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Antipsychotic dose is not associated with cognitive function in patients with schizophrenia aged under 40: a cross-sectional observational study with retrospective dose estimation

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Abstract

Background This study aimed to examine the relationship between antipsychotic dosage and cognitive performance in young patients with schizophrenia. A relatively homogeneous sample was selected to reduce clinical heterogeneity and improve sample comparability.

Methods In this cross-sectional observational study, psychotic symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS), and cognitive performance was evaluated with the Montreal Cognitive Assessment (MoCA) in clinically stable patients with schizophrenia under the age of 40 who were followed at a Community Mental Health Center. Total antipsychotic dose was calculated using olanzapine equivalents, and 1-year cumulative exposure was estimated using the mg×day formula. Both frequentist and Bayesian analytical approaches were applied.

Results No significant correlations were found between either daily or cumulative antipsychotic doses and MoCA scores ($r=0.067$; $p=0.675$; $BF_{10}=0.260$; and $r=0.028$; $p=0.864$; $BF_{10}=0.554$, respectively). Longer illness duration and higher scores on all PANSS subscales were associated with lower MoCA scores, whereas longer education and older age at diagnosis were positively correlated with cognitive performance.

Conclusions Although prior research has suggested dose-related cognitive impairment, our findings did not provide evidence supporting this association in young, well-characterised patients within the constraints of a cross-sectional observational design. These results indicate that effective therapeutic dosing can be pursued with appropriate clinical monitoring, while acknowledging that potential cognitive effects should still be taken into consideration.

Highlights

- Cognitive deficits are present from an early age of schizophrenia.
- Cognitive scores are not significantly associated with antipsychotic dose.

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- Higher psychotic symptoms are linked to lower cognitive scores.
- A longer illness duration is associated with poorer cognitive function.
- A homogeneous and clinically stable sample reduces clinical heterogeneity and improves comparability across participants.

Keywords Schizophrenia, Cognitive impairment, Antipsychotics, Young adults, MoCA

Background

Most patients with schizophrenia exhibit impairments across multiple domains of cognitive functioning [2]. These cognitive difficulties may emerge immediately before or several years after the onset of psychotic symptoms [43], and they often persist and remain relatively stable throughout the course of the illness [3, 19, 30].

Several factors contribute to the etiology of cognitive impairment in schizophrenia. Prior research has shown that both positive and negative symptoms are associated with poor cognitive performance [17, 28, 45]. Many studies have also suggested that medications used in treatment may negatively affect cognitive functions [10, 16]. The cognitive effects of antipsychotics are thought to occur primarily through two mechanisms: dopamine receptor blockade and cholinergic blockade [29, 36, 42].

Research investigating the relationship between antipsychotic dosage and cognitive impairment has yielded inconsistent findings, likely due to methodological variability and major confounding factors. Some studies have reported significant cognitive improvement following dose reduction [40], whereas others have suggested that antipsychotics may contribute to cognitive enhancement in patients with schizophrenia [7, 31].

To help clarify these mixed results, further investigation in carefully characterized samples remains essential to better understand how antipsychotic exposure relates to cognitive performance. A clearer understanding of this relationship may help clinicians avoid unnecessary dose restrictions based solely on concerns about potential cognitive side effects.

Objective

This study aimed to investigate whether antipsychotic medication dose is associated with cognitive performance in patients with schizophrenia. Given the conflicting findings in the literature and the potential influence of confounding variables, we examined this relationship in a clinically stable, relatively young, and homogeneous sample. In addition, by calculating the cumulative antipsychotic dose used over the past year, we sought to determine whether longer-term medication exposure was related to cognitive functioning.

Methods

Sample and data collection tools

This was a single-center, cross-sectional observational study. Between 1 January 2024 and 29 February 2024, all patients who presented for treatment or rehabilitation at the Kanuni Sultan Süleyman Training and Research Hospital Küçükçekmece Community Mental Health Centre during their routine follow-up visits were screened for age and diagnostic eligibility to reduce selection bias. Patients who met these initial criteria were subsequently evaluated through face-to-face interviews conducted by the psychiatrist in charge of the clinic. Those who fulfilled all inclusion and exclusion criteria were invited to participate in the study. Written informed consent was obtained from all volunteers; for patients under legal guardianship, written consent was additionally obtained from their guardians.

A case report form developed by the researchers was used to collect sociodemographic information and relevant clinical data (e.g., medication doses, age at diagnosis, disease duration). Information was gathered from patients and, when available, their relatives. Medical records from the Community Mental Health Centre were also reviewed.

Cognitive functioning and clinical severity were assessed using the Turkish versions of the Montreal Cognitive Assessment (MoCA) and the Positive and Negative Syndrome Scale (PANSS), both of which have demonstrated validity and reliability [26, 32]. The MoCA was preferred because it is more sensitive than the Mini-Mental State Examination in detecting cognitive deficits [8] and is supported as an appropriate tool for identifying neurocognitive impairment in patients with schizophrenia [15].

Inclusion and exclusion criteria

Patients were included if they (1) met DSM-5 criteria for schizophrenia, (2) were between 20 and 40 years of age, (3) were Turkish-speaking, (4) had at least eight years of formal education, and (5) provided informed consent.

Patients were excluded if they (1) had a history of mood episodes (i.e., bipolar disorder or schizoaffective disorder); (2) had an additional diagnosis of intellectual disability; (3) were outside the 20–40 age range; (4) had a diagnosis of psychosis before age 18; (5) had fewer than eight years of formal education; (6) had a past or current alcohol or substance use disorder; (7) had a history of

head trauma with loss of consciousness; (8) were pregnant; (9) had neurological disorders such as epilepsy, multiple sclerosis, or cerebrovascular disease; (10) had systemic illnesses such as diabetes, rheumatic disease, or renal failure; (11) were not Turkish-speaking; or (12) did not consent to participate.

Sample size determination

The required sample size was calculated using G*Power. Assuming a medium-to-large expected effect size ($f^2 = 0.30$), a power level of 0.80, and up to four potential confounders in the regression model, a minimum of approximately 40 participants was considered sufficient for both correlation and multiple linear regression analyses. This effect-size assumption was informed by prior literature. Meta-analytic evidence indicates that cognitive impairment in schizophrenia is generally observed in the medium-to-large range compared with healthy controls [37], and observational studies have reported small-to-moderate to moderate associations between antipsychotic exposure and cognitive outcomes in related regression analyses [10, 23]. Therefore, a medium effect-size assumption was adopted as a pragmatic choice for sample size estimation, but this should be interpreted cautiously because the prior studies are not directly equivalent to the present multivariable model and small effects may have gone undetected.

Medication dose calculations

To determine total antipsychotic doses, all medications used at the time of the interview were recorded on the case report form. To reduce information bias, medication exposure data were obtained through both medical records and direct reports from patients and, when available, their relatives. Olanzapine-equivalent doses for all antipsychotics were subsequently calculated, and the total daily dose was determined [6, 12].

The one-year cumulative antipsychotic dose was calculated retrospectively by multiplying the daily dose recorded at each follow-up visit by the number of days until the next visit, based on clinic records. In routine clinical practice, follow-up visits were generally scheduled monthly, and medication-related information was routinely documented using previous medical records together with patient report and, when available, caregiver report. When face-to-face visits were delayed or not feasible, follow-up information could also be obtained by telephone. Accordingly, cumulative dose estimates were derived from the available clinical records and reported treatment history rather than from directly verified medication adherence.

Anticholinergic burden was assessed using the Anticholinergic Cognitive Burden (ACB) scale. For each participant, all psychotropic medications—including

antipsychotics, antidepressants, and biperiden—were entered into the ACB calculator, and total burden scores were obtained [4, 24]. A detailed list of anticholinergic burden scores for each medication is provided in Supplementary Table 1.

This study is reported in accordance with the STROBE reporting guideline [11], and the completed STROBE checklist is provided as supplementary material.

Statistical analyses

The independent variables in this study were the patients' sociodemographic and clinical characteristics, including PANSS scores, medication doses at the time of the interview, age at diagnosis, and illness duration. The dependent variable was the MoCA score. The distribution of each variable was assessed using both visual (histogram) and analytical (Shapiro–Wilk test) methods. Correlations were examined using Pearson's test for variables with a parametric distribution and Spearman's test for non-parametric distributions. For Bayesian analyses, Kendall's tau-b was used for nonnormally distributed variables. To account for multiple comparisons, we applied a Benjamini–Hochberg false discovery rate (FDR) correction. Variables showing a statistically significant association with MoCA scores and meeting parametric assumptions were subsequently entered into a multiple linear regression model. A p -value < 0.05 was considered statistically significant.

In addition, we constructed H_0 (independence) and H_1 (correlation) hypotheses and conducted Bayesian analyses to quantify the strength of evidence using Bayes factors (BF10). BF10 values between 1 and 3 indicate anecdotal evidence, 3–10 moderate evidence, 10–30 strong evidence, 30–100 very strong evidence, and > 100 extreme evidence in favor of H_1 (the correlation hypothesis). BF10 values between 1/3 and 1 indicate anecdotal evidence for H_0 , 1/3–1/10 moderate evidence, 1/10–1/30 strong evidence, and 1/30–1/100 very strong evidence supporting the null hypothesis. A prior width of 0.707 was selected because it reflects a conventional medium-effect assumption commonly used in Bayesian correlation analyses.

All analyses were performed using the Jamovi statistical software (version 2.6.44.0).

No missing data were present for the variables included in the analyses; therefore, all analyses were conducted using complete-case data.

Results

Sample

Between 1 January 2024 and 29 February 2024, a total of 501 patients with schizophrenia, schizoaffective disorder or bipolar disorder presented to the Kanuni Sultan Süleyman Training and Research Hospital Küçükçekmece

Community Mental Health Centre. Of these, 194 patients were between 20 and 40 years old. A total of 307 patients were excluded because they were older than 40 years; no patients younger than 20 years were identified.

Among the 194 patients aged 20–40 years, 16 were excluded due to a diagnosis of schizoaffective disorder and 71 due to bipolar disorder. Of the remaining 107 patients with schizophrenia, 16 were excluded because the onset age was below 18 years, 16 due to insufficient educational background, 9 due to an active or past substance use disorder, 9 due to comorbid intellectual disability, and 10 due to systemic or neurological conditions such as epilepsy, familial Mediterranean fever, or renal failure. Six eligible patients declined to participate.

Ultimately, 41 patients volunteered and were included in the study (Fig. 1). Sociodemographic characteristics of the sample are presented in Table 1.

Clinical features and correlation analysis

All patients in the sample were clinically stable outpatients who attended regular follow-up visits and received routine treatment. All were taking second-generation antipsychotics; only one patient was receiving a first-generation antipsychotic (haloperidol) in combination with a second-generation agent. Some patients were using antidepressants. None of the patients were taking benzodiazepines or mood stabilizers. Clinical characteristics, medication use patterns, and scale scores are presented in Table 2.

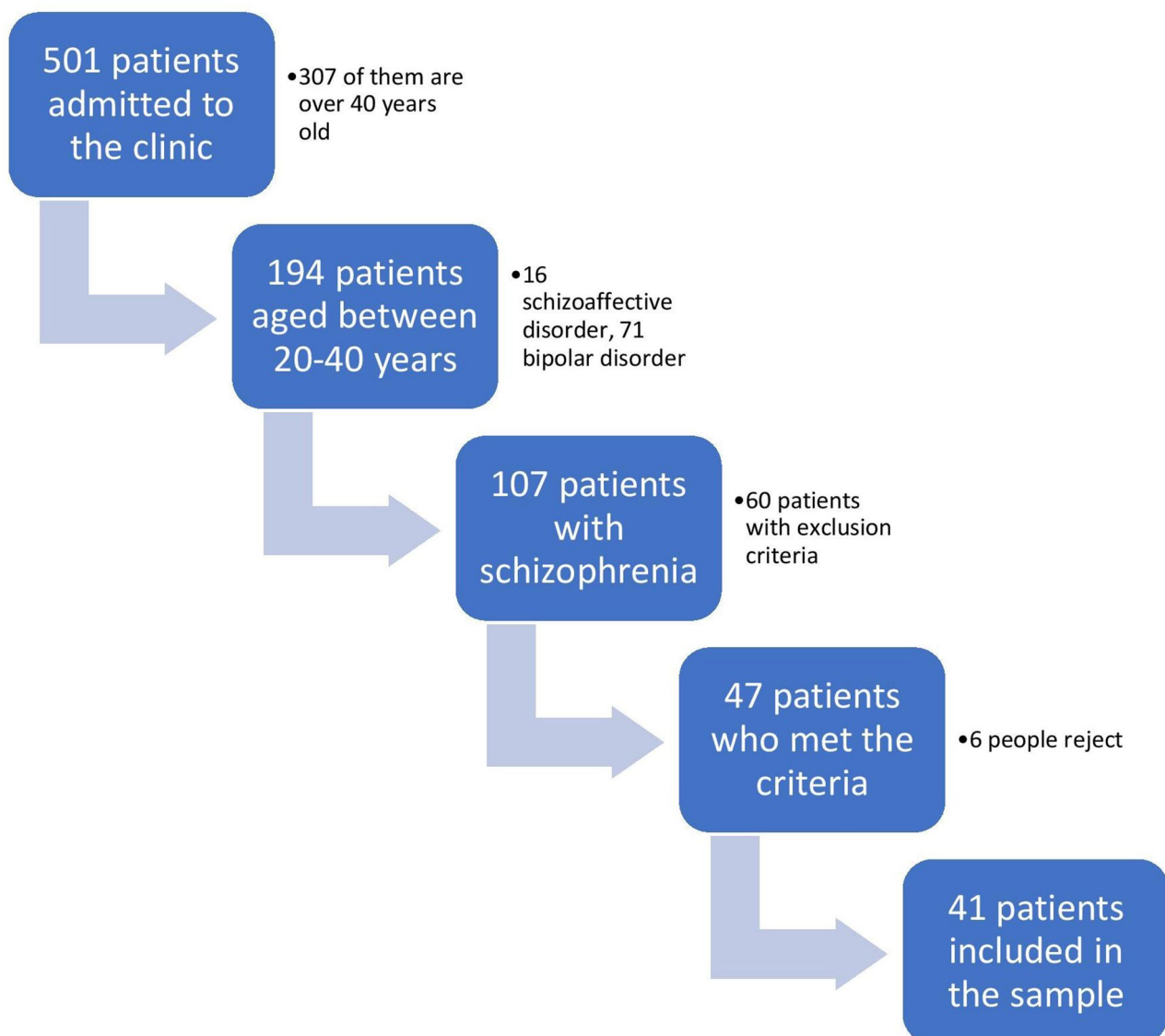


Fig. 1 Sample selection

Table 1 Sociodemographic characteristics of the sample

Variable	Statistic
Age (years)	32.0 ± 4.4 (range: 22–40)
Gender (Male/Female)	32/9
Marital Status (Married/Single or Divorced)	7/34
Duration of Education (years)	11 [IQR: 5] (range: 8–16)
Employment Status (Yes/No)	13/28
Legal Guardianship (Yes/No)	8/33
Smoking Status (Yes/No)	24/17

± standard deviation; IQR: interquartile range

At the time of the assessment, MoCA scores showed no significant correlation with daily antipsychotic dose, the number of antipsychotics used, or cumulative antipsychotic exposure ($r=0.067$, $p=0.675$; $r=0.166$, $p=0.301$;

and $r=0.028$, $p=0.864$, respectively). Similarly, no significant associations were found between MoCA scores and biperiden dose, daily anticholinergic burden, or cumulative anticholinergic burden ($r=0.167$, $p=0.297$; $r=0.097$, $p=0.544$; and $r=0.229$, $p=0.149$, respectively).

In contrast, MoCA scores were negatively correlated with PANSS Positive ($r=-0.327$, $p=0.037$), PANSS Negative ($r=-0.524$, $p<0.001$), PANSS General ($r=-0.564$, $p<0.001$), and PANSS Total scores ($r=-0.659$, $p<0.001$). MoCA scores were positively associated with duration of education ($r=0.429$, $p=0.005$) and age at diagnosis ($r=0.473$, $p=0.002$), and negatively associated with disease duration ($r=-0.559$, $p<0.001$) (Table 3).

Bayesian analyses supported these findings with moderate to extremely strong evidence (BF₁₀=3.487 for

Table 2 Sociodemographic and clinical characteristics of the sample

Variable	Mean ± SD or Median [IQR]	Range
Age at Diagnosis (years)	23.0 [IQR: 4.5]	18–35
Illness Duration (years)	9.3 ± 5.2	1–20
Number of Antipsychotic Agents	2 [IQR: 1]	1–4
Monotherapy/Combination Therapy	13/28	–
Olanzapine Equivalent Dose (mg/day)	26.6 [IQR: 25.7]	1.7–71.0
One-Year Cumulative Dose (mg)	9 737 [IQR: 6 553]	888–28 652
Anticholinergic (Biperiden) Use (Yes/No)	17/24	–
Antidepressant use (Yes/No)	12/29	–
Daily Anticholinergic Burden Score	4 [IQR: 5]	0–9
One-Year Cumulative Burden Score	146 [IQR: 1419]	1–3482
MoCA Total Score	20.2 ± 4.1	10–29
PANSS Positive Subscale	7 [IQR: 4]	7–16
PANSS Negative Subscale	16.6 ± 5.9	7–29
PANSS General Psychopathology Subscale	23 [IQR: 10]	17–42
PANSS Total Score	51.2 ± 12.5	33–80

IQR: interquartile range; ± standard deviation

Table 3 Bivariate correlations (r) between MoCA scores and demographic, clinical, and medication-related variables

Variable	Correlation Coefficient (r)	95% CI	p	Bayes Factor (BF ₁₀)
Daily Antipsychotic Dose ^a	0.067	[-0.209, 0.345]	0.675	0.260
Cumulative Antipsychotic Dose ^a	0.028	[-0.267, 0.306]	0.864	0.554
Biperiden Dose ^a	0.167	[-0.127, 0.455]	0.297	0.504
Daily Anticholinergic Burden ^a	0.097	[-0.232, 0.387]	0.544	0.271
Cumulative Anticholinergic Burden ^a	0.229	[-0.084, 0.502]	0.149	0.554
Number of Antipsychotic Agents ^a	0.166	[-0.084, 0.408]	0.301	0.460
Age	-0.276	[-0.554, 0.075]	0.080	1.010
Duration of Education ^a	0.429**	[0.141, 0.664]	0.005	16.147
Age at Diagnosis ^a	0.473**	[0.175, 0.704]	0.002	34.042
Illness Duration	-0.559**	[-0.753, -0.272]	<0.001	221.570
PANSS Positive Subscale ^a	-0.327*	[-0.573, 0.017]	0.037	3.487
PANSS Negative Subscale	-0.524**	[-0.700, -0.310]	<0.001	82.806
PANSS General Psychopathology Subscale ^a	-0.564**	[-0.771, -0.288]	<0.001	440.944
PANSS Total Score	-0.659**	[-0.794, -0.484]	<0.001	7749.516

BF: Bayes factor; PANSS: Positive and Negative Syndrome Scale. * $p<0.05$; ** $p<0.01$

^a Since the data fit a nonparametric distribution, the Spearman test was used for the classical method, and Kendall's tau-b test was used for the Bayesian calculation. The Pearson test was used for other data for both the classical and Bayesian methods

For all correlation analyses, 95% confidence intervals were calculated via the bootstrap method with 1000 resamples

Table 4 Multiple linear regression analysis predicting cognitive performance (MoCA score)

Predictor	B (Estimate)	95% CI	SE	β (Beta)	t	p
(Intercept)	20.244	-	0.460	-	44.028	< 0.001
PANSS Total	-0.172	[-0.251, -0.085]	0.042	-0.512	-4.052	< 0.001
Disease Duration	-0.345	[-0.594, -0.048]	0.135	-0.440	-2.558	0.015
Antipsychotic Dose	0.023	[-0.030, 0.077]	0.026	0.115	0.881	0.384
Age	0.150	[-0.239, 0.431]	0.150	0.157	1.000	0.324

Model fit: $F(4, 36) = 10.8$, $p < 0.001$, Adjusted $R^2 = 0.496$. No multicollinearity ($VIF = 1.05$ – 2.21); homoscedasticity confirmed (Breusch–Pagan $p = 0.892$)

The dependent variable was the MoCA total score. SE = standard error; β = standardized coefficient

For all correlation analyses, 95% confidence intervals were calculated via the bootstrap method with 1000 resamples

PANSS Positive; 82.806 for PANSS Negative; 440.944 for PANSS General; 7,749.516 for PANSS Total; 16.147 for education duration; 221.57 for disease duration; and 34.042 for age at diagnosis). Variables with $BF_{10} < 1$ provided evidence in favor of the null hypothesis. In particular, the daily antipsychotic dose and daily anticholinergic burden showed moderate evidence for the null hypothesis ($BF_{10} = 0.260$ and 0.271 , respectively), whereas the cumulative antipsychotic dose and cumulative anticholinergic burden provided only anecdotal evidence for the null (both $BF_{10} = 0.554$) (Table 3).

After application of the Benjamini–Hochberg false discovery rate (FDR) correction, only the association between PANSS Positive scores and MoCA lost statistical significance (adjusted $p = 0.069$); all other previously significant correlations remained unchanged.

Intercorrelations among demographic, clinical, and medication-related variables are presented in Supplementary Table 5 (summary correlation matrix), with detailed correlation results provided in Supplementary Tables 2–4.

Regression analysis

Finally, a standard multiple linear regression was conducted with the MoCA score as the dependent variable and PANSS total score, illness duration (years), daily antipsychotic dose (olanzapine equivalents), and age as covariates. PANSS total was selected due to its strong correlations with all PANSS subscales (positive: $r = 0.733$; negative: $r = 0.789$; general: $r = 0.877$; all $p < 0.001$) and its parametric distribution.

Education duration and age at diagnosis were also correlated with illness duration ($r = -0.357$, $p = 0.022$; $r = -0.558$, $p < 0.001$, respectively). However, only illness duration showed a parametric distribution, supporting its inclusion as the primary clinical variable. Although both variables were associated with MoCA scores in the bivariate analyses, adding them to the multivariable model produced aliased coefficients due to linear dependence with age and illness duration, preventing stable estimation. Illness duration also showed the strongest association with MoCA scores, both in terms of correlation magnitude ($r = -0.559$) and Bayes factors ($BF_{10} = 221.57$), providing

substantially stronger evidence than the alternative clinical variables (education duration and age at diagnosis).

Age was retained as a demographic covariate, and daily antipsychotic dose was included as the main predictor. The one-year cumulative dose was excluded because of its strong correlation with daily dose ($r = 0.620$, $p < 0.001$).

Model diagnostics indicated good fit. The model was statistically significant, $F(4, 36) = 10.8$, $p < 0.001$, and explained approximately half of the variance in MoCA scores (adjusted $R^2 = 0.496$). Homoscedasticity was confirmed using the Breusch–Pagan test ($p = 0.892$). No multicollinearity concerns were detected (all $VIFs = 1.05$ – 2.21).

Among the covariates, PANSS total score ($B = -0.172$, $SE = 0.042$, $\beta = -0.512$, $p < 0.001$) and illness duration ($B = -0.345$, $SE = 0.135$, $\beta = -0.440$, $p = 0.015$) significantly predicted cognitive performance. Higher symptom severity and longer duration of illness were associated with lower MoCA scores. However, daily antipsychotic dose ($B = 0.023$, $SE = 0.026$, $\beta = 0.115$, $p = 0.384$) and age ($B = 0.150$, $SE = 0.150$, $\beta = 0.157$, $p = 0.324$) were not significant predictors (Table 4). Bayesian analyses also provided moderate evidence for illness duration ($BF_{10} = 3.71$) and extremely strong evidence for PANSS total score ($BF_{10} = 170.49$).

Discussion

According to our findings, the mean MoCA score in this young sample was below the commonly accepted cutoff of 21 points, indicating that a substantial proportion of patients exhibited cognitive impairment despite their age. There were no statistically significant correlations between MoCA scores and either cross-sectional or one-year cumulative antipsychotic dose, nor with anticholinergic burden. Bayesian analyses likewise supported the null hypothesis with moderate evidence for daily antipsychotic dose and daily anticholinergic burden, while evidence for the null hypothesis regarding cumulative exposures remained anecdotal. In contrast, PANSS scores, age at diagnosis, illness duration, and years of education showed significant associations with cognitive performance, supported by moderate to extremely strong Bayes factors.

Incorporating Bayesian inference provided complementary evidence alongside traditional statistical methods and strengthened the interpretability of our results, particularly given the modest sample size. To our knowledge, Bayesian analysis is still uncommon in the existing schizophrenia literature, and our study contributes to the growing methodological diversification in this field.

There is consistent evidence that cognitive impairment is already present at the first episode of schizophrenia [33]. Cognitive difficulties have also been reported prior to the onset of psychosis and even in some healthy relatives of individuals with schizophrenia [43]. Supporting this view, Solís-Vivanco et al., found that unmedicated patients with first-episode schizophrenia and those with chronic schizophrenia exhibited comparable levels of cognitive impairment [39]. In line with these findings, our results indicate that cognitive deficits are already evident in young patients, despite their relatively early stage in the illness course.

In contrast to our findings, Elie et al., reported that high-dose or combination antipsychotic treatment was associated with poorer cognitive performance. Their study was conducted in 56 inpatients with schizophrenia or schizoaffective disorder, who had higher PANSS scores, and cognition was assessed using the BACS [10]. In a similar study, both inpatients and outpatients were included, the mean PANSS scores were high, and the authors noted that symptom severity may have influenced the results [21]. Another study reporting an inverse relationship between anticholinergic or antipsychotic dose and cognition included patients using mood stabilizers—unlike our sample—and demonstrated that mood stabilizers exerted an independent negative effect on cognitive functioning [16]. Several additional studies in schizophrenia populations have likewise found that poorer cognition is associated with higher antipsychotic or anticholinergic burden [13].

On the other hand, consistent with our results, a meta-analysis of 34 studies found no association between antipsychotic dose and cognition [31]. Similarly, a cross-sectional study of 53 patients with chronic schizophrenia reported no significant differences in cognitive performance between polypharmacy and monotherapy groups or between patients receiving excessive versus standard antipsychotic doses, suggesting that the cognitive effects of antipsychotics may be minimal [25].

In our study, no significant correlation was observed between 1-year cumulative antipsychotic exposure and cognitive performance. By contrast, a study with a shorter follow-up period found that reducing antipsychotic dose within the first five years of illness improved cognitive scores over six months [38]. Two studies with longer follow-up durations—one over nine years and the other across the lifetime—reported that higher cumulative

exposure predicted poorer cognitive outcomes [22, 23]. Differences in follow-up duration, the younger age of our sample, and the shorter window of cumulative exposure may partly account for these discrepancies. Cognitive assessment methods also varied. Importantly, in the 2016 Husa et al., study, the association between cumulative dose and cognition disappeared after controlling for disorganization symptoms and school performance at age 16. This finding supports our decision to exclude patients with early-onset illness, low education, or comorbid intellectual disability to reduce potential confounding.

Studies examining the effects of antipsychotic dose and anticholinergic burden on cognition in schizophrenia have yielded mixed results. Much of this variability appears to arise from three major sources: differences in sample characteristics (e.g., inclusion of diagnoses other than schizophrenia, variable age distributions, inpatient vs. outpatient status, or concomitant mood stabilizer use); differences in cognitive assessment tools; and heterogeneity in antipsychotic treatment profiles. Many earlier studies included clinically complex or heterogeneous samples, used cognitive batteries with varying sensitivity across cognitive domains, or involved treatment regimens with substantial pharmacodynamic variability. In addition, psychotropic medications may influence cognitive functioning through mechanisms beyond anticholinergic burden, including dopaminergic, serotonergic, or sedative effects, which further complicates the interpretation of medication-related cognitive findings.

In designing our study, we sought to minimize these sources of heterogeneity by applying strict exclusion criteria and recruiting a relatively young, clinically stable outpatient sample. This approach reduced clinical heterogeneity and may have limited the influence of some confounding factors observed in earlier studies, thereby allowing a more focused descriptive examination of the dose-cognition relationship within a relatively homogeneous clinical context. Furthermore, the 1-year cumulative dose was calculated as precisely as possible through detailed review of medical records, strengthening the reliability of exposure estimates.

From a clinical perspective, our findings suggest that, in young and clinically stable patients, antipsychotic dosage may not be a major determinant of cognitive performance. This may alleviate clinicians' concerns about compromising cognition when titrating antipsychotics to achieve optimal symptom control. However, the lack of a dose-cognition association in this sample should not be interpreted as evidence that antipsychotics have no cognitive impact. The strong negative association between illness duration and MoCA scores indicates that long-term disease burden and cumulative treatment exposure may contribute to cognitive outcomes. The interplay between chronic illness trajectory, cumulative medication

exposure, and neurobiological processes likely shapes the cognitive profile observed in schizophrenia. Therefore, treatment decisions should continue to rely on individualized risk–benefit assessments, and our findings should be interpreted within the broader longitudinal context of the disorder rather than as a definitive statement regarding the cognitive safety of antipsychotics. Longitudinal research is needed to clarify how medication exposure influences cognitive trajectories over time.

In a cross-sectional study conducted by Yang et al., in 64 patients with schizophrenia, total MoCA scores were not associated with age, sex, or years of education [44]. Another study, however, reported significant associations between MoCA scores, age, and education level [14]. In our study, no significant relationship was observed between current age and MoCA performance, likely because the sample consisted exclusively of younger adults. Consistent with the literature, MoCA scores increased with longer duration of education [35].

Several studies examining cognitive impairment across different domains have shown that patients with more severe cognitive deficits tend to have an earlier age of illness onset than cognitively preserved patients [27]. Individuals with early-onset schizophrenia typically exhibit more pronounced cognitive impairment, whereas those with late-onset illness often demonstrate relatively preserved functioning [34]. Deficits—particularly in memory-related areas—are more strongly associated with early onset [20]. For this reason, excluding patients with very early-onset illness in our study contributed to a more homogeneous sample.

Other studies comparing patients across different IQ levels have reported that individuals with greater cognitive impairment tend to have longer disease durations than cognitively healthier patients [5]. One study found that patients with more than two years of illness exhibited greater cognitive dysfunction [41]. In a study conducted in Lebanon with 120 patients diagnosed with schizophrenia, longer illness duration was significantly associated with lower MoCA scores [15]. Our findings likewise showed that higher age at diagnosis and shorter illness duration were related to better cognitive performance.

Research in schizophrenia has demonstrated that both negative symptoms and cognitive deficits share similarities in terms of early onset, persistence over time, and association with functional impairment—suggesting a link between these two symptom domains [18]. A systematic review of 58 studies (5009 individuals) found that higher levels of negative symptoms were associated with poorer cognitive functioning, whereas positive symptoms showed no consistent relationship [9]. Conversely, another study reported that cognitive function was more strongly associated with positive symptoms [1]. In our study, cognitive functioning was related to both

positive and negative symptoms, though the association was stronger for negative symptoms. These results are broadly consistent with findings from the prior literature.

Our study has several limitations. First, the sample was small and demographically unbalanced. Although an *a priori* power analysis indicated that the minimum required sample size was achieved, the limited number of participants may still have reduced our ability to detect weak associations. In addition, the predominance of young, male, unemployed, and unmarried patients limits the representativeness and generalizability of the findings. While the correlation coefficients were very close to zero—suggesting that strong relationships are unlikely even in a larger sample—some subtle effects may nonetheless have remained undetected.

Second, the cross-sectional design precludes any causal inferences regarding the relationship between antipsychotic dose and cognitive function and does not rule out the possibility of reverse causality. We used numerous exclusion criteria to minimize confounding in our sample, which further limits generalizability but allowed us to obtain a more homogeneous clinical group and better isolate the associations of interest.

Third, one year may be a relatively short period for calculating cumulative antipsychotic exposure. Moreover, the intertwined nature of illness duration and treatment duration makes it difficult to determine whether long-term cognitive changes arise from disease burden itself or cumulative treatment effects.

Fourth, cognitive performance was assessed solely with the MoCA, which—despite its sensitivity—does not provide a detailed evaluation of specific cognitive domains (e.g., executive function, verbal fluency, working memory). In addition, the use of olanzapine equivalents does not fully account for pharmacodynamic heterogeneity among antipsychotic medications, which may exert distinct cognitive effects despite equivalent dosing. Furthermore, because a substantial proportion of patients were receiving more than one antipsychotic, drug-specific cognitive effects could not be meaningfully separated, and our sample size did not permit comparisons across individual agents. Taken together, the use of an olanzapine-equivalent dose-based approach in combination with a global screening tool such as the MoCA may limit the ability to draw firm conclusions regarding the cognitive effects of antipsychotics, particularly with respect to potential dose-related associations.

Finally, inaccuracies in self-reported or caregiver-reported medication histories are common in clinical settings. Although medication-related information was cross-checked with available medical records, some degree of misreporting is still possible. In addition, one-year cumulative antipsychotic exposure was estimated retrospectively from routine clinical records and reported

treatment history and may not fully reflect actual medication intake, as adherence could not be independently verified and follow-up intervals were not always uniform. Nevertheless, given that all patients were clinically stable and regularly followed at the Community Mental Health Center, the likelihood of substantial exposure misclassification is probably lower than average.

Conclusions

Our findings are consistent with the view that cognitive impairment may emerge early in patients with schizophrenia and appears more strongly associated with illness duration and the severity of psychotic symptoms than with antipsychotic medication dosage. Although we did not observe a significant association between cognitive scores and antipsychotic dose in a relatively young sample within the constraints of a cross-sectional observational design, these results should be interpreted with caution and do not exclude the possibility of long-term cognitive effects of treatment. Nevertheless, within the clinical context of our findings, concerns about cognitive side effects alone should not automatically preclude the use of adequately therapeutic doses when required for symptom control. Ongoing monitoring of cognitive functioning remains essential, and longitudinal studies with larger, more diverse samples are needed to clarify the temporal and causal relationships among illness progression, treatment exposure, and cognitive outcomes.

Abbreviations

ACB	Anticholinergic Cognitive Burden
BF10	Bayes factor
CI	Confidence interval
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FDR	False discovery rate
IQR	Interquartile range
MoCA	Montreal Cognitive Assessment
PANSS	Positive and Negative Syndrome Scale
SD	Standard deviation
STROBE	Strengthening of Reporting of Observational Studies in Epidemiology
VIF	Variance inflation factor

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12888-026-08086-x>.

Supplementary Material 1

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Author contributions

Study conceptualization and design: ÖÖ, NT, EK, FU. Data collection: ÖÖ. Analysis and interpretation of results: ÖÖ. Manuscript preparation: ÖÖ, NT, EK, FU. All authors reviewed the results and approved the final version of the manuscript.

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Data availability

The datasets analysed during the current study are not publicly available due to patient privacy and institutional restrictions but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. All procedures involving human subjects/patients were approved by the Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee with the letter number 2023.12.176. Written informed consent was obtained from all participants prior to their inclusion in the study. For patients under legal guardianship, written consent was also obtained from their guardians.

Consent for publication

Not applicable.

Generative AI disclosure

During the preparation of this work, the authors used ChatGPT (OpenAI) to improve the readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the final version. All scientific content, analyses, and interpretations were developed solely by the authors.

Competing interests

The authors declare no competing interests.

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