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Cognitive burden of anticholinergic medications in psychotic disorders

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Contributors

J.R.B. developed the idea for the application of anticholinergic burden estimates to B-SNIP drug regimens to study in relation to cognitive data. Authors S.E. and J.R.B. conducted the analyses and wrote the first draft with conceptual and statistical assistance from S.K.H., L.H.R., and J.A.S. Author R.M.C. developed ADS and assisted with updates and application to medication regimens in this study. Author S.E. applied ADS scoring to all medication data. Authors C.A.T., G.D.P., B.A.C., E.S.G., M.S.K., and J.A.S. are B-SNIP PIs, who designed the parent study, wrote the overarching B-SNIP protocol and phenotyping approaches and oversaw data collection. Authors E.I.I., J.L.R., and J.R.B. evaluated and validated medication assessments of participants. R.S.K. provided the BACS battery. S.K.H. oversaw training and quality control of the BACS throughout the study. All authors contributed to and have approved the final manuscript.

Conflict of interest

C.A.T. has received support from Intracellular Therapies (ITI, Inc.), PureTech Ventrues, Eli Lilly Pharmaceuticals, Sunovion, Astellas, Merck (ad hoc consulting), International Congress on Schizophrenia Research (unpaid volunteer), NAMI (unpaid volunteer), American Psychiatric Association (Deputy Editor), and Finnegan Henderson Farabow Garrett & Dunner, LLP. J.L.R. has received investigator initiated support from Naurex, Inc. R.S.E.K. has received investigator initiated support from the Department of Veteran's Affair, Feinstein Institute for Medical Research, GlaxoSmithKline, National Institute of Mental Health, Novartis, Psychogenics, Research Foundation for Mental Hygiene, Inc., and the Singapore National Medical Research Council. R.S.E.K. has received honoraria, served as a consultant, or advisory board member for Abbvie, Akebia, Amgen, Astellas, Asubio, AviNeuro/ChemRar, BiolineRx, Biomarin, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, EnVivo, Helicon, Lundbeck, Merck, Mitsubishi, Otsuka, Pfizer, Roche, Shire, Sunovion, Takeda, Targacept. R.S.E.K. is a shareholder in Sengenix and NeuroCog Trials, Inc. and receives royalties from the BACS testing battery and the MATRICS Battery (BACS Symbol Coding). M.S.K. has received support from Forum Pharmaceuticals. J.A.S. has received support from Takeda, BMS, Roche, and Eli Lilly and research funding from Janssen. The other authors report no related conflict of interest.

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Abstract

Background—Patients with psychotic disorders are often treated with numerous medications, many of which have anticholinergic activity. We assessed cognition in relation to the cumulative anticholinergic burden of multiple drugs included in treatment regimens of participants from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study.

Method—Clinically stable participants with schizophrenia (n=206), schizoaffective disorder (n=131), and psychotic bipolar disorder (n=146) were examined. Anticholinergic properties of all scheduled drugs were quantified using the Anticholinergic Drug Scale (ADS). ADS scores were summed across individual drugs to create a total ADS burden score for each participant and examined in relation to the Brief Assessment of Cognition in Schizophrenia (BACS).

Results—Anticholinergic burden aggregated across all medications was inversely related to cognitive performance starting at ADS scores of 4 in participants with schizophrenia. Those with ADS scores ≥4 had lower composite BACS scores compared to those with ADS<4 (p=0.004). Among BACS subtests, Verbal Memory was the most adversely affected by high anticholinergic burden. Despite similar anticholinergic burden scores across groups, a significant effect of anticholinergic burden was not detected in schizoaffective or psychotic bipolar disorder.

Conclusion—We identified an adverse effect threshold of anticholinergic burden on cognition in clinically stable participants with schizophrenia. This relationship was not identified in affective psychoses. Examination of other medications, doses, and clinical measures did not account for these findings. Patients with schizophrenia may have increased cognitive susceptibility to anticholinergic medications and the aggregate effects of one's medication regimen may be important to consider in clinical practice.

Keywords

Anticholinergic medication burden; cognitive impairments; psychotic disorders

1. Introduction

Neuropsychological impairment is a core feature of schizophrenia (Hill et al., 2004b; Keefe et al., 2007; Lam et al., 2014). Impairments have been reported in many cognitive domains, including verbal learning and memory, verbal fluency, working memory, processing speed, and executive function (Bilder et al., 2002; Hill et al., 2013, 2004a; Saykin et al., 1994). Similar neuropsychological deficits, albeit less severe, are reported in other psychotic disorders (Hill et al., 2013, 2009, 2008; Lee et al., 2016). Cognitive impairment relates directly to functional outcomes in patients such as psychosocial skill acquisition, performing daily activities, and vocational attainment and contributes to poor quality of life (Green et al., 2000; Leifker et al., 2009). Identifying and minimizing factors exacerbating cognitive deficits is essential for enhancing quality of life and compliance to treatments in patients with psychotic disorders.

Medications with high anticholinergic activity may adversely affect cognition. One biological mechanism for this effect relates to the suppression of the central cholinergic system via direct blockade of muscarinic cholinergic receptors which can disrupt memory (Bartus et al., 1982; Everitt and Robbins, 1997). Among the five distinct muscarinic receptor subtypes (M1–M5), antagonism of the muscarinic M1 receptor is thought to be most closely linked to cognitive impairments, especially those involving memory processes (Everitt and Robbins, 1997). These M1 receptor relationships are linked to cognition in multiple central nervous system (CNS) disorders (Gray and Roth, 2007).

The adverse cognitive effects of anticholinergic medications are established from studies primarily in the elderly whereby anticholinergic burden is associated with increases in delirium, falls, and cognitive deficits (Ancelin et al., 2006; Campbell et al., 2009; Risacher et al., 2016). Furthermore, the aggregate contribution of numerous medications in treatment regimen can collectively contribute to these effects (Campbell et al., 2016; Gray et al., 2015). Studies of anticholinergic medication effects on cognition in schizophrenia (Baitz et al., 2012; Baker et al., 1983; Brébion et al., 2004; Fayen et al., 1988; Minzenberg et al., 2004; Mori et al., 2002; Perlick et al., 1986; Strauss et al., 1990; Sweeney et al., 1991; Tune et al., 1982; Wojtalik et al., 2012) typically have smaller sample sizes and focus on specific anticholinergic medications (i.e. benztropine or trihexyphenidyl) (Baitz et al., 2012; Baker et al., 1983; Brébion et al., 2004; Fayen et al., 1988; Mori et al., 2002; Sweeney et al., 1991) used to treat movement disorder side effects of antipsychotic drugs. However, investigations considering other medications with anticholinergic properties in patient regimens are lacking and these relationships in affective psychosis are relatively understudied.

Patients with psychosis-spectrum disorders often take a number of psychotropic medications, which have varying degrees of anticholinergic properties (Chakos et al., 2006). High medical comorbidities in psychosis often result in the utilization of many non-psychotropic medications, some of which have anticholinergic properties (Carnahan et al., 2006; Jeste et al., 1996). Due to known differences in medication utilization, clinical features, and cognitive deficits across psychotic disorders (Hill et al., 2013), it is important to better understand the adverse cognitive implications of net anticholinergic burden and to examine such effects in each of these diagnoses. In the present study, we assessed cognition

in relation to anticholinergic burden aggregated across all medications included in individual treatment regimens of clinically stable patients with schiaophrenia, schizoaffective disorder, or psychotic bipolar disorder from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study (Tamminga et al., 2013).

2. Methods

2.1 Participants

Participants in this study were selected from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) consortium, which is a study designed to examine an array of candidate endophenotypes including cognition across psychotic disorders (Tamminga et al., 2013). Inclusion criteria for B-SNIP included: (1) age between 15 and 65; (2) age-corrected Wide Range Achievement Test Fourth Edition (WRAT-IV) Reading Score > 65; (3) sufficient English proficiency to complete cognitive testing; (4) no history of seizures or organic brain insults with loss of consciousness > 10 minutes; (5) no diagnosis of substance abuse in the past 30 days or substance dependence during the previous 6 months; (6) negative urine toxicology screen for commonly abused drugs the day of testing; (7) no history of unstable medical or neurological conditions (see reference (Hill et al., 2013)). We focused on a subgroup of B-SNIP probands (206 schizophrenia, 131 schizoaffective, and 146 psychotic bipolar disorder) who were taking at least one antipsychotic medication and had detailed dosing information available. Given the known relationships of dopamine antagonism properties and cognition (Reilly et al., 2006; Sweeney et al., 1991), we selected patients with antipsychotic exposure that could be consistently examined across diagnoses in our analyses.

DSM-IV diagnoses were established via consensus diagnostic meetings using information obtained from the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 1995), available medical charts, and interviews with relatives. Clinical symptom assessments included the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Young Mania Rating Scale (YMRS) (Young et al., 1978), and the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). The Schizo-Bipolar Scale (SBS) ranging from 0 (the most bipolar-like disorder) to 9 (the most schizophrenia-like disorder) (Keshavan et al., 2011) was also assessed in relation to medication variables. All patients were clinically stable with no major changes in medication regimen for at least 4 weeks. Institutional review board approvals were obtained at each B-SNIP site (Hartford, Baltimore, Chicago, Dallas, Boston and Detroit). After the study was explained in detail, all participants provided written informed consent.

2.2 Medication assessments

A medication history interview was performed for both prescription and non-prescription medications. Estimated anticholinergic potency was assigned a numerical value for each scheduled medication in regimens using an updated version of the Anticholinergic Drug Scale (ADS) (Carnahan et al., 2006). This is currently the most comprehensive scale available to quantify anticholinergic burden for the majority of medications commonly used to treat psychotic symptoms and has been validated against serum anticholinergic activity

(SAA) (Carnahan et al., 2006). Since the initial development of the ADS, additional information about the anticholinergic properties of some older medications (Chew et al., 2008; http://kidbdev.med.unc.edu/databases/kidb.php), as well as newly available medications with anticholinergic properties, were incorporated for the current analyses. Examples include modification of scores for selected medications (i.e. olanzapine, quetiapine, etc.) based on more recent reports of anticholinergic activity (Chew et al., 2008) and available inhibitory constant (Ki) values for muscarinic receptors (http://kidbdev.med.unc.edu/databases/kidb.php). The original ADS is available in Carnahan et al (Carnahan et al., 2006), and the updated items for this analysis are highlighted in Supplement Table 1. Supplement Table 2 shows the number of participants for each total ADS score. Total ADS scores for each patient were calculated by summing the values of all scheduled medications used by each participant. Total ADS scores based on the aggregate accumulation of many medications each with different anticholinergic burden values were not normally distributed (due to many participants having no exposure), and the linear nature of ADS scores in relation to serum anticholinergic activity has not been established. Thus ADS scores were treated as ordinal data (0, 1, 2, 3, 4, 5…12).

Finally, to estimate relative antipsychotic dose, a chlorpromazine dose equivalent (CPZeq) was calculated using the Andreasen method (Andreasen et al., 2010). CPZeq was not normally distributed and required a log transformation to normalize the distribution in each diagnostic group for statistical analyses.

2.3 Neuropsychological performance

Participants completed the Brief Assessment of Cognition in Schizophrenia (BACS) battery to assess neuropsychological function (Keefe et al., 2008, 2004). The BACS consists of six subtests: Verbal Memory, Digit Sequencing, Token Motor, Verbal Fluency, Symbol Coding, and Tower of London. BACS composite and subtest z-scores were derived from age, sex, and race stratified norms as in previous studies (Hill et al., 2013; Keefe et al., 2008). Primary outcomes included BACS total scores, and also the Verbal Memory subtest given the established impact of anticholinergic drugs on this cognitive domain (Brébion et al., 2004; Minzenberg et al., 2004; Sweeney et al., 1991). Other BACS subtests were evaluated as secondary outcomes.

2.4 Statistical analyses

Diagnostic group differences in baseline demographics and clinical characteristics were examined using analysis of variance (ANOVA) for continuous variables and chi-square (χ^2) analyses for categorical variables. To examine the relationship of anticholinergic burden with cognitive performance in each diagnostic group, we conducted a series of multivariable linear regression analyses controlling for symptom severity (PANSS total score) and antipsychotic burden (CPZeq). Analyses were stratified by diagnostic group given that the larger B-SNIP sample (Hill et al., 2013) as well as analyses of the current study sample identified significant group differences on a number of demographic and clinical parameters (see Table 1). Linear regression was first used to identify whether ADS scores ≥ 1 were collectively related to BACS scores in each diagnosis. We then examined whether there was a threshold at which anticholinergic burden impacted neuropsychological performance, each

ordinal ADS level was compared to no anticholinergic exposure. Findings indicated a threshold of 4+ on the ADS before neuropsychological scores (primary outcomes) were significantly impacted in the schizophrenia group (Supplement Figures 1 and 2). This threshold was then used to set anticholinergic burden strata (None: ADS = 0; Low: ADS = 1–3; High: ADS = 4+) for subsequent analyses.

In additional post hoc analyses, we explored other ways to examine the influence of disease or symptom severity and overall medication burden. This included analyses examining the total number of psychotropic medications or total number of all medications as additional covariates as well as focused analyses of ADS relationships with BACS in patients with and without clozapine. We examined the influence of other medication groups (e.g. other psychotropic classes such as sedative-hypnotics, anticonvulsants, stimulants, lithium, antidepressants, etc.) as well as premorbid intelligence. In addition, analyses were repeated stratified by age (two age groups: ≤ 50 years and > 50 years) to examine the potential effect of age. Finally, dosing of benztropine, as a representative highly anticholinergic drug, was compared across diagnosis groups to assess potential dosing differences beyond antipsychotic drugs. In these analyses, all major findings remained consistent with the primary analysis and of similar magnitude.

Lastly, the relationship between neuropsychological performance and SBS scores was examined using Spearman's correlation within no (ADS=0), low (ADS=1–3), and high (ADS≥4) ADS burden strata in all psychosis participants to examine the cognitive impact of anticholinergic properties in relation to a dimensional assessment of disease presentation, rather than discrete diagnosis categories.

All statistical analyses were performed using SPSS version 23 (IBM Corp, Armonk, NY), and significance was set at a two-tailed p-value < .05 for all analyses.

3. Results

3.1 Participant characteristics

The demographic and clinical data are summarized in Table 1. There were no significant differences in the total ADS scores across diagnostic groups. However, there was a higher frequency of medication use in general, greater psychotropic medication use, and lower antipsychotic dose among the bipolar group compared to the other diagnostic groups (p-values < 0.05).

3.2 Association between anticholinergic burden and neuropsychological performance

When examining the overall effect of any anticholinergic exposure on BACS performance, ADS scores ≥ 1 were collectively associated with composite BACS scores as compared to those with ADS=0 in schizophrenia (p-value 0.022) and schizoaffective disorder (p-value 0.027), but not in psychotic bipolar disorder (p-value 0.508). After further examination of incremental increases in anticholinergic burden, we identified that among schizophrenia participants, the ADS burden score of 4 was the point at which adverse cognitive influence became statistically significant and further that a high (ADS≥4) versus no (ADS=0) or low (ADS=1–3) anticholinergic burden was significantly associated with lower performance on

the BACS composite and Verbal Memory (Figure 1 and 2). The unstandardized coefficient (B) of the ADS ≥ 4 for composite BACS was −0.576 [95% confidence interval (CI) −0.964 to −0.189, p-value = 0.004], indicating that schizophrenia patients with high ADS scores had lower composite BACS scores (on average a 0.58 standard deviations (SDs) lower) compared to their counterparts with lower ADS scores. Verbal Memory scores were 0.55 SDs worse in schizophrenia patients with high as compared to no or low anticholinergic burden. Additionally, among schizophrenia participants, there was a significant association between high anticholinergic burden and lower performance on the Token Motor and Symbol Coding (Table 2). Because there were education differences across anticholinergic burden strata (p-value = 0.024) within the schizophrenia group, we repeated these analyses adding years of education as a covariate, which did not change the pattern of results. In addition, there were no differences in the pattern of findings among men and women with schizophrenia. These patterns were not statistically significant among either schizoaffective or psychotic bipolar groups on the BACS composite or any subtest (Table 2). It was noted that higher antipsychotic dose was associated with lower performance on Token Motor performance among all diagnostic groups; however, all other cognitive outcomes were not related to antipsychotic dose in schizophrenia participants.

3.3 Anticholinergic burden and neuropsychological performance in relation to dimensional assessment of psychotic disorders

The relation of anticholinergic burden and neuropsychological performance was assessed along a psychotic illness dimension. A significant negative correlation was seen for BACS composite in which scores decreased (worsened) as SBS scores increased from most bipolar-like symptoms (SBS score 0) to most schizophrenia-like symptoms (SBS score 9), but only in those within the high anticholinergic burden group (Spearman's rho = −0.258, p-value = 0.004).

4. Discussion

To our knowledge, this is the first study to identify a potential threshold effect of cumulative anticholinergic burden on neuropsychological performance using medication regimen data from clinically stable patients with schizophrenia. Furthermore, this threshold effect was not observed in participants with schizoaffective or psychotic bipolar disorder. The negative influence of anticholinergic burden on neurocognitive performance in schizophrenia participants was observed when total ADS scores calculated from all currently scheduled medications were 4+. Among the BACS subtests, Verbal Memory, Token Motor, and Symbol Coding were significantly related to total ADS scores exceeding this threshold. The magnitude of this effect was ~0.5–0.6 standard deviation greater cognitive impairment in high anticholinergic schizophrenia patients compared to their low or no anticholinergic burden counterparts.

Verbal Memory was the BACS subtest most robustly influenced by anticholinergic burden and this is consistent with previously established effects of anticholinergic medications on verbal learning and memory in schizophrenia patients (Brébion et al., 2004; Minzenberg et al., 2004; Sweeney et al., 1991) and in the elderly (Bartus et al., 1982); however, the

diagnostic sensitivity of this effect is a novel finding. Schizophrenia participants receiving a high anticholinergic load showed deficits in Verbal Memory approximately twice as large as those with lower anticholinergic burden. In contrast, no significant differences in Verbal Memory scores were found among the schizoaffective and psychotic bipolar disorder participants in this study, although trends of smaller but noticeable effects for this subtest may be indicative of sensitivity at higher burden levels (Figure 2). While this does not indicate an absence of effect in non-schizophrenia diagnoses, it is consistent with the observation of cognitive sensitivity at lower anticholinergic burden in patients with schizophrenia compared to the other disorders. Whereas anticholinergic load was the most significant predictor of Verbal Memory in patients with schizophrenia, increasing dose of antipsychotic medications was associated with worse Token Motor scores in all diagnostic categories (similar effect sizes). Other BACS subtests were not significantly associated with antipsychotic dosage in schizophrenia participants.

The notion that there may be an increased cognitive sensitivity to anticholinergic effects in schizophrenia relative to other psychotic disorders is intriguing, as it is consistent with previously described molecular studies. Numerous post-mortem studies measuring M1/M4 selective radio-ligand binding (i.e. [^{3}H]pirenzepine) (Crook et al., 2001, 2000, 1999; Dean et al., 2002, 1996; Deng and Huang, 2005; Gibbons et al., 2013; Zavitsanou et al., 2004), as well as the levels of protein and mRNA (Dean et al., 2002; Mancama et al., 2003), have observed a widespread reduction of muscarinic receptors, notably M1, in postmortem brain samples of schizophrenia patients. Additionally, *in vivo* analyses identified a 20–35% decrease of muscarinic receptor availability in multiple brain regions in unmedicated patients with schizophrenia compared to the healthy controls (Raedler et al., 2003). Studies comparing M1 and M4 muscarinic receptor density across diagnosis groups identified reductions in patients with schizophrenia, but not in bipolar disorder or major depression (Gibbons et al., 2009; Zavitsanou et al., 2004). Antipsychotic medication use or dose does not appear related to decreased muscarinic receptor density (Crook et al., 2001, 2000, 1999; Dean et al., 2002; Deng and Huang, 2005; Gibbons et al., 2013, 2009; Zavitsanou et al., 2004). Given the already decreased central cholinergic activity through fewer muscarinic receptors in schizophrenia patients, even a small amount of anticholinergic load may cause a significant adverse impact on cognition due to M1 receptor saturation, which may in turn make them more vulnerable to cognitive impairing effects of anticholinergic medication burden compared to those with mood-related psychotic disorders or healthy controls who have greater M1 availability (Tani et al., 2015).

These findings may have significant clinical relevance. O'Reilly et al. recently reported that anticholinergic burden negatively impacted the outcomes of psychosocial treatment focusing on cognitive impairment in patients with schizophrenia (O'Reilly et al., 2016). Because cognitive impairment related to anticholinergic burden may affect skills necessary for independent living and vocational success, it is important for clinicians to appreciate the cumulative effects of anticholinergic drug regimen properties on cognition. Our findings provide some insight into a potential threshold effect of this phenomenon and provide preliminary evidence indicating that clinically accessible tools such as the ADS may be helpful in assessing cumulative anticholinergic burden and its relation to cognitive deficits in specific patients.

When examining this relationship along a disease dimension (SBS), correlations with cognitive performance stratified by anticholinergic burden load groups (no load, low load, high load), we again identified these relationships with participants scoring 'most schizophrenia like' most robustly in those with highly anticholinergic drug regimens. Including patients taking at least one antipsychotic drug may have led to including more severely ill bipolar patients in our analyses. However, anticholinergic effects on cognition were not evident in this potentially more severe group of bipolar patients. Furthermore, given different prescribing practices across psychotic disorders, it is possible that bipolar patients might have less anticholinergic exposure and a lower cumulative impact on cognition. However, ADS burden estimates were similar across diagnostic groups. Another consideration is that the increased cognitive sensitivity to anticholinergic burden in schizophrenia may be due to their cognitive impairment, which possibly indicates reduced cognitive reserve. Post hoc exploratory analyses of schizoaffective and bipolar groups stratified by composite BACS score subgroups (Low: BACS ≤ −1.5; Medium: BACS = −1.5~−0.5; High: BACS ≥ −0.5), however, did not identify such effects in the low performance (BACS ≤ 1.5) group. Finally, secondary analyses examining or adjusting for alternative factors (drug types, dosing, clinical ratings, estimated premorbid intelligence, etc.) did not account for anticholinergic-cognition relationships.

Our study has several limitations that need to be considered when interpreting study findings. The cross-sectional nature of our study design limits the ability to establish causal relationships regarding the observed relationship between anticholinergic burden and neuropsychological performance. While we examined many clinical, medication, and other demographic factors, it is difficult to rule out the possibility of disease severity confounding the findings. Nonetheless, adverse drug effect thresholds in clinically stable patients remain intriguing and consistent with prior molecular studies showing muscarinic receptor differences in brains of those with schizophrenia as compared to primary mood disorders. Second, medication dose is not taken into account in ADS scoring assignments, as dose-weighting approaches in the development of this scale did not enhance correlations with serum anticholinergic activity (Carnahan et al., 2006). Nonetheless differences in dosing strategies across diagnostic groups beyond antipsychotic drugs could be a potential confounding source in our analyses. We addressed several potential confounds by looking at differences in dosing for benztropine as a representative anticholinergic agent (data not shown), and did not observe differences in dosing across diagnostic groups. Third, the duration of anticholinergic medication use was not available for our study participants, and thus it may be likely that schizophrenia patients may have longer duration of anticholinergic exposure than the other groups. Although all patients had been exposed to the estimated anticholinergic burden for a minimum of 4 weeks before cognitive assessments, further studies to examine the influence of the duration of anticholinergic exposure on our findings are warranted. Last, the ADS scoring approach has intuitive clinical appeal, but lacks direct *in vivo* assessment of central anticholinergic drug effect. Thus, our study has advantages in showing a consistency of clinical effect in a large sample, but less direct linkage to CNS biology.

In conclusion, we identified an adverse effect threshold of anticholinergic burden on cognition in patients with schizophrenia. These findings are novel in terms of the methods

with which anticholinergic burden was quantified based on overall medication regimens, the assessment of these relationships in clinically stable patients, and the sensitivity of these effects in those with schizophrenia as compared to schizoaffective and bipolar disorder. Prior molecular studies have identified differences in muscarinic receptor expression in patients with schizophrenia as opposed to those with mood disorders, and our findings may represent a differential clinical sensitivity to drug effects consistent with those differences. However, the mechanisms underlying this effect require further investigation. While it is difficult to dissociate illness severity and different baseline of cognitive impairment from pharmacologic effects in the current study, our findings support the hypothesis that patients with schizophrenia may have increased cognitive sensitivity to anticholinergic medications and that the aggregate effects of one's anticholinergic medication regimen on cognition is sufficiently robust to be important to consider in clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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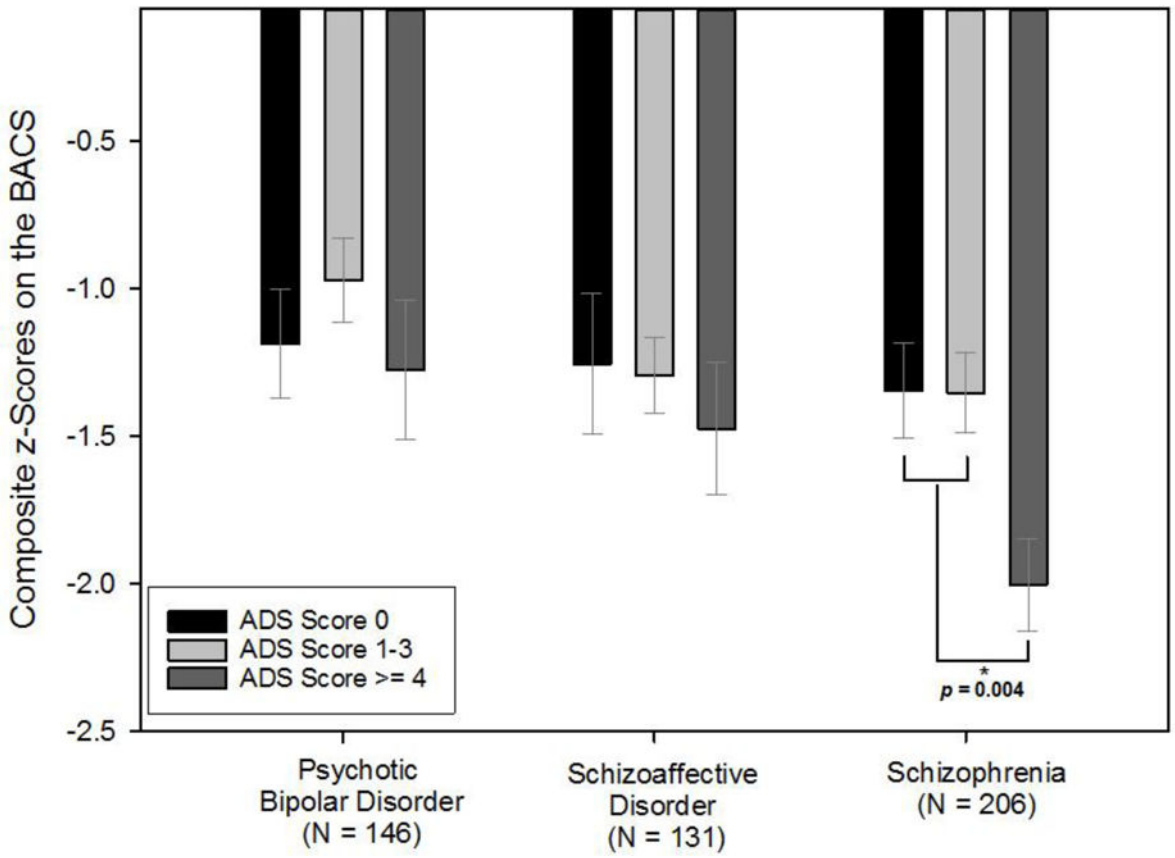

Figure 1.

Anticholinergic burden and global neuropsychological performance across psychotic disorders. Abbreviations: BACS=Brief Assessment of Cognition in Schizophrenia; ADS=Anticholinergic Drug Scale.

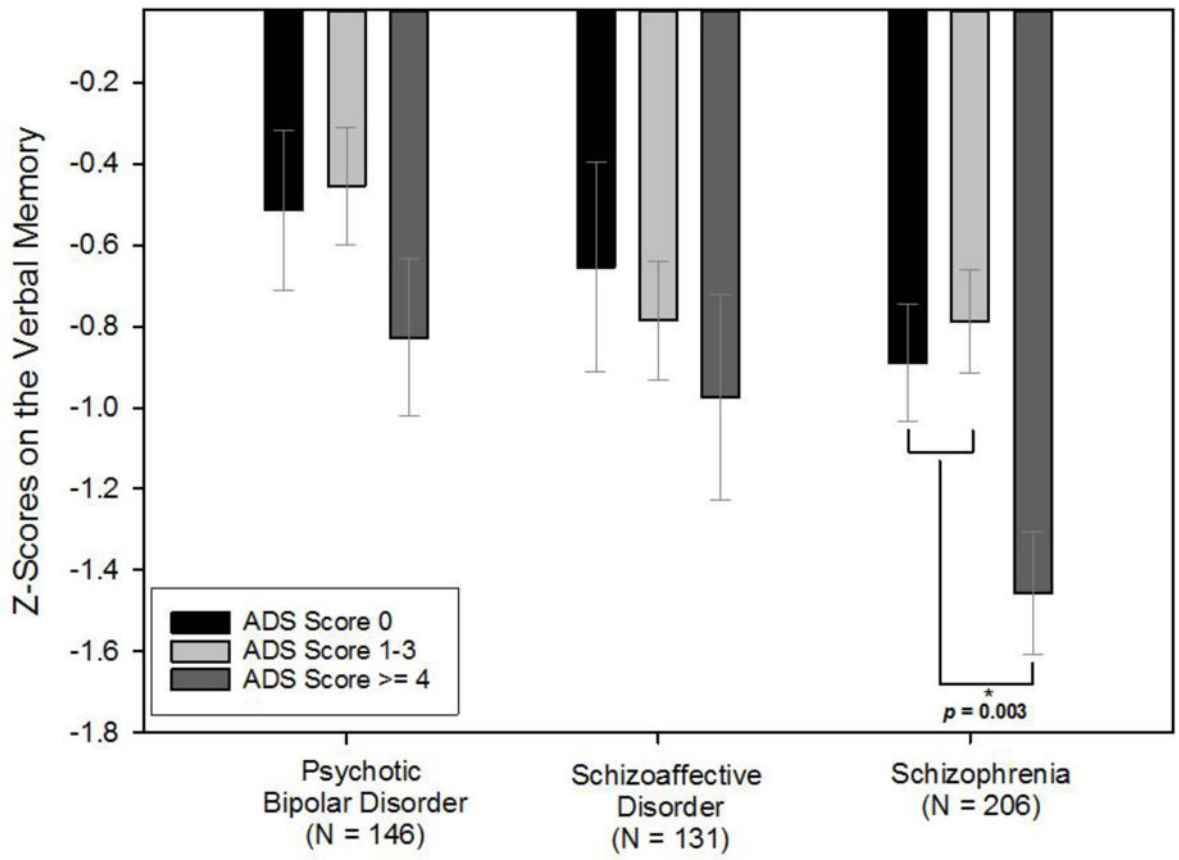

Figure 2.

Anticholinergic burden and Verbal Memory performance across psychotic disorders score.

Abbreviations: ADS=Anticholinergic Drug Scale.

Table 1

Demographic and clinical data of participants

Variable.[a]	Schizophrenia (N=206)		Schizoaffective Disorder (N = 131)		Psychotic Bipolar Disorder (N=146)	
	N	%	N	%	N	%
Male[b, ***]	137	66.5	53	40.5	55	37.7
Race[c]						
Caucasian[***]	101	49	74	56.5	106	72.6
African American[***]	94	45.6	54	41.2	34	23.3
Other	11	5.3	3	2.3	6	4.1
	Mean	SD	Mean	SD	Mean	SD
Age (years)	36.37	13.21	36.83	11.84	35.08	12.20
Education (years)	12.77	2.42	13.04	2.17	13.97	2.28
WRAT-IV Reading[d, **]	93.90	15.50	95.67	14.25	99.92	13.65
PANSS Total Score[e, ***]	64.23	17.10	69.65	15.49	53.58	13.55
SBS Score[f, ***]	7.96	1.16	5.24	1.46	1.15	1.13
BACS Composite Score[g, **]	−1.52	1.27	−1.34	1.19	−1.09	1.23
BACS Subtest Score						
Verbal Memory[g, **]	−1.00	1.19	−0.82	1.33	−0.55	1.21
Digit Sequencing[*]	−0.94	1.06	−0.70	1.06	−0.68	1.01
Token Motor[h, *]	−1.19	1.15	−1.28	1.04	−0.93	1.14
Verbal Fluency[*]	−0.87	1.09	−0.59	1.04	−0.65	1.13
Symbol Coding	−1.40	1.18	−1.36	1.13	−1.21	1.17
Tower of London	−0.63	1.28	−0.55	1.16	−0.31	1.16
Medications						
Total Number of All Medications[g, **]	4.21	2.57	4.93	3.35	5.40	3.63
Total Number of Psychotropic Medications[i, ***]	2.51	1.39	3.30	1.54	3.40	1.53
Chlorpromazine Equivalents (mg/day)[j, ***]	527.61	422.23	539.07	507.18	354.67	325.68

Variable.[a]	Schizophrenia (N=206)		Schizoaffective Disorder (N = 131)		Psychotic Bipolar Disorder (N=146)	
	N	%	N	%	N	%
Total ADS Score	2.46	2.37	2.67	2.21	2.28	2.04

*P-value < 0.05;

**p-value < 0.01;

***p-value < 0.001

[a]WRAT-IV Reading=Wide-Range Achievement Test 4th Edition, reading subtest; PANSS=Positive and Negative Syndrome Scale; SBS= Schizo-Bipolar Scale; BACS= Brief Assessment of Cognition in Schizophrenia; ADS=Anticholinergic Drug Scale

[b]Disproportionate number of males across diagnostic groups

[c]Disproportionate number of Caucasian and African-American across diagnostic groups

[d]Psychotic bipolar > schizophrenia and schizoaffective group

[e]Schizoaffective > schizophrenia > psychotic bipolar group

[f]Schizophrenia > schizoaffective > psychotic bipolar group

[g]Psychotic bipolar > schizophrenia group

[h]Psychotic bipolar > schizoaffective group

[i]Psychotic bipolar, schizoaffective > schizophrenia group

[j]Schizophrenia, schizoaffective > psychotic bipolar group

Table 2

Unstandardized coefficients of high anticholinergic burden when controlling for current symptom severity (PANSS total score) and antipsychotic dose (CPZeq)[a]

	High Anticholinergic Burden (ADS[b] score of ≥ 4)					
	Schizophrenia (N=206)		Schizoaffective Disorder (N = 131)		Psychotic Bipolar Disorder (N=146)	
	Unstandardized Coefficients (B)	p-value	Unstandardized Coefficients (B)	p-value	Unstandardized Coefficients (B)	p-value
Composite BACS[c]	**−0.576**	**0.004**	−0.08	0.725	−0.104	0.671
Verbal Memory	**−0.55**	**0.003**	−0.152	0.557	−0.297	0.231
Digit Sequencing	−0.148	0.387	−0.146	0.482	−0.103	0.622
Token Motor	**−0.523**	**0.003**	0.044	0.823	−0.061	0.791
Verbal Fluency	−0.207	0.225	0.123	0.545	−0.086	0.698
Symbol Coding	**−0.512**	**0.006**	−0.299	0.163	0.142	0.536
Tower of London	−0.386	0.061	0.056	0.804	−0.001	0.995

[a] **Bold**: statistically significant (p-value < 0.05)

[b] ADS=Anticholinergic Drug Scale

[c] BACS=Brief Assessment of Cognition in Schizophrenia