The Impact of Medication Anticholinergic Burden on Cognition in People With Schizophrenia

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Abstract:
Background: Cognitive deficits are prevalent in people with schizophrenia and associated with functional impairments. In addition to antipsychotics, pharmacotherapy in schizophrenia often includes other psychotropics, and some of these agents possess anticholinergic properties, which may impair cognition. The objective of this study was to explore the association between medication anticholinergic burden and cognition in schizophrenia.

Methods: Seven hundred five individuals with schizophrenia completed a neuropsychological battery comprising Judgment of Line Orientation Test, Wechsler Abbreviated Scale of Intelligence Matrix Reasoning, Continuous Performance Test–Identical Pairs Version, and the Brief Assessment of Cognition in Schizophrenia. Cognitive g and 3 cognitive factor scores that include executive function, memory/fluency, and speed of processing/vigilance, which were derived from a previously published analysis, were entered as cognitive variables. Anticholinergic burden was computed using 2 anticholinergic scales: Anticholinergic Burden Scale and Anticholinergic Drug Scale. Duration and severity of illness, antipsychotic dose, smoking status, age, and sex were included as covariates.

Results: Anticholinergic burden was associated with poorer cognitive performance in cognitive g, all 3 cognitive domains and most cognitive tasks in multivariate analyses. The associations were statistically significant, but the effect sizes were small (for Anticholinergic Burden Scale, Cohen $f^2 = 0.008$; for Anticholinergic Drug Scale, Cohen $f^2 = 0.017$).

Conclusions: Although our results showed a statistically significant association between medications with anticholinergic properties and cognition in people with schizophrenia, the impact is of doubtful or minimal clinical significance.

Key Words: anticholinergic, cognition, schizophrenia

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Cognitive deficits are prevalent and stable in people with schizophrenia and are associated with functional outcomes. Both the dopaminergic and cholinergic systems and the balance of the dopaminergic-cholinergic system have been thought to be essential in cognition. Evidence from animal, neuropharmacological, and magnetic resonance imaging studies shows that the cholinergic system is involved in the modulation of attention and memory encoding. Sellin et al suggested that muscarinic acetylcholine receptors, especially M1 receptors, may be altered in schizophrenia, and this may contribute to deficits in memory and learning in schizophrenia. Goff et al reviewed the treatment of cognitive impairment in schizophrenia and suggested strong evidence in the role of muscarinic and nicotinic acetylcholine receptors in cognitive impairment in schizophrenia. A review by Spohn and Strauss suggested that anticholinergics affect memory in schizophrenia patients, whereas researchers suggested that muscarinic and nicotinic agonists, cholinesterase inhibitors, and allosteric activators may be efficacious in treating cognitive impairment in schizophrenia. Taken together, these findings suggest that cholinergic neurotransmission plays a vital role in cognition and that abnormal cholinergic regulation is associated with cognitive impairment.

Antipsychotic medications form the mainstay of pharmacological interventions in schizophrenia, whereas concomitant medications such as antidepressants, mood stabilizers, and anxiolytics are not uncommon. Some of these medications possess anticholinergic properties, which have been suggested to impair cognitive functions. Furthermore, anticholinergic medications are often coprescribed to ameliorate the extrapyramidal adverse effects brought on by antipsychotics, specifically the typical agents.

Most of the studies on the association between anticholinergic burden and cognition were conducted in the elderly. A review of studies on anticholinergic burden and cognition in the elderly found that all but 2 of 27 studies showed an association between the use of anticholinergic medications and poorer cognition, with specific deficits in processing speed, attention, language, problem solving, and psychomotor performance. Ancelin et al found anticholinergic drug use to be a strong predictor of mild cognitive impairment in the elderly. Multsant et al found that even low serum anticholinergic activity (SAA) was significantly associated with cognitive impairment in community geriatric sample. Dose–response relationship between Anticholinergic Burden Scale (ACB) total score and cognition as measured by a 6-item orientation memory concentration test was observed, and drug use as identified by ACB scale has been associated with more severe cognitive impairment in elderly people. Similarly, an 8-year longitudinal study on patients with Parkinson disease reported that anticholinergic load and duration of anticholinergic drug use were associated with decline in Mini–Mental State Examination.

Studies on the association between medication anticholinergic burden and cognition in schizophrenia are limited. Serum anticholinergic activity, a suggested biomarker for anticholinergic burden, was found to be higher in schizophrenia patients with poorer verbal recall and poorer verbal working memory, verbal learning, and memory. In addition, SAA level was inversely
associated with improvements from a computerized cognitive training in individuals with schizophrenia. In another study, exposure to medications with anticholinergic properties was shown to impair attention and declarative memory in schizophrenia, but had no effects on other aspects of cognition, including intelligence, working memory, executive functioning, and motor speed. The studies cited above were conducted on relatively small samples, ranging from 10 to 106 participants, which might have affected the consistency in findings between the elderly and people with schizophrenia and even within schizophrenia studies. In addition, the different anticholinergic scales and different cognition measures adopted might have contributed to the variations. The objective of the present study was to examine the association between anticholinergic burden and cognition in people with schizophrenia. For increased reliability, we adopted 2 independently established anticholinergic rating scales to examine the concordance in findings. We hypothesized that a higher anticholinergic burden is associated with poorer cognitive performance in schizophrenia.

**MATERIALS AND METHODS**

**Study Participants**

Seven hundred five Chinese individuals with schizophrenia, aged 21 to 55 years, were included in this study. Patients were recruited from both outpatient and inpatient settings in the Institute of Mental Health, Singapore, as well as from community care centers and rehabilitation centers in Singapore. The diagnosis of schizophrenia was ascertained on the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Exclusion criteria were a history of mental retardation, current substance use, clinically significant neurological disorder or brain injuries, and color blindness. Ethics approval for this study was granted by the National Healthcare Group Domain Specific Review Board. All participants provided informed consent to participate in the study.

**Cognitive Assessments**

All participants were assessed on a comprehensive cognitive battery composed of Benton’s Judgment of Line Orientation Test, Wechsler Abbreviated scale of Intelligence Matrix Reasoning, Continuous Performance Test (CPT)—Identical Pairs Version, and Brief Assessment of Cognition in Schizophrenia (BACS). The BACS includes Verbal Memory (VM), Digit Sequencing, Token Motor Task (TMT), Semantic Fluency (SF), Symbol Coding (SC), and Tower of London. The SF test includes 3 measures of semantic fluency—animal, fruits, and vegetable. A cognitive model comprising 3 domains, namely, executive function, fluency/memory; and speed/vigilance, was previously published using the same data set. The executive function domain consisted of Judgment of Line Orientation Test and Wechsler Abbreviated scale of Intelligence Matrix Reasoning items. The fluency/memory domain consisted of BACS SF and VM items. The speed/vigilance domain consisted of CPT—Identical Pairs Version and BACS TMT and SC items. Cognitive scores for these 3 domains were generated from the model using regression.

**Assessment of Anticholinergic Burden**

Medication data were collected from the participants’ medical record. Total anticholinergic burden was computed using the ACB and Anticholinergic Drug Scale (ADS). Anticholinergic Burden Scale is an expert-rated scale based on systematic review of the literature. Information from the MEDLINE database from 1966 to 2007 on drug anticholinergic properties and cognitive function in older adults was provided to a multidisciplinary team composed of geriatricians, pharmacists, psychiatrists, general physicians, nurses, and aging-brain researchers who categorized the medications into 3 classes of mild, moderate, and severe cognitive anticholinergic negative effects. The ADS was previously referred to as the Clinician-Rated Anticholinergic Scale—modified version. Clinician-Rated Anticholinergic Scale has 340 medications that were rated by 3 geriatric clinicians based on their experience and knowledge. The median of the ratings has strong agreement with Summers’ Drug Risk Number and laboratory data. Clinician-Rated Anticholinergic Scale was then renamed as ADS and validated by Carnahan et al. The ADS was also reported to be associated with serum anticholinergic activities. Effect sizes of cognitive g were estimated using Cohen’s f, where 0.02, 0.15, and 0.35 represent small, medium, and large effect sizes, respectively.

**Statistical Analyses**

To explore the association between total anticholinergic loading and cognition, bivariate correlation analyses were performed. Univariate analyses were conducted with total anticholinergic loading of each scale as an independent variable and each normalized cognitive score as a dependent variable. Covariates such as sex, age, smoking status, duration of illness, severity of illness (measured by Positive and Negative Syndrome Scale [PANSS] total score), and impact of antipsychotics were included in subsequent multivariate regression analyses with anticholinergic loading as an independent variable and cognitive score as a dependent variable. The analyses were repeated for each cognitive variable. All statistical analyses were performed using IBM SPSS statistics 23 (IBM Corp, Armonk, NY). Statistical significance was determined at P < 0.05.

**RESULTS**

The demographic information of the study sample is presented in Table 1. Correlational analyses revealed statistically significant but weak associations between anticholinergic burden with diagnoses of schizophrenia. Table 1 shows the mean and standard deviation of demographic characteristics of the study participants. The mean age of the participants was 39.18 years (SD, 9.71). The majority of the participants were male (52.8%). The mean antipsychotic dose was 460.32 mg (SD, 448.83). The mean duration of illness was 15.48 years (SD, 9.89). The mean smoking status was 175 (24.8%). The mean ACB score was 4.73 (SD, 2.93). The mean ADS score was 3.89 (SD, 2.89). The mean number of medication per patient was 3.26 (SD, 1.81). The mean type of antipsychotic prescribed was 301 (42.7%). The mean antipsychotic dose was 460.32 mg (SD, 448.83).

| Variable                      | Mean (SD) or n (%)       |
|-------------------------------|--------------------------|
| Sex (male)                    | 372 (52.8%)              |
| Age, y                        | 39.18 (SD, 9.71)         |
| Duration of illness, y        | 15.48 (SD, 9.89)         |
| Smoking status                |                          |
| Smoker                        | 175 (24.8%)              |
| Ex smoker                     | 65 (9.2%)                |
| Nonsmoker                     | 465 (66%)                |
| ACB                           | 4.73 (SD, 2.93)          |
| ADS                           | 3.89 (SD, 2.89)          |
| No. medication (per patient)  | 3.26 (SD, 1.81)          |
| Type of antipsychotic prescribed |                         |
| Typical antipsychotics only   | 301 (42.7%)              |
| Atypical antipsychotics only  | 259 (36.7%)              |
| Both typical and atypical antipsychotics | 144 (20.4%)          |
| Antipsychotic dose,* mg       | 460.32 (SD, 448.83)      |
| Antidepressants               | 218 (30.9%)              |
| Anticholinergics              | 370 (52.5%)              |
| Mood stabilizers              | 131 (18.6%)              |
| Benzodiazepines               | 150 (21.3%)              |

*Antipsychotic doses were converted into total daily chlorpromazine equivalents.
(both ACB and ADS total scores) and all cognitive variables (for ACB, \( r = -0.080 \) to \(-0.238\), all \( P < 0.05\); for ADS, \( r = -0.094 \) to \(-0.272\), all \( P < 0.05\)). The results showed a trend suggesting patients with higher ACB and ADS total scores performed poorer in all cognitive tasks, but the impact of medication on cognition may be minimal. The association between cognitive \( g \) and ACB and association between cognitive \( g \) and ADS are presented in Figures 1 and 2. Frequency and rating of medications with anticholinergic activity are presented in Table 2.

**Anticholinergic Burden Scale**

Linear regression analyses revealed that higher ACB total scores significantly predicted poorer performance in all cognitive variables (\( P < 0.001 \) to \( 0.040\)). However, the variances explained by the models were small (\( R^2 = 0.006 \) to \( 0.057\)), and the regression coefficients of ACB total scores were small (\( \beta = -0.028 \) to \(-0.105\)). After adjusting for covariates, ACB total scores were significantly and negatively associated with poorer cognitive scores for most cognitive variables. The coefficients for ACB total scores were small (\( B = 0.004 \) to \(-0.047\)). Effect size of cognitive \( g \) was also small (Cohen \( f^2 = 0.008\)). Results of the analyses are presented in Table 3.

**Anticholinergic Drug Scale**

All cognitive test scores, 3-factor scores and global cognition \( g \), were significantly associated with ADS total scores, with \( P \) values ranging from \( P < 0.001 \) to \( 0.013\). The results indicated that a higher ADS total score was associated with poorer cognitive performance (Table 4). The variances accounted by ADS total scores were small (\( R^2 = 0.009 \) to \( 0.074\)), and the coefficients of ADS total scores were small (\( B = -0.034 \) to \(-0.119\)). Similar to the results in ACB, after adjusting for covariates, ADS total scores had significant inverse association with most cognitive variables. The unique effects of ADS total scores on cognition were small (\( B = -0.006 \) to \(-0.064\)). Effect size of cognitive \( g \) was small (Cohen \( f^2 = 0.017\)). The results are shown in Table 4.

**TABLE 2. Frequency and Rating of Medications With Anticholinergic Activity**

| Drug Name                  | Frequency | ADS | ACB |
|----------------------------|-----------|-----|-----|
| Alprazolam                 | 4         | 1   | 1   |
| Amisulpride                | 4         | -   | 1   |
| Amitriptyline              | 7         | 3   | 3   |
| Aripiprazole               | 16        | -   | 1   |
| Atenolol                   | 3         | 0   | 1   |
| Benzetxol/trihexyphenidyl  | 343       | 3   | 3   |
| Benztpine                  | 36        | 3   | 3   |
| Carbamazepine              | 6         | 2   | 2   |
| Chlorphenamine/chlorpheniramine | 2       | 3   | 3   |
| Chlorpromazine             | 127       | 3   | 3   |
| Clonipramine               | 12        | 3   | 3   |
| Clozapine                  | 8         | 1   | -   |
| Diazepam                   | 43        | 3   | 3   |
| Dizepam                    | 1         | 1   | 1   |
| Famotidine                 | 1         | -   | 1   |
| Fluoxetine                 | 66        | 1   | -   |
| Fluphenazine               | 88        | 1   | -   |
| Flupentinox                | 132       | -   | 1   |
| Fluoxamine                 | 99        | 1   | 1   |
| Haloperidol                | 90        | 0   | 1   |
| Hydrocortisone/hydrocortisone 1% cream | 2       | 1   | 1   |
| Hydroxyzine                | 96        | 3   | 3   |
| Imiprime                   | 3         | 3   | 3   |
| Lorazepam                  | 39        | 1   | -   |
| Nifedipine                 | 4         | 1   | 1   |
| Nortriptyline              | 1         | 3   | 3   |
| Olanzapine                 | 77        | 1   | 3   |
| Orphenadrine               | 2         | 3   | 3   |
| Paroxetine                 | 2         | 1   | 3   |
| Prochlorperazine           | 1         | 1   | 1   |
| Quetiapine                 | 26        | 0   | 3   |
| Risperidone                | 196       | -   | 1   |
| Trifluoperazine            | 105       | 1   | 3   |
| Valproate sodium/valproic acid | 106     | 1   | -   |

Anticholinergic cognitive burden scale (ACB) is available at: www.agingbraincare.org/uploads/products/ACB_scale_-_legal_size.pdf.

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anticholinergic burden have their limitations. Serum anticholinergic activity as the criterion standard measure of cumulative anticholinergic activity may only reflect a transitional cholinergic state outside the brain, whereas the expert-based scales may still be biased by the professionals’ boundary of expertise. The scales also assume that medications have additive anticholinergic properties. Also, medication dose and frequency were not considered in estimating anticholinergic burden in these scales. Although dose-adjusted ADS score did not improve the variance explained in SAA than the traditionally calculated ADS score,40 this adjustment may strengthen the association between medication burden and physical functional capacity and cognitive measures.42 Therefore, these anticholinergic measures would serve only as an estimate that approximates medication anticholinergic burden. Despite the limitation, they may still serve as a simple and practical guide for practitioner in prescribing medication.

Although statistically significant, the magnitude of the associations between anticholinergic burden and cognition in our data was small. The significant results may also be due to the large sample size in this study.43 Therefore, it seems that the impact of
TABLE 3. Linear Regression Analyses on ACB Total Scores

| Dependent Variables                  | Unadjusted Analyses |                    |                  | Adjusted Analyses* |                    |                  |
|--------------------------------------|---------------------|--------------------|------------------|--------------------|--------------------|------------------|
|                                      | B       | SE    | P       | R²     | B       | SE    | P       | Adjusted R²   |
| Cognitive g                          | −0.105  | 0.016 | <0.001 | 0.057  | −0.047  | 0.019 | <0.001 | 0.146        |
| Executive function                   | −0.100  | 0.016 | <0.001 | 0.053  | −0.043  | 0.019 | <0.001 | 0.120        |
| Judgment of Line Orientation         | −0.037  | 0.014 | 0.007  | 0.010  | −0.016  | 0.016 | 0.001  | 0.028        |
| Matrix Reasoning                     | −0.074  | 0.013 | <0.001 | 0.047  | −0.030  | 0.015 | <0.001 | 0.104        |
| Memory/fluency                       | −0.101  | 0.016 | <0.001 | 0.054  | −0.047  | 0.018 | <0.001 | 0.138        |
| SF-H01                               | −0.039  | 0.012 | 0.001  | 0.016  | −0.010  | 0.014 | <0.001 | 0.065        |
| VM                                   | −0.056  | 0.012 | <0.001 | 0.032  | −0.042  | 0.014 | <0.001 | 0.056        |
| Speed of processing/vigilance        | −0.097  | 0.015 | <0.001 | 0.054  | −0.039  | 0.018 | <0.001 | 0.156        |
| CPT-H01                              | −0.028  | 0.014 | 0.040  | 0.006  | 0.004   | 0.016 | <0.001 | 0.082        |
| TMT                                  | −0.049  | 0.011 | <0.001 | 0.027  | −0.022  | 0.013 | <0.001 | 0.088        |
| SC                                   | −0.052  | 0.009 | <0.001 | 0.041  | −0.021  | 0.011 | <0.001 | 0.116        |

*Adjusted for age, sex, smoking, duration of illness, severity of illness (PANSS total scores), and antipsychotic dose (total daily chlorpromazine equivalents).

The total anticholinergic burden of each scale may not be fully indicative of the true anticholinergic burden of patients. This might be due to other undocumented concomitant medications that the participants were taking at the time of the study. Interaction between ACB or ADS and whether typical antipsychotics were taken was not controlled for in the analyses. This may be a potential confounder because the use of anticholinergic medications is associated with the use of typical antipsychotics, resulting in higher ACB and ADS scores. Concomitant disorders were not recorded in this study; therefore, the impact of other disorders on cognition is not controlled. Also, it should be noted that the significant association between anticholinergic burden and cognition does not indicate causal relationship between the variables.

To conclude, the findings in this study shed light on the impact of medication anticholinergic burden on different cognitive domains in patients with schizophrenia, indicating that all cognitive aspects were inversely associated with medication anticholinergic burden. However, this impact seems to be of little clinical significance.

AUTHOR DISCLOSURE INFORMATION

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TABLE 4. Linear Regression Analyses on ADS Total Scores

| Dependent Variables                  | Unadjusted Analyses |                    |                  | Adjusted Analyses* |                    |                  |
|--------------------------------------|---------------------|--------------------|------------------|--------------------|--------------------|------------------|
|                                      | B       | SE    | P       | R²     | B       | SE    | P       | Adjusted R²   |
| Cognitive g                          | −0.119  | 0.016 | <0.001 | 0.071  | −0.064  | 0.018 | <0.001 | 0.153        |
| Executive function                   | −0.109  | 0.016 | <0.001 | 0.062  | −0.055  | 0.019 | <0.001 | 0.125        |
| Judgment of Line Orientation         | −0.034  | 0.014 | 0.013  | 0.009  | −0.019  | 0.016 | <0.001 | 0.028        |
| Matrix Reasoning                     | −0.080  | 0.013 | <0.001 | 0.055  | −0.037  | 0.015 | <0.001 | 0.108        |
| Memory/fluency                       | −0.114  | 0.016 | <0.001 | 0.067  | −0.063  | 0.018 | <0.001 | 0.144        |
| SF-H01                               | −0.040  | 0.012 | 0.001  | 0.016  | −0.012  | 0.014 | <0.001 | 0.066        |
| VM                                   | −0.065  | 0.012 | <0.001 | 0.042  | −0.052  | 0.014 | <0.001 | 0.063        |
| Speed of processing/vigilance        | −0.115  | 0.015 | <0.001 | 0.074  | −0.059  | 0.017 | <0.001 | 0.165        |
| CPT-H01                              | −0.039  | 0.014 | 0.005  | 0.012  | −0.006  | 0.016 | <0.001 | 0.082        |
| TMT                                  | −0.062  | 0.011 | <0.001 | 0.043  | −0.036  | 0.013 | <0.001 | 0.094        |
| SC                                   | −0.062  | 0.009 | <0.001 | 0.057  | −0.033  | 0.011 | <0.001 | 0.124        |

*Adjusted for age, gender, smoking, duration of illness, severity of illness (PANSS total score) and antipsychotic dose (total daily chlorpromazine equivalents).
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