.178	0.804	1.725	0.401
10-15 years	0.994	0.495	1.996	0.986
≥16 years	2.578	0.301	22.058	0.387
Predominant symptoms				
Positive	2.080	1.117	3.875	0.021
Negative	1			
Initial drug				0.024
Amisulpride	0.000	0.000		0.999
Aripiprazole	1.260	0.132	12.017	0.841
Clozapine	0.000	0.000		0.999
Haloperidol	4.896	0.536	44.682	0.159
Olanzapine	2.289	0.254	20.599	0.460
Paliperidone	3.368	0.345	32.924	0.296
Quetiapine	3.351	0.355	31.655	0.291
Risperidone	2.658	0.283	24.930	0.392
Trifluoperazine	1			
Substance use				
Cannabis	1.463	0.861	2.487	0.160
Amphetamine	0.950	0.492	1.834	0.879
Khat	2.614	1.312	5.207	0.006

Note: Abbreviation: CI, Confidence interval.

moderate users who consumption this drug on a daily basis.[21] A recent study by our research group found that, in patients with new-onset schizophrenia, excessive khat use can aggravate the psychotic symptoms and hinder the response to treatment with antipsychotic medications.[22]

Epidemiological studies from the United States, Europe, and Australia have consistently demonstrated that half of the first episode psychosis patients have co-occurring substance use disorders (in particular alcohols, cannabis, and stimulants), which is at least three times higher than that in the general population.[23-25] Co-occurrence may result in more psychotic symptoms (including hyperactivity, mood liability, impulsivity, hostility, and uncooperativeness), depressive symptoms, and greater perceived stigma.[17-20] Importantly, patients with schizophrenia and co-occurring substance use tend to have lower adherence to treatment and a poorer long-term prognosis than those without such disorders. In Saudi Arabia, the research found that 2.7% of Saudi youth (age 15-24) are diagnosed with drug abuse sometime in their life (The Saudi National Health and Stress Survey; unpublished technical report 2019).[6] The current study also found that approximately 30% of patients with new-onset schizophrenia had a positive screening test for amphetamine or cannabis, and those patients were more likely not to respond to the initial drug compared to the non-users, but this was not statistically significant.

This study has limitations due to its retrospective nature. Individuals with schizophrenia may be underrepresented in medical records data because they may receive little or no health care. However, this study included a large cohort from long-running independent "adult psychiatry clinic" with rapid assessment and protocol-driven interviews and investigations. In addition, the psychiatric assessment of symptoms, the causative relationship between substance use and antipsychotic efficacy, and reasons for antipsychotic switching were audited from the records and reaffirmed by three consultant psychiatrists.

5 | CONCLUSIONS

This clinical record study demonstrated a significant variation in clinic characteristics and treatment outcomes for individuals with new-onset schizophrenia. Insight into these findings will facilitate interpretation and utilization, and planning of future research. Potential further research includes the assessment of co-occurring medical, mental, and behavioral conditions, the risk of premature mortality after the first psychotic episode, in addition to the clinic administrative settings, and costs of patient care.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

AUTHOR CONTRIBUTIONS

The author has made substantial contributions to the conception and design of the work, and acquisition, analysis, and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

The study was approved by the Jazan Health Human Research Ethics Committee (HREC No. 1437-SCBRE-03). Patient confidentiality was maintained by coding patients' files without disclosure of any private information.

INFORMED CONSENT

None.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

None.

ANIMAL STUDIES

None.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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