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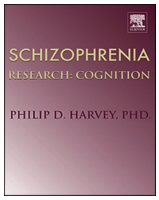

Anticholinergic load: A commonly neglected and preventable risk to cognition during schizophrenia treatment?

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ABSTRACT

Background: Cognitive impairment is a widespread feature of schizophrenia, affecting nearly 80 % of patients. Prior research has linked the anticholinergic burden of psychiatric medications to these cognitive deficits. However, the impact of the anticholinergic burden from medications for physical morbidity remains underexplored. This study aimed to evaluate the anticholinergic burden of psychiatric and physical medications in patients with schizophrenia and assess its impact on cognitive function.

Methods: A total of 178 patients with schizophrenia were recruited. The assessments included an *ad hoc* questionnaire for collecting demographic and clinical data. Anticholinergic burden was evaluated using the cumulative Drug Burden Index (cDBI) for each participant, and cognitive function was assessed using MATRICS. Psychopathology was measured using the PANSS, CDSS, CAINS, and the CGI-S. Statistical analysis included Student's *t*-tests, ANOVA, Pearson correlations, and multiple linear regressions.

Results: The average cDBI was 1.3 (SD = 0.9). The model developed explained 40.80 % of the variance. The variable with the greatest weight was the cDBI (B = −11.148, $p = 0.010$). Negative-expression (B = -2.740, $p = 0.011$) and negative-experiential (B = −1.175, $p = 0.030$) symptoms were also associated with lower global cognitive score. However, more years of education (B = 5.140, $p < 0.001$) and cigarettes per day (B = 1.331, $p < 0.001$) predicted a better global cognitive score.

Conclusion: This study identified specific predictors of global cognition in schizophrenia, with anticholinergic burden emerging as the strongest factor. Our findings underscore the importance of considering the anticholinergic burden of treatments, in addition to negative symptoms, when designing interventions to optimize or maintain cognitive function in patients with schizophrenia.

1. Introduction

The presence of positive and negative symptoms has traditionally defined schizophrenia. However, cognitive impairment has also become a defining characteristic of the disorder, as it affects almost 80 % of patients with schizophrenia (Allen et al., 2003; Keefe et al., 2005). These deficits primarily affect cognitive domains such as attention, working memory, speed of processing, learning, and social cognition (Gebreegziabhere et al., 2022; Harvey et al., 2004). Moreover, cognitive deficits persist throughout the disorder, even before its onset and after symptomatic remission (Kahn and Keefe, 2013; Kahn, 2020).

Despite the significant impact of this cognitive impairment on patient functioning (Kharawala et al., 2022; Garcia-Portilla et al., 2021), no effective treatment has yet been approved. As a result, researchers have become increasingly interested in identifying the factors associated with cognition in these patients (McCutcheon et al., 2023). Studies have demonstrated that multiple factors have an impact on cognition, including clinical variables such as duration of untreated psychosis, length of illness, and psychopathological factors, e.g., negative and disorganized symptoms (Gebreegziabhere et al., 2022; Gracia et al.,

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2009; Mu et al., 2020). Moreover, treatment-related factors and substance use also play an essential role (Gebreegziabhere et al., 2022).

Regarding medications, although antipsychotics improve positive psychotic symptoms, high doses have been associated with increased cognitive deficits (Georgiou et al., 2021; Kim et al., 2019). There are several explanations for how antipsychotic drugs may contribute to cognitive impairment, the most common being their anticholinergic burden (Chahine, 2023; Haddad et al., 2023; Joshi et al., 2021; Kim et al., 2019; Minzenberg et al., 2004; Rehse et al., 2016; Spohn and Strauss, 1989; Verdoux et al., 2021; Vinogradov et al., 2009). In the short term, anticholinergic drugs may induce confusion and memory loss; while, in the long term, they increase the risk of dementia (Coupland et al., 2019; Gray et al., 2015; Villalba-Moreno et al., 2016).

It is important to note that anticholinergic burden extends beyond psychiatric drugs, as several medications for physical morbidity also possess anticholinergic properties (López-Álvarez et al., 2019). This is particularly concerning for patients with schizophrenia, who face an increased risk of physical health problems (Baandrup, 2020; Chan et al., 2022; Filipčić et al., 2020; Kugathasan et al., 2020). Specifically, Kugathasan et al. (2020) found that 64 % of patients with schizophrenia had physical multimorbidity, with endocrine and neurological disorders being the most prevalent (Chan et al., 2022; Kugathasan et al., 2020). Consequently, a significant proportion of schizophrenia patients require pharmacological treatment for physical morbidity, often involving complex polypharmacy regimens (Filipčić et al., 2020).

Nevertheless, to the best of our knowledge, few studies have comprehensively examined the impact of the anticholinergic burden of psychiatric and physical drugs on cognition in these patients. Additional research on this topic would allow us to formulate more precise prescribing guidelines and identify variables that will improve cognitive interventions. Thus, the present study aims to describe the anticholinergic burden of medications, both psychiatric and physical, and to analyse the impact of anticholinergic burden on the global cognition and on the different cognitive domains affected by patients with schizophrenia. In addition to the anticholinergic burden, sociodemographic, clinical, and psychopathological characteristics are also incorporated into the analysis, thus offering a comprehensive understanding of the factors influencing cognition. We hypothesize that the impact of anticholinergic load will be among the most significant on cognition, even greater than psychopathology.

2. Method

2.1. Design

This is a secondary-analysis, naturalistic, cross-sectional study that aims to develop a staging model for schizophrenia (Martínez-Cao et al., 2024). The study followed the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. It was approved by the Clinical Research Ethics Committee of Hospital Universitario Central de Asturias (protocol numbers Ref. 36/2012, 25/2014). Written informed consent was obtained from all participants before enrolment.

2.2. Patients

Of the 212 patients with schizophrenia who participated in the original study, 178 were selected based on availability in the literature of the anticholinergic load scores of their medications. The inclusion criteria were as follows: (1) individuals diagnosed with schizophrenia according to the ICD-10 (International Classification of Diseases 10th Edition); (2) over 17 years of age; and (3) providing written informed consent for study participation.

The exclusion criteria were intentionally kept minimal to ensure a heterogeneous and representative sample. Consequently, the study excluded only individuals with intellectual developmental disabilities or acquired brain injuries.

2.3. Assessment

Comprehensive assessments of all participants were conducted by trained psychologists. These assessments included an *ad hoc* questionnaire with demographic and clinical information, such as duration of illness, number of hospitalizations, and substance consumption.

In addition, the assessments included the Spanish versions of the following instruments:

2.3.1. Psychopathology

Positive and Negative Syndrome Scale (PANSS) (Peralta and Cuesta, 1994), Clinical Assessment Interview of Negative Symptoms (CAINS) (Valiente-Gómez et al., 2015), and Calgary Depression Scale for Schizophrenia (CDSS) (Sarró et al., 2004).

To assess negative symptoms, we calculated the Marder Negative Factor (PANSS-MNF) scores. The PANSS-MNF includes all items of the PANSS Negative subscale (PANSS-N) except for difficulty in abstract thinking and stereotyped thinking. Furthermore, the PANSS-MNF includes motor retardation and active social avoidance from the PANSS General Psychopathology subscale (PANSS-GP). Additionally, we employed the CAINS scale, which focuses on the patient's subjective experience of negative symptoms. The CAINS scale comprises two different subscales: motivation and pleasure (MAP), which assesses abulia and anhedonia, and emotional expression (EXP), which measures alogia and blunted affect. It provides scores for each subscale and a total score obtained by combining the two subscale scores, with higher scores indicating greater symptom severity.

2.3.2. Global severity

We used the score on the Clinical Global Impression-Schizophrenia Severity scale (CGI-S) (Haro et al., 2003) to assess the severity of the disorder.

2.3.3. Cognition

We employed the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MATRICS-CCB) (Rodriguez-Jimenez et al., 2012), which consists of 10 tests that assess seven cognitive domains: Speed of Processing (Trail Making Test: Part A; Brief Assessment of Cognition in Schizophrenia: Symbol Coding and Category Fluency Test: Animal Naming); Attention/Vigilance (Continuous Performance Test: Identical Pairs); Working Memory (Wechsler Memory Scale Spatial Span-III and Letter-Number Span Test); Verbal Learning (Hopkins Verbal Learning Test-Revised); Visual Learning (Brief Visuospatial Memory Test-Revised); Reasoning/Problem-Solving (Neuropsychological Assessment Battery: Mazes); and Social Cognition (Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions [D and H sections]). We first obtained the raw score for each of the subtests. Then, we transformed the raw scores, according to age and sex, into t-scores. Finally, we summed the t-scores from each domain and transformed them into a global cognitive score (range: 20–80) using the tables provided by MATRICS.

2.3.4. Anticholinergic burden scores

The mean-daily-dose-related anticholinergic burden was calculated using the Drug Burden Index (DBI) scale (Hilmer et al., 2007). The DBI is the only anticholinergic burden scale that takes into account doses of medications with anticholinergic properties, making it a more accurate measure. The DBI score ranges from 0 to 1, with a higher score indicating greater anticholinergic burden. In our study, we calculated the DBI for each of the drugs prescribed to each participant. Then, the scores for each medication were combined to obtain a total or cumulative DBI for each participant (cDBI). These scores were calculated as a continuous variable and then transformed into a categorical variable with three exposure levels: score 0 (none), score < 1 (low), and score ≥ 1 (high). This reflects categories previously used in the literature (Chahine, 2023; O'Connell et al., 2018; Hilmer et al., 2007; Hilmer et al., 2009; Best et al.,

2013).

To calculate the DBI, we used the "Anticholinergic Burden Calculator" available on the website: https://www.anticholinergicscales.es/ (Tristancho-Pérez et al., 2022; Villalba-Moreno et al., 2016). This online calculator allows quick and easy calculation of a patient's anticholinergic load based on their medications (see Table 1).

2.4. Statistical Analysis

Data were analyzed using IBM SPSS Version 27.0.1.0 (IBM Corp., Armonk, NY). The two-tailed level of significance was set at <0.050. Data are presented as mean (standard deviation [SD]) for continuous variables and as frequencies and percentages for categorical variables. To explore the relationships between global cognitive score and sociodemographic, clinical, and psychometric variables versus cDBI, we used Student's *t*-tests and ANOVA with Duncan's *post hoc* test or bivariate Pearson correlations. Finally, to model the relationships between global cognitive score and all variables found to be significantly associated with it in the univariate analysis, we performed a multiple linear regression (forward stepwise regression). These analyses were independently repeated for each cognitive domain of the MATRICS (Supplementary Materials). We excluded total scale scores or any redundant measures from the regression analyses to avoid collinearity. We also calculated the variance inflation factor (VIF) to diagnose collinearity, with values below 5 indicating no collinearity.

Table 1
Frequencies of drugs with anticholinergic properties.

Variables	n (%)
Antipsychotics	
No. of antipsychotics [mean (sd)]	1.30 (0.71)
None	12 (6.74)
One antipsychotic	114 (64.00)
Two antipsychotics	41 (23.00)
More than two antipsychotics	11 (6.20)
Paliperidone	92 (51.70)
Aripiprazole	40 (22.50)
Olanzapine	39 (21.90)
Risperidone	25 (14.03)
Quetiapine	15 (8.42)
Clozapine	11 (6.20)
Fluphenazine	3 (1.70)
Haloperidol	2 (1.12)
Levomepromazine	2 (1.12)
Ziprasidone	1 (0.60)
Antidepressants	
Antidepressants (yes)	39 (21.90)
Escitalopram	14 (7.90)
Mirtazapine	6 (3.40)
Sertraline	6 (3.40)
Paroxetine	3 (1.70)
Clomipramine	3 (1.70)
Amitriptyline	2 (1.12)
Maprotiline	1 (0.60)
Vortioxetine	1 (0.60)
Citalopram	1 (0.60)
Duloxetine	1 (0.60)
Trazodone	1 (0.60)
Bupropion	1 (0.60)
Venlafaxine	1 (0.60)
Benzodiazepines	
Benzodiacepines (yes)	73 (41.00)
Lorazepam	43 (24.15)
Clonazepam	11 (6.20)
Clorazepate	10 (5.70)
Diazepam	8 (4.50)
Alprazolam	2 (1.12)
Ketazolam	1 (0.60)
Flurazepam	1 (0.60)
Other psychotropic treatments	
Biperiden	18 (10.11)
Acid Valproic	4 (2.24)
Gabapentin	3 (1.70)
Lithium	1 (0.60)
Oxcarbazepine	1 (0.60)
Trihexyphenidyl	2 (1.12)
Somatic treatments	
Bromocriptine	1 (0.60)
cDBI score [mean (sd)]	1.31 (0.94)
None (0)	8 (4.50)
Low <1	75 (42.10)
High ≥1	95 (53.40)

cDBI: Cumulative Drug Burden Index.
Note: The DBI values of each drug have not been collected since they depend on the dose of the drug. To calculate the DBI, we used the "Anticholinergic Burden Calculator" available on the website: *https://www.anticholinergicscales.es/*

3. Results

3.1. Sociodemographic and clinical characteristics

The mean age of the patients was 39.2 (12.9), 66.3 % were males, and 58.4 % had a secondary school degree. Most of the patients were never married (74.2 %) and not working (68.5 %), and more than a third were receiving mental disability benefits (34.8 %). Additional clinical and sociodemographic data can be found in Supplementary Table 1.

The pharmacological medications with anticholinergic burden are detailed in Table 1. Most of the sample (64 %) were taking one antipsychotic, 23 % two antipsychotics, and 6.2 % more than two. In addition, 41 % of them were also taking benzodiazepines and 21.9 % were taking antidepressants. Regarding anticholinergic burden scores, more than half of the sample had a cDBI score greater than one (53.4 %). Furthermore, the average cDBI of our sample was 1.3 (0.9) (Table 1). Only bromocriptine was the physical treatment with anticholinergic properties (see Table 1). The more frequently physical treatments prescribed were statins, oral antidiabetics, diuretics, and acetaminophen.

Psychometric test scores indicate that the patients in our study had predominantly negative symptoms, minimal signs of positive and depressive symptomatology, and poor performance on the seven cognitive dimensions assessed by MATRICS (see Table 2). The mean global cognitive score was 31.7 (12.4), corresponding to the 3.6th

Table 2
Psychometric and cognitive scores of the sample.

Variables	Mean (sd)
Psychometric scores	
PANSS-Positive	12.86 (5.24)
PANSS-Negative	17.96 (5.56)
PANSS-Marder Negative Factor	17.84 (6.04)
PANSS-General Psychopathology	29.17 (7.50)
CAINS-Total	27.21 (12.46)
CAINS-MAP	20.51 (9.14)
CAINS-EXP	6.70 (4.55)
CDSS	2.70 (3.87)
CGI-Global	4.15 (0.94)
Cognition scores (MATRICS)	
Speed of Processing	32.48 (14.92)
Attention/Vigilance	33.97 (11.19)
Working Memory	38.76 (13.23)
Verbal Learning	38.95 (10.27)
Visual Learning	36.37 (13.88)
Reasoning/Problem-Solving	37.00 (9.49)
Social Cognition	42.18 (16.97)
Global Cognition	31.74 (12.43)

sd: standard deviation; PANSS: Positive and Negative Syndrome Scale; CAINS: Clinical Assessment Interview for Negative Symptoms; CAINS-EXP: Expression subscale; CAINS-MAP: Motivation and Pleasure subscale; CDSS: Calgary Depression Scale for Schizophrenia; CGI: Clinical Global Impression-Severity; MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia.

percentile. Furthermore, on average, the mean severity level for our sample was 4.1 (sd = 0.9).

3.2. Predictors of global cognition

As shown in Tables 3 and 4, several independent variables were significantly associated with the patient global cognitive score. Individuals with higher levels of education and who used tobacco and alcohol were associated with higher cognitive scores (Table 3). Furthermore, all the variables involving negative symptoms showed the strongest correlations, followed by global severity, general psychopathological symptoms, the cDBI, length of illness, age, and number of cigarettes per day (CPD) (Table 4).

After verifying that there was no collinearity, all variables significantly related to global cognition were included in the multiple linear regression. Our model explained 40.80 % of the variance ($R^2 = 0.408$, standard error of the estimate = 49.392), and the model was a significant predictor of global cognition [$F(5,172) = 25.359$, $p < 0.001$]. The variables retained in our model are shown in Table 5. The variable with the greatest weight was cDBI (B = -11.148, $p = 0.010$). With respect to negative symptoms, the CAINS-EXP (B = −2.740, $p = 0.011$) and the CAINS-MAP (B = -1.175, $p = 0.030$) subscales were associated with lower global cognitive scores. However, more years of education (B = 5.140, $p < 0.001$) and a higher number of CPD (B = 1.331, p < 0.001) predicted a better global cognitive score (see Table 5).

3.3. Predictors of cognitive domains

The results of the univariate analysis for each cognitive domain can be found in Supplementary Tables 2 and 3. After verifying that there was no collinearity, multiple linear regression models included all variables significantly related to each cognitive domain (Supplementary Table 4). The variable years of education remained a significant predictor in the regression models for all cognitive domains, except for Reasoning/Problem-Solving. In terms of clinical variables, we found that length of illness was negatively associated with Social Cognition (B = -0.325, $p = 0.002$), and history of hospitalizations was the variable with the most significant weight in Verbal Learning (B = -3.285, $p = 0.023$), indicating that hospitalizations were associated with poorer performance in this cognitive domain.

Table 4
Person's correlations between global cognitive score and independent (continuous) variables.

Variables	Statistical test[a]	p
Years	−0.201	0.007
Length of illness	−0.231	0.002
Years of education	0.458	<0.001
No. of hospitalizations	−0.131	0.082
No. of suicide attempts	0.017	0.820
No. of coffee (daily)	0.109	0.146
CPD	0.201	0.007
SDU (weekly)	0.072	0.343
cDBI	−0.272	<0.001
PANSS-Positive	−0.120	0.110
PANSS-Negative	−0.454	<0.001
PANSS-Marder Negative Factor	−0.401	<0.001
PANSS-General Psychopathology	−0.307	<0.001
CAINS-Total	−0.506	<0.001
CAINS-MAP	−0.466	<0.001
CAINS-EXP	−0.449	<0.001
CDSS	−0.029	0.705
CGI-Global	−0.452	<0.001

MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia; CPD: Cigarettes Per Day; SDU: Standard Drink Unit; cDBI: Cumulative Drug Burden Index; PANSS: Positive and Negative Syndrome Scale; CAINS: Clinical Assessment Interview for Negative Symptoms; CAINS-MAP: Motivation and Pleasure subscale; CAINS-EXP: Expression subscale; CDSS: Calgary Depression Scale for Schizophrenia; CGI: Clinical Global Impression-Severity.
[a] Bivariate Pearson Correlation.

Regarding substance consumption, tobacco use emerged as a predictive variable with substantial influence on Speed of Processing (B = 4.239, $p = 0.047$). CPD also emerged as a predictor in Attention/Vigilance (B = 0.207, $p = 0.003$) and Working Memory domains (B = 0.287, $p < 0.001$). It should be noted that the cDBI emerged as a predictive variable only for Working Memory, with the greatest impact on this domain (B = −2.626, $p = 0.007$).

In terms of psychopathology, negative symptoms were consistently associated with poorer performance across all cognitive domains. Specifically, the CAINS-EXP and CAINS-MAP subscales were significant predictors for Verbal and Visual Learning. The CAINS-EXP also extended

Table 3
Associations between global cognitive score and independent (categorical) variables.

Variables	Categories	Global cognitive score (sd)	Statistical test, p
Sex	Males	256.30 (62.96)	−1.005[a], 0.316
	Females	266.52 (66.50)	
Marital status	Never Married	264.46 (65.67)	1.669[a], 0.097
	Married	246.22 (58.22)	
Educational level	Primary school	215.44 (44.32)	18.242[b], <0.001 Primary≠Secondary≠Post−secondary
	Secondary school	263.03 (62.62)	
	Post-secondary school	297.03 (60.11)	
Work status	Working	271.18 (55.62)	0.949[b], 0.389
	Not working	267.79 (67.24)	
	Homemaker or student	267.79 (10.73)	
Mental disability benefit	No	269.63 (62.31)	2.868[a], 0.056
	Yes	241.25 (63.99)	
Suicide attempts	No	260.16 (65.43)	0.210[a], 0.834
	Yes	257.30 (57.33)	
Hospitalizations	No	274.35 (67.56)	1.912[a], 0.057
	Yes	254.04 (62.14)	
Coffee use	No	252.16 (65.94)	−1.364[a], 0.174
	Yes	265.40 (62.55)	
Tobacco use	No	251.01 (63.12)	−2.076[a], 0.039
	Yes	270.95 (64.16)	
Alcohol use	No	251.66 (60.38)	−2.663[a], 0.008
	Yes	279.35 (69.30)	

sd: standard deviation.
[a] Student T-test.
[b] Anova.

Table 5
Multiple linear regression model predicting global cognitive score.

Variables	B	SE	Beta	t	*p*	VIF
Intersection	234.593	18.038		13.006	<0.001	
Years of education	5.140	0.860	0.368	5.974	<0.001	1.134
CPD	1.331	0.348	0.227	3.820	<0.001	1.056
cDBI	−11.148	4.279	−0.165	−2.605	0.010	1.197
CAINS-EXP	−2.740	1.064	−0.194	−2.576	0.011	1.702
CAINS-MAP	−1.175	0.538	−0.167	−2.186	0.030	1.752

SE: Standard Error; VIF: Variable Inflation Factors; CPD: Cigarettes Per Day; cDBI: Cumulative Drug Burden Index; CAINS: Clinical Assessment Interview for Negative Symptoms; CAINS-EXP: Expression subscale; CAINS-MAP: Motivation and Pleasure subscale.

its predictive influence to the Speed of Processing and Attention/Vigilance domains (Supplementary Table 4). The CAINS-MAP was also associated with Working Memory (B = -0.328, $p = 0.002$). Furthermore, the PANSS-MNF emerged as a significant predictor in Social Cognition (B = -0.526, $p = 0.009$) and was the sole predictor variable for Reasoning/Problem-Solving (B = -0.462, $p < 0.001$). Lastly, positive symptoms emerged as predictors of decreased performance for Attention/Vigilance (B = -0.418, $p = 0.004$).

4. Discussion

To our knowledge, this is one of the few studies to analyze the impact of anticholinergic load from both psychiatric and physical medications on global cognitive performance in patients with schizophrenia. As we hypothesized, anticholinergic load was the main predictor of global cognitive score. Regarding psychopathology, negative symptoms were the only psychopathological dimension that predicted global cognitive performance, and expressive negative symptoms exhibited a greater impact than experiential ones.

Our study also identified several sociodemographic and clinical characteristics that emerged as significant predictors of cognitive performance. Among these factors, educational level emerged as a significant predictor of cognitive performance, positively associated with both global cognition and most cognitive domains. This finding does not surprise us, since the association between educational level and cognition is a well-established fact, supported by a wealth of scientific evidence (Ayesa-Arriola et al., 2016; Ayesa-Arriola et al., 2023; Cámara et al., 2021; Lövdén et al., 2020). Regarding clinical characteristics associated with cognition, a history of psychiatric hospitalization was associated with poorer performance in Verbal Learning, consistent with prior findings linking a higher number of hospitalizations to diminished Verbal Learning (Hori et al., 2020). Additionally, our study revealed an association between more extended illness duration and impaired Social Cognition. While Social Cognition is generally considered to remain relatively stable during schizophrenia (Green et al., 2012), deficits in recognition of emotions and reading of facial expressions are influenced by the chronic course of the disorder (García et al., 2018; Green and Leitman, 2008; Ntouros et al., 2018).

Cumulative anticholinergic load, as measured by the DBI, emerged as the most critical predictor of global cognitive score. This finding aligns with growing evidence suggesting that anticholinergic medications negatively impact global cognitive function in patients with schizophrenia (Chahine, 2023; Haddad et al., 2023; Joshi et al., 2021; Kim et al., 2019; Minzenberg et al., 2004; Rehse et al., 2016; Spohn and Strauss, 1989; Verdoux et al., 2021; Vinogradov et al., 2009). In addition to antipsychotics, our patients also received antidepressants and benzodiazepines for comorbid symptoms, and these medications, as well as antiparkinsonian drugs prescribed to manage extrapyramidal side effects, further contribute to cumulative anticholinergic burden (Chakos et al., 2006; Durán et al., 2013; Salahudeen et al., 2015; Su et al., 2017). However, although the cDBI emerged as the main predictor of global cognition, its predictive value was limited to a single cognitive domain: Working Memory. These findings are consistent with previous research demonstrating the cholinergic system's modulation of Working Memory neurocircuits (Furey et al., 2000; Newman et al., 2012; Störmer et al., 2012). In further support of this association, a recent neuroimaging study by Selvaggi et al. (2023) revealed that higher anticholinergic load was associated with reduced brain activity in the frontoparietal network and lower performance during Working Memory tasks. These findings emphasize the critical role of anticholinergic load in modulating Working Memory performance, a central component of executive functions.

Considering the high prevalence of multimorbidity in schizophrenia patients (Baandrup, 2020; Chan et al., 2022; Filipčić et al., 2020; Kugathasan et al., 2020), we also took their medications for physical morbidity into account when calculating cumulative anticholinergic burden. However, bromocriptine was the only physical medication with an anticholinergic load the DBI identified in our sample. The low prevalence of such medications with anticholinergic burden in our study could be attributed to several reasons. First, the anticholinergic loads of certain drugs, such as metformin, remain unclear. While generally considered a non-anticholinergic medication, metformin has been shown to exhibit anticholinergic activity at high doses (Chew et al., 2008). Second, our sample's relatively young mean age suggests a reduced risk of physical comorbidities and, therefore, medications. This demographic characteristic may contribute to our study's limited prevalence of such anticholinergic-loaded medications. Finally, the physical well-being of individuals with severe mental illnesses has historically been neglected, and this persists even today (Kisely et al., 2009; Nasrallah et al., 2006; Roberts et al., 2007; Peritogiannis et al., 2022; Tidemalm et al., 2008; Vancampfort et al., 2019). As Hert et al. (2011) noted, patients with severe mental disorders continue to face challenges in accessing and receiving high-quality medical care, often leading to untreated physical health conditions.

Cognitive deficits and negative symptoms are two defining characteristics of schizophrenia whose relationship is complex and not yet fully understood (Huo et al., 2023). A significant limitation of previous studies examining this association is that they considered negative symptoms a single domain (Khalil et al., 2020; Sevy et al., 2020; Yolland et al., 2021; Yang et al., 2019). Therefore, we used the CAINS scale, which in addition to differentiating between expressive and experiential negative symptoms, evaluates the negative syndrome of schizophrenia by focusing on the patient's subjective experience. This could provide more clarity about this relationship (Khan et al., 2021; Yolland et al., 2021). Our findings corroborate this association, as negative symptoms emerged as predictors of both global cognitive score and all cognitive domains. In particular, expressive negative symptoms exhibited a greater weight than experiential symptoms. These results align with a recent systematic review and meta-analysis by Au-Yeung et al. (2023), which found a stronger association between expressive than experiential negative symptoms and MATRICS cognitive dimensions. More research is needed to elucidate the intricate association between these two dimensions, as interventions targeting neurocognition, such as cognitive remediation, demonstrate superior efficacy in alleviating expressive negative symptoms than other evidence-based treatments (Riehle et al., 2020). On the other hand, positive symptoms emerged as a significant predictor only of Attention/Vigilance. The role of positive symptoms in cognition has been considered secondary due to their relatively weak association with cognitive function (Carbon and Correll, 2014). However, there is evidence that the presence of positive symptoms can lead to inhibitory control deficits, resulting in attentional failures (Galaverna et al., 2012; Navalón et al., 2022).

Our findings also reveal a positive association between higher CPD and global cognitive score. This finding is consistent with the hypothesis that nicotine, a primary psychoactive component of tobacco, may have cognitive-enhancing effects in schizophrenia. Nicotine has been shown to upregulate nicotinic acetylcholine receptors (Newhouse et al., 2001;

Nordberg et al., 2002) and increase dopaminergic and glutamatergic neurotransmission in the prefrontal cortex (Ahlers et al., 2014; Conway, 2009; Hahn et al., 2012). Our findings align with this, as tobacco use emerged as a variable associated with better performance in Speed of Processing, Attention/Vigilance, and Working Memory, cognitive domains related to the prefrontal cortex. Previous studies have also reported positive associations between smoking and cognitive function in schizophrenia (Dondé et al., 2020; Spasova et al., 2022). However, the relationship between smoking and cognitive function in schizophrenia is complex and multifaceted, with evidence suggesting both beneficial and detrimental effects (Stramecki et al., 2018; Wang et al., 2019; Zhang et al., 2012). Therefore, further research is needed to determine the precise nature of this relationship and identify the mechanisms underlying the different results obtained.

4.1. Limitations and strengths

One of the main limitations of this study was its cross-sectional design and small sample size. Longitudinal studies conducted over long periods could identify trajectories and potential predictors. Another limitation of our study is that we have not assessed patients' treatment adherence. On the other hand, the strengths of the study lie in its methodological approach and selection of evaluation tools. The DBI, the only anticholinergic scale that considers medication dose, was used to accurately assess total anticholinergic burden. This scale assigns higher scores to medications with higher doses, providing a more accurate assessment of overall anticholinergic burden. Furthermore, the use of CAINS to assess negative symptoms in schizophrenia allowed for a comprehensive evaluation of the negative syndrome, focusing on the patient's subjective experience. Furthermore, the inclusive and non-restrictive nature of the inclusion and exclusion criteria improved the sample's representativeness, thus increasing the generalizability of the findings to clinical practice.

4.2. Conclusions

Our study identified specific predictors of global cognition in patients with schizophrenia. Anticholinergic load was identified as the strongest predictor of global cognitive performance, even greater than psychopathology. Additionally, educational level and negative symptoms, particularly expressive negative symptoms, were found to be predictors of global cognition. Our findings also reveal a positive association between cigarettes per day and better cognitive performance, suggesting potential cognitive-enhancing effects of nicotine in this population.

While the factors that influence cognitive performance in schizophrenia are multifaceted, clinicians should pay particular attention to the impact of drugs and primarily secondary negative symptoms on patient cognition. Mental health teams must be aware of these factors and use them to guide interventions to improve or maintain cognitive function. In this sense, careful management of psychiatric medications, particularly with respect to anticholinergic load, represents the main preventive intervention and a readily implementable strategy that can significantly contribute to reducing cognitive deficits in this population.

CRediT authorship contribution statement

Clara Martínez-Cao: Writing – original draft, Investigation, Data curation, Conceptualization. **Ainoa García-Fernández:** Writing – review & editing, Investigation. **Leticia González-Blanco:** Writing – review & editing, Supervision, Investigation. **Pilar A. Sáiz:** Writing – review & editing, Supervision, Resources, Investigation. **Julio Bobes:** Writing – review & editing, Supervision, Resources, Conceptualization. **María Paz García-Portilla:** Writing – original draft, Supervision, Resources, Investigation, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest related to the submitted work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scog.2024.100317.

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