The effect of anticholinergic burden on cognitive and daily living functions in patients with schizophrenia

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ABSTRACT

Objective: This study aimed to explore the association between medication-associated anticholinergic burden and cognitive and daily living functions in patients with schizophrenia.
Methods: Sixty patients with schizophrenia were recruited. We used the Anticholinergic Drug Scale (ADS) for evaluating medication-associated anticholinergic burden. The MATRICS Consensus Cognitive Battery (MCCB) and the University of California San Diego Performance-based Skills Assessment (UPSA) were used for evaluating cognitive and daily living functions. To assess clinical symptoms, psychiatrists conducted interviews using the Positive and Negative Syndrome Scale and the Calgary Depression Scale for Schizophrenia.
Results: Subjects were divided into low (n = 31) and high (n = 29) anticholinergic burden based on ADS scores of 3 or more. The "high ADS" group had poorer cognitive (composite MCCB score, $p < 0.001$) and daily living functions (total UPSA score, $p = 0.001$) than the "low ADS" group. Medication-associated anticholinergic burden was negatively correlated with cognitive functions (composite MCCB score, $r = -0.512$, $p < 0.001$) and daily living functions (total UPSA score, $r = -0.355$, $p = 0.005$). A regression analysis showed that anticholinergic burden significantly explained the decline in cognitive functions (composite MCCB score, $R^2 = 0.262$, $p < 0.001$) and daily living functions (total UPSA score, $R^2 = 0.126$, $p = 0.005$). Explanatory power was reduced after a covariate adjustment, but the effects of the composite MCCB score ($p = 0.013$) and of the transportation domain score of the UPSA ($p = 0.048$) remained significant.
Conclusions: Our analysis shows that anticholinergic burden reduces cognitive and daily living functions in patients with schizophrenia. A drug strategy with minimal anticholinergic burden may be helpful to patients if it does not adversely affect clinical symptoms.

1. Introduction

Schizophrenia is a chronic mental illness with a prevalence rate of about 1% worldwide (Insel, 2010). In addition to the positive and negative symptoms, cognitive symptoms have recently emerged as a major problem in schizophrenia (Green, 2007). Many studies show decreased cognitive functions, such as attention, memory, speed of processing, as well as executive functions, in patients with schizophrenia compared to normal controls (Corigliano et al., 2014). According to a meta-analysis conducted by Rajji et al. (2009), worse cognitive decline is observed with younger onset age. Some studies have reported that cognitive decline can be observed in some patients

with schizophrenia even before the onset of the illness (Seidman et al., 2013). The cognitive symptoms of patients with schizophrenia were found to have significant correlations with functional outcomes (Fett et al., 2011; Rispaud et al., 2016). Green et al. (2004) analyzed 18 longitudinal studies with follow-ups of at least 6 months, and found that future functional outcomes could be predicted by measuring cognitive functions. In the patients who showed significant effects of the rehabilitation treatment, functional changes were more frequent in individuals with higher cognitive functions at baseline (Brekke et al., 2007). Functional outcomes include aspects of daily living, social and occupational functioning, and independent living, and are the main goal to achieve in the rehabilitation of schizophrenia, along with

improved cognitive functions (Green et al., 2004). The improvement of cognitive functions in patients with schizophrenia not only reduces distress and increases self-efficacy, but can also help the patient acquire various social skills (Spaulding et al., 1999).

Several antipsychotic drugs have been developed for the treatment of schizophrenia in the past decade, but no medication has yet been approved by the US Food and Drug Administration (FDA) to help cognitive recovery (Opler et al., 2014). Even though some studies have shown that currently used antipsychotic drugs may be helpful in improving clinical symptoms in patients with schizophrenia, they may also exacerbate the decline in cognitive functions (Husa et al., 2017). The use of high doses or a combination of various types of antipsychotic drugs has been associated with a decrease in cognitive functions, and an improvement was observed when the treatment was simplified or the dose was reduced (Kawai et al., 2006; Takeuchi et al., 2013).

There are several explanations regarding the mechanism by which antipsychotic drugs may be involved in cognitive decline, the most common one being anticholinergic action. Most antipsychotic drugs have anticholinergic effects of varying severity, which are related to various side effects (Lieberman, 2004). Anticholinergic action causes side effects such as dry mouth and constipation when acting on the peripheral nervous system and a decrease in cognitive functions when acting on the central nervous system, and it can, in severe cases, lead to delirium (Feinberg, 1993). High anticholinergic burden due to antipsychotic drugs in patients with schizophrenia has been reported to be associated with decreased cognitive functions including verbal learning and executive functions (Tracy et al., 2001). As there are many cases where anticholinergic drugs are used in addition to antipsychotic drugs, many experts recommend that the anticholinergic drugs be used in as short a time and as low a dose as possible, taking into consideration the side effects (Lehman et al., 2004). In clinical practice, however, anticholinergic drugs are often, inevitably, used for preventive purposes related to compliance and to control extrapyramidal side effects of antipsychotic drugs. Dong et al. (2019) analyzed the psychotropic prescription patterns of patients with schizophrenia in a cross-sectional survey across 15 Asian countries, and found that 42.6% were taking antipsychotic polypharmacy and 45.6%, anticholinergic drugs.

A variety of attempts have been made to evaluate the anticholinergic burden of drugs currently used to treat patients with schizophrenia. The first such method is to directly assess the degree of anticholinergic activity in the serum using a blood sample (Vinogradov et al. (2009), which provides accurate figures but comes with problems regarding cost and complexity, the ineffectiveness of the serum activity to properly reflect central nervous system activity, and the difficulty of distinguishing what causes the activity (Carnahan et al., 2006). The second proposed method to evaluate anticholinergic burden is to construct a panel of experts from various fields, based on literature reviews on the anticholinergic action of certain drugs (Boustani et al., 2008). The Anticholinergic Cognitive Burden (ACB) scale, the Anticholinergic Drug Scale (ADS), and the Anticholinergic Risk Scale (ARS) have produced scores and classifications that are used in a variety of drug-related studies, because of their ease of use and application (Lertxundi et al., 2013).

Several studies in patients with schizophrenia have assessed associations with cognitive functions using anticholinergic action scales, and have associated high anticholinergic burden with low cognitive functions (Ang et al., 2017; Eum et al., 2017). An increase in anticholinergic burden has been shown to worsen daily living functions, described as activities of daily living (ADL) and instrumental activities of daily living (IADL), in elderly subjects living in a nursing home or the community (Landi et al., 2014; Salahudeen et al., 2015), but studies that directly evaluate the association between daily living functions and anticholinergic burden in patients with schizophrenia are rare. Understanding the relationships between cognitive functions, daily living functions, and anticholinergic burden in patients with schizophrenia may be helpful not only in predicting the patient's functions but also in

determining drug prescription guidelines and predicting success factors for rehabilitation treatment. Therefore, in this study, we investigated whether anticholinergic drug burden in patients with schizophrenia is related to cognitive functions, and whether it affects daily living functions.

2. Methods

2.1. Subjects

This study was performed in a group of patients aged 18 to 60 years who were diagnosed with schizophrenia on the basis of the DSM-5 (American Psychiatric Association, 2013) criteria by a psychiatrist. All subjects were recruited from one university hospital and two mental hospitals. They participated voluntarily, and were included in the study after the purpose of the research was explained to them. All subjects had been taking the same dose of antipsychotic drug for 3 months, their symptoms were stable, and they were all currently unemployed and either in day-hospital care or undergoing vocational rehabilitation. Patients with coexisting psychiatric or neurological disorders and those with a level of intelligence that would make it difficult to perform the tests properly were excluded from the study. All subjects provided written informed consent. The study was approved by the institutional review board of Busan Paik Hospital, Inje University College of Medicine.

2.2. Demographic and clinical characteristics

Information on the patients' sex, age, education level, duration of illness, and type and dose of current medications was obtained via interviews and retrieved from medical records. Antipsychotic drug doses were converted to chlorpromazine equivalent doses (CPZE) (Gardner et al., 2010).

2.3. Anticholinergic Drug Scale (ADS)

The ADS was developed by Carnahan et al. (2006), with anticholinergic drug burden scored by an expert panel from 0 to 3 points: A score of 0 means no known anticholinergic properties, 1 point indicates a potential anticholinergic action in receptor binding studies, a 2-point score means that anticholinergic side effects are reported occasionally for high drug doses, and 3 points indicate pronounced anticholinergic action. The total ADS score is the sum of all ADS scores for the drug currently being taken by the subject. In this study, we used the version of Eum et al. (2017), in which some drug scores were updated. The scores for all major drugs are summarized in Supplementary Table 1.

2.4. MATRICS Consensus Cognitive Battery (MCCB)

The MCCB was developed through a standardization study conducted by the Expert Committee of the National Institute of Mental Health (NIMH). It is recommended for the assessment of therapeutic effects in clinical trials of new drugs related to cognitive function enhancement in patients with schizophrenia (Nuechterlein et al., 2008). The MCCB evaluates seven cognitive domains and consists of 10 subtests: (1) speed of processing (Brief Assessment of Cognition in Schizophrenia (BACS): symbol coding, category fluency: animal naming, trail making test), (2) attention/vigilance (continuous performance test-identical pairs), (3) working memory (Wechsler memory scale-III: spatial span, letter-number span), (4) verbal learning (Hopkins verbal learning test-revised), (5) visual learning (brief visuospatial memory test-revised), (6) reasoning and problem solving (neuropsychological assessment battery: mazes), and (7) social cognition (Mayer-Salovey-Caruso emotional intelligence test: managing emotion). All cognitive tests were performed on the same day; completion of the whole battery took about 90 min. Right after the MCCB, the UPSA was conducted (see

Table 1
Demographic and clinical characteristics of patients by group.

	Low ADS (N = 31) (mean ± SD)	High ADS (N = 29) (mean ± SD)	t-Value	p-Value
Sex				
Male, n (%)	23 (74.19)	20 (68.97)	0.202*	0.653
Female, n (%)	8 (25.81)	9 (31.03)		
Age (years)	35.61 ± 7.26	42.59 ± 10.66	−2.941	0.005
Education (years)	13.77 ± 1.67	12.45 ± 1.82	2.941	0.005
Duration of illness (months)	69.03 ± 67.71	111.34 ± 116.11	−1.709	0.094
ADS	1.42 ± 0.92	3.24 ± 0.79	−8.249	< 0.001
Average daily neuroleptic dose (mg, CPZE)	540.91 ± 281.29	637.05 ± 361.79	−1.153	0.254
PANSS				
Positive subscale	15.61 ± 3.61	17.55 ± 3.60	−2.081	0.042
Negative subscale	18.23 ± 4.63	22.21 ± 3.88	−3.598	0.001
General psychopathology subscale	36.77 ± 7.80	40.00 ± 6.26	−1.759	0.084
Total score	70.61 ± 13.22	79.76 ± 9.63	−3.044	0.004
CDSS	3.52 ± 2.93	4.38 ± 4.42	−0.897	0.373

ADS, Anticholinergic Drug Scale; CDSS, Calgary Depression Scale for Schizophrenia; CPZE, Chlorpromazine Equivalent; PANSS, Positive and Negative Syndrome Scale; SD, Standard Deviation.

  * Chi-square value.

below), separated by a break of 30 min.

2.5. University of California San Diego Performance-based Skills Assessment (UPSA)

The UPSA evaluates the daily life functions of patients with schizophrenia. It takes about 30 min to evaluate five domains of basic living skills, that is, finance, communication, comprehension/planning, transportation, and household skills, through role-play activities. The financial domain evaluates the subject's ability to count money, give the correct change, and understand and pay bills, and is scored from 0 to 11 points. The communication domain is scored from 0 to 12 points, using a phone and letters to assess the subject's ability to understand certain situations and express themselves appropriately. The comprehension/planning domain evaluates the subject's ability to read newspaper articles, understand their content, and identify necessary items, and is scored from 0 to 14 points. The transportation domain evaluates whether a subject can accurately plan transfers or estimate time when using public transportation, and is scored from 0 to 9 points. The household skills domain assesses the selection of necessary ingredients after a subject has been provided with a recipe, and provides a score ranging from 0 to 4 points. We used the Korean version of the UPSA (Kim et al., 2017).

2.6. Positive and Negative Syndrome Scale (PANSS)

The PANSS is an assessment tool that was developed to evaluate a patient's psychopathology. It consists of 30 items in total, seven items evaluating positive symptoms, seven items evaluating negative symptoms, and 16 items evaluating general psychopathology. The assessment is scored from 1 to 7 points according to the evaluation criteria for each item, and higher scores indicate more severe psychopathology. We used the Korean version of the PANSS (Yi et al., 2001).

2.7. Calgary Depression Scale for Schizophrenia (CDSS)

The CDSS is a structured interview tool composed of nine items to assess depression in patients with schizophrenia. Depression, hopelessness, self-depreciation, guilty ideas of references, pathological guilt, morning depression, early morning waking, suicide, and observed depression are evaluated, on a scale from 0 to 3 for each item. The higher the score, the more serious the symptom. We used the Korean version of the CDSS (Kim et al., 2005).

2.8. Statistical analysis

Continuous variables are reported as means and standard deviations, and discrete variables as frequencies and percentages. Subjects were classified into a "low ADS" and a "high ADS" group, based on the degree of anticholinergic burden indicated by their ADS score. An ADS score of 3 indicates pronounced anticholinergic action. Subjects with a score of 3 or more points were therefore categorized into the high ADS group, and subjects with less than 3 points were categorized into the low ADS group. T-tests and Chi-square tests were used for comparisons between the two groups. In order to exclude factors that could affect the subjects' cognitive and daily living functions, an analysis of variation (ANCOVA) was performed with age, education level, and PANSS total score as covariates, as these factors appeared to significantly differ between the two groups in Table 1. A correlation analysis was performed to examine the correlations between cognitive and daily living functions and total ADS score. The partial correlation coefficients of Model 1, which controlled for demographic data (age, duration of illness, education level), Model 2, which controlled for clinical characteristics (CDSS score, PANSS total score, CPZE), and Model 3, which controlled for all factors of Model 1 and 2 that can affect cognitive and daily living functions, were also calculated. In order to infer the influence of the total ADS score on each cognitive and daily living function, a linear regression analysis was performed and some variables were adjusted in Model 1, 2, and 3, analogue to the correlation analysis. SPSS version 25.0 (IBM Corp, Armonk, NY, USA) was used for all analyses, and the significance level for all tests was set at $p < 0.05$.

3. Results

3.1. Demographic and clinical characteristics

A total of 60 subjects participated in this study; 29 had a total ADS score of less than 3 (low ADS group), and 31 had a score of 3 or higher (high ADS group). The demographic and clinical characteristics of all subjects are summarized in Table 1.

There was no significant difference in the sex ratio between the two groups. The mean age was significantly lower in the low ADS (35.61 ± 7.26 years) than in the high ADS group (42.59 ± 10.66 years). The mean education level was significantly higher in the low ADS group. There were no significant differences between the groups in the mean duration of illness or in CPZE. The total PANSS score was significantly higher in the high ADS group; when sub-classified into subscales, there were significant differences between the two groups on both the positive subscale and the negative subscale. There were no

Table 2
Cognitive and daily living functions of patients by group.

	Low ADS (N = 31) (mean ± SD)	High ADS (N = 29) (mean ± SD)	t-Value	p-Value	p-Value*
MCCB					
Speed of processing	37.03 ± 9.83	26.10 ± 9.64	4.345	< 0.001	0.022
Attention/Vigilance	42.23 ± 10.29	31.59 ± 6.60	4.795	< 0.001	0.002
Working memory	37.35 ± 10.66	25.28 ± 8.25	4.884	< 0.001	0.003
Verbal learning	33.81 ± 7.48	27.14 ± 5.43	3.930	< 0.001	0.005
Visual learning	52.71 ± 65.24	29.69 ± 9.06	1.882	0.065	0.093
Reasoning/Problem-solving	46.13 ± 11.45	37.31 ± 7.30	3.582	0.001	0.039
Social cognition	28.06 ± 9.62	22.07 ± 9.59	2.416	0.019	0.312
Composite score	30.61 ± 8.31	15.41 ± 6.05	8.136	< 0.001	< 0.001
UPSA					
Finance	17.73 ± 2.99	16.46 ± 2.68	1.733	0.088	0.462
Communication	13.72 ± 4.65	10.39 ± 4.59	2.790	0.007	0.071
Comprehension/Planning	11.34 ± 5.39	9.63 ± 5.15	1.249	0.217	0.565
Transportation	16.45 ± 3.90	13.50 ± 4.10	2.849	0.006	0.259
Household skills	15.97 ± 7.35	10.52 ± 8.38	2.682	0.010	0.079
Total score	75.26 ± 16.94	60.85 ± 14.58	3.521	0.001	0.044

ADS, Anticholinergic Drug Scale; CPZE, Chlorpromazine Equivalent; MCCB, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery; PANSS, Positive and Negative Syndrome Scale; SD, Standard Deviation; UPSA, University of California San Diego (UCSD) Performance-based Skills Assessment.
 * Using analysis of covariance (covariate: age, education, PANSS total score).

significant differences in general psychopathology subscale scores or CDSS scores between the two groups.

3.2. Cognitive and daily living functions

The MCCB scores for each domain are listed in Table 2. Domain scores differed between the two groups, except for the visual learning domain. The ANCOVA with age, education level, and PANSS total scores as covariates revealed significant differences for all domains except for visual learning and social cognition.

There were also significant differences in total UPSA scores and in the communication, transport, and household skills domains between the two groups. When covariances were considered in the ANCOVA, only the significant difference in the total UPSA score remained (Table 2).

3.3. Effects of anticholinergic burden on cognitive and daily living functions

We confirmed the correlations between some cognitive and daily living functions and anticholinergic burden assessed with the total ADS score (see Table 3). The ADS score had a significant negative correlation with the MCCB speed of processing, attention/vigilance, working memory, verbal learning, and composite score. Model 1 showed a negative correlation with the working memory, verbal learning, social cognition, and composite score. In Model 2, significantly negative correlations were found with the attention/vigilance, working memory, verbal learning, and composite score. In Model 3, a significant correlation was found between the composite score of the MCCB and the total ADS score.

There was a significant negative correlation between the ADS and the UPSA finance, communication, transportation, household skills, and total score. In Model 1, there was a significant negative correlation with the finance, communication, transportation, and total score. In Models 2 and 3, only the correlation with the transportation domain was significant.

The results of the regression analysis on the effects of anticholinergic burden on cognitive functions and daily living functions are shown in Table 4. Total ADS scores were found to have a significant effect on speed of processing, attention/vigilance, working memory, verbal learning, and composite scores of the MCCB. In Model 1, a significant effect on working memory, verbal learning, social cognition, and composite scores of the MCCB was confirmed. In Model 2, the ADS score was found to have a significant effect on attention/vigilance,

Table 3
Correlations between cognitive and daily living functions and anticholinergic burden.

	ADS	Model 1	Model 2	Model 3
MCCB				
Speed of processing	−0.321*	−0.172	−0.235	−0.075
Attention/Vigilance	−0.367†	−0.221	−0.335*	−0.192
Working memory	−0.369†	−0.294*	−0.283*	−0.214
Verbal learning	−0.389†	−0.310*	−0.281*	−0.173
Visual learning	−0.125	−0.179	−0.102	−0.180
Reasoning/Problem-solving	−0.252	−0.142	−0.248	−0.143
Social cognition	−0.234	−0.284*	−0.131	−0.224
Composite score	−0.512‡	−0.410†	−0.454‡	−0.336*
UPSA				
Finance	−0.330*	−0.319*	−0.227	−0.215
Communication	−0.260*	−0.295*	−0.104	−0.153
Comprehension/Planning	−0.055	−0.022	−0.011	0.016
Transportation	−0.367†	−0.300*	−0.328*	−0.271*
Household skills	−0.262*	−0.240	−0.143	−0.119
Total score	−0.355†	−0.325*	−0.228	−0.199

ADS, Anticholinergic Drug Scale; CDSS, Calgary Depression Scale for Schizophrenia; CPZE, Chlorpromazine Equivalent; MCCB, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery; PANSS, Positive and Negative Syndrome Scale; UPSA, University of California San Diego (UCSD) Performance-based Skills Assessment.
Model 1, using partial correlation analysis (controlling for age, duration of illness, education); Model 2, using partial correlation analysis (controlling for CDSS, CPZE, PANSS total score); Model 3, using partial correlation analysis (controlling for age, duration of illness, education, CDSS, CPZE, PANSS total score).
 * p < 0.05.
 † p < 0.01.
 ‡ p < 0.001.

working memory, verbal learning), and composite scores. In Model 3, the ADS score was found to have a significant effect on the composite score of the MCCB.

The total ADS score was significantly predictive of the UPSA finance, communication, transportation, household skills, and total score. The ADS score had a significant effect on the finance, communication, transportation, and total score of the UPSA, even after the variables in Model 1 were adjusted. In Models 2 and 3, there was a significant effect on the transportation domain.

Table 4
Linear regression analyses for cognitive and daily living function and anticholinergic burden.

	ADS		Model 1		Model 2		Model 3	
	β	R^2	β	Adjusted R^2	β	Adjusted R^2	β	Adjusted R^2
MCCB								
Speed of processing	−0.321*	0.103	−0.175	0.158	−0.231	0.165	−0.078	0.211
Attention/Vigilance	−0.367†	0.134	−0.227	0.161	−0.349*	0.118	−0.210	0.153
Working memory	−0.369†	0.136	−0.307*	0.164	−0.278*	0.183	−0.230	0.188
Verbal learning	−0.389†	0.151	−0.337*	0.107	−0.271*	0.211	−0.183	0.203
Visual learning	−0.125	0.016	−0.199	0.001	−0.110	−0.047	−0.218	−0.047
Reasoning/Problem-solving	−0.252	0.063	−0.154	0.039	−0.233	0.241	−0.148	0.230
Social cognition	−0.234	0.055	−0.303*	0.129	−0.127	0.160	−0.239	0.207
Composite score	−0.512‡	0.262	−0.396†	0.351	−0.404‡	0.423	−0.301*	0.477
UPSA								
Finance	−0.330*	0.109	−0.356*	0.066	−0.226	0.131	−0.245	0.090
Communication	−0.260*	0.067	−0.323*	0.087	−0.097	0.214	−0.161	0.206
Comprehension/Planning	−0.055	0.003	−0.025	−0.060	−0.012	−0.011	0.019	−0.060
Transportation	−0.367†	0.135	−0.320*	0.136	−0.322*	0.213	−0.294*	0.198
Household skills	−0.262*	0.069	−0.270	0.004	−0.136	0.185	−0.130	0.141
Total score	−0.355†	0.126	−0.359*	0.093	−0.206	0.290	−0.205	0.250

ADS, Anticholinergic Drug Scale; CDSS, Calgary Depression Scale for Schizophrenia; CPZE, Chlorpromazine Equivalent; MCCB, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery; PANSS, Positive and Negative Syndrome Scale; UPSA, University of California San Diego (UCSD) Performance-based Skills Assessment.
Model 1, adjusted for age, duration of illness, education; Model 2, adjusted for CDSS, CPZE, PANSS total score; Model 3, adjusted for age, duration of illness, education, CDSS, CPZE, PANSS total score.

* p < 0.05.
† p < 0.01.
‡ p < 0.001.

4. Discussion

The current study investigated how anticholinergic burden correlates with cognitive functions and daily living functions in patients with schizophrenia. Patients with schizophrenia commonly take various kinds of drugs, due to the complex nature of their disease. According to Chew et al. (2006), antipsychotic drugs such as clozapine, olanzapine, and quetiapine have clinically significant anticholinergic activity at the therapeutic dose, while aripiprazole, risperidone, and ziprasidone do not have such effects. In addition to antipsychotics, anticholinergics, antidepressants, and benzodiazepines are used to control side effects and other symptoms in patients with schizophrenia, and many of these are known to have anticholinergic actions (Chakos et al., 2006).

Various scales are used to evaluate the anticholinergic actions of drugs, such as the ACB, ADS, and ARS. However, there are differences in the kinds of drugs that can be evaluated with these scales, and the ADS was selected in this study as the only one that included all the drugs taken by the subjects. The ADS is a proven tool for predicting anticholinergic burden in a variety of clinical situations, including community care, outpatient care, and hospital admission (Chatterjee et al., 2010; Fox et al., 2014).

We found that the subjects taking drugs with high anticholinergic burden had significantly lower cognitive functions in this study. This is in line with the results of previous studies that investigated the correlation between anticholinergic action and cognitive functions in patients with schizophrenia. Tsoutsoulas et al. (2017) conducted a study in older patients with schizophrenia and reported that the more severe the anticholinergic burden, assessed with the ACB, the more cognitive problems similar to those of early Alzheimer's dementia were observed. Eum et al. (2017) reported a significant difference in cognitive functions assessed by the BACS when an ADS score of 4 or more was set as the criterion for grouping in 206 patients with schizophrenia. Here, subjects were classified into groups on the basis of a 3-point ADS criterion of "markedly anticholinergic action", which we considered the more clinically meaningful comparison. It is well known that depressive symptoms have negative effects on cognitive functions and daily living functions in patients with schizophrenia (Holthausen et al., 1999; Reichenberg et al., 2014). In the present study, however, there was no

significant difference in depressive symptoms, as assessed by the CDSS, between the two groups, which indicates that these effects have been controlled for. As shown in Table 1, the low ADS group was younger and more educated overall, and the subjects' clinical symptoms, evaluated with the PANSS, were milder than those of the subjects in the high ADS group. When these factors were controlled, a significant difference between the two groups remained, indicating that anticholinergic burden did indeed have an effect on cognitive functions. Although a clear neurobiological mechanism for how anticholinergic actions may degrade cognitive functions in patients with schizophrenia is not known, such a mechanism has been suggested to be related to the action of drugs on muscarinic receptors. Muscarinic receptors act on five subtypes in the central nervous system, with M1, M2, and M4 subtypes known to be involved in cognitive functions such as memory and learning (Matsui et al., 2004). In a recent fMRI study, serum anticholinergic activity was found to be associated with low activity in the dorsolateral and anterior prefrontal cortex in 39 patients with early-stage schizophrenia (Schreiber et al., 2018). Some studies have shown that muscarinic cholinergic activity can affect the clinical symptoms of patients with schizophrenia by acting on several systems, including the dopaminergic system (Tandon, 1999). Tandon et al. (1992) reported that the anticholinergic agent biperiden increased positive and decreased negative symptoms in patients with schizophrenia.

Several previous studies of dementia and the general elderly population have shown how anticholinergic action by drugs could affect physical and living functions other than cognitive functions and even death rates (Salahudeen et al., 2015). On the other hand, previous studies that directly compare changes in daily living functions due to anticholinergic action in patients with schizophrenia are scarce. Here, we confirm significant differences between a low and high ADS group in daily living functions evaluated by the UPSA. Various factors, such as psychotic symptoms and cognitive functions, can affect daily living functions and daily life in patients with schizophrenia (Green et al., 2000), and the results of this study show that significant differences in total UPSA scores persist even after controlling for a number of potentially confounding variables. We therefore assume that differences in cognitive function due to the anticholinergic action of the drug are the main cause of the differences in daily living functions we find.

However, these differences are minor compared to the differences in MCCB scores, and, considering that the UPSA is a more basic tool and was not designed to assess very subtle differences, it may not be able to reflect cognitive decline due to anticholinergic action in great detail.

The correlation analysis revealed that anticholinergic burden is negatively correlated with cognitive functions and daily living functions. These results persisted in Model 1, which controlled for the demographic factors age, duration of illness, and education level. However, in Model 2, which controlled for clinical factors reflected in the CDSS and PANSS total scores, significant relationships were mainly found for cognitive functions. In Model 3, which controlled for both the Model 1 and the Model 2 variables, only the MCCB composite score and the UPSA transportation domain score were significantly correlated. The results were identical in the linear regression analysis, which confirmed the significant effect of the total ADS score on cognitive and daily living functions. In addition, we found that overall daily living functions evaluated with the UPSA differed significantly depending on the presence of a markedly anticholinergic burden (based on the 3-point ADS criterion), but when considering continuous propensity, there were no significant differences, except for one specific domain (transportation). Tsoutsoulas et al. (2016) used the ACB scale to evaluate anticholinergic burden and a correlation with total UPSA scores but found no significant results. The study by Tsoutsoulas et al. differs from the current study in that all participants were older than 50, which means that some subjects were already experiencing daily living impairments due to their age, and, although the scales were different, their total ACB score of 2.75 points is closer to the definite anticholinergic burden of 3 points.

In order to better understand the meaning of anticholinergic burden in patients with schizophrenia, the precise evaluation of anticholinergic burden should be prioritized. In addition to the ADS score used in this study, various other scales such as the ACB and ARS have been developed and used to evaluate anticholinergic burden. However, some drugs have different scores on different scales, which is especially found for psychiatric medications (Lertxundi et al., 2013; Salahudeen et al., 2015). When using anticholinergic action scales in psychiatric patients in clinical settings, it is therefore necessary to pay attention to such details. Nonetheless, estimating the risk of anticholinergic action of a drug using the aforementioned scales in patients with schizophrenia is simple and efficient. Clinicians have to deal with a variety of cognitive and daily living function impairments in addition to psychiatric symptoms while treating patients with schizophrenia, and considering the anticholinergic burden of drugs may provide them with explanations and thus help the treatment of their patients. It is also known that the anticholinergic burden of drugs has a negative effect on the participation in or the response to a psychosocial program, which requires more attention in clinical practice (O'Reilly et al., 2016). However, there are also clinical dilemmas where patients with poor outcomes are forced to choose drugs that have more potent antipsychotic effects but a higher anticholinergic burden, such as olanzapine or clozapine.

This study has several limitations. First, our evaluation of the anticholinergic effects of drugs with the ADS is limited by differences in dosage. Antipsychotic drugs were compared using chlorpromazine equivalent doses, but such a correction was not applied to other classes of drugs. Second, the premorbid IQ, which may be related to cognitive functions, could not be assessed; its potential effects should be considered in subsequent studies. Third, the subjects were all in day-hospital care or undergoing vocational rehabilitation, and the duration of such care or the participation in adjunctive treatments might have affected the patients' cognitive and daily living functions.

To summarize, we confirm that anticholinergic drug burden in patients with schizophrenia significantly decreases cognitive functions and daily living functions. In the future, in patients with stable symptoms and a low risk of recurrence, a drug strategy that can reduce the anticholinergic burden based on sufficient clinical observations and pharmacological reviews could help improve patients' cognitive and daily living functions.

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