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Anticholinergic Medication Burden–Associated Cognitive Impairment in Schizophrenia

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Abstract

Objective: Many psychotropic medications used to treat schizophrenia have significant anticholinergic properties, which are linked to cognitive impairment and dementia risk in healthy subjects. Clarifying the impact of cognitive impairment attributable to anticholinergic medication burden may help optimize cognitive outcomes in schizophrenia. The aim of this study was to comprehensively characterize how this burden affects functioning across multiple cognitive domains in schizophrenia outpatients.

Methods: Cross-sectional data were analyzed using inferential statistics and exploratory structural equation modeling to determine the relationship between anticholinergic medication burden and cognition. Patients with a diagnosis of schizophrenia or schizoaffective disorder (N = 1,120) were recruited from the community at five U.S. universities as part of the Consortium on the Genetics of Schizophrenia–2. For each participant, prescribed medications were rated and summed according to a modified Anticholinergic Cognitive Burden (ACB) scale. Cognitive functioning was assessed by performance on domains of the Penn Computerized Neurocognitive Battery (PCNB).

Results: ACB score was significantly associated with cognitive performance, with higher ACB groups scoring worse than lower ACB groups on all domains tested on the PCNB. Similar effects were seen on other cognitive tests. Effects remained significant after controlling for demographic characteristics and potential proxies of illness severity, including clinical symptoms and chlorpromazine-equivalent antipsychotic dosage.

Conclusions: Anticholinergic medication burden in schizophrenia is substantial, common, conferred by multiple medication classes, and associated with cognitive impairments across all cognitive domains. Anticholinergic medication burden from all medication classes—including psychotropics used in usual care—should be considered in treatment decisions and accounted for in studies of cognitive functioning in schizophrenia.

Cognitive impairment is a key disabling feature of schizophrenia, with a large literature showing significant deficits in attention, learning, memory, executive functioning, and social cognition (1). Cognitive impairment persists even in the context of antipsychotic medication therapy and is directly linked to poor psychosocial outcomes, including limited skill acquisition, lower educational attainment, compromised vocational success,

and reduced quality of life (2). The sources of cognitive impairment in schizophrenia are multifactorial, but among the molecular and neural circuit abnormalities identified in the disorder, central cholinergic dysfunction has consistently been reported (3). Cholinergic dysfunction is particularly relevant since psychotropic medications commonly used in the treatment of schizophrenia often possess strong anticholinergic properties, and medications with high anticholinergic burden are frequently used to treat the side effects of acute and chronic psychotropic use. Patients with schizophrenia are also more vulnerable to medical comorbidities, which independently increase the chance of being exposed to additional medications with anticholinergic properties. Furthermore, polypharmacy is often seen in patients with psychiatric conditions, and patients with chronic psychotic disorders in particular are more vulnerable to prescribing cascades, which increase the risk and severity of anticholinergic medication burden.

Recent studies of healthy older adults have highlighted the negative cumulative impact of anticholinergic medication exposure and have suggested strong and potentially causal associations between increased anticholinergic medication burden, cognitive impairment, and dementia risk (4, 5). For example, in a large nested case-control study, Coupland et al. (5) calculated anticholinergic drug exposure for up to 11 years in >50,000 case patients age 55 and older and >250,000 age-matched control subjects. They reported that taking even a single medication with strong anticholinergic properties for 3 years was associated with a 50% increase in the odds of developing dementia over the study period. While some research suggests that anticholinergic burden may similarly confer additional cognitive impairment beyond schizophrenia itself, most studies investigating anticholinergic medication burden in schizophrenia have been modest in size, have focused predominantly on specific anticholinergic medications, or have assessed narrowly circumscribed cognitive tests (3, 6–8). Our aims in the present study were 1) to characterize the magnitude of anticholinergic medication burden, 2) to identify its sources, 3) to examine the link between anticholinergic medication burden and cognition, and 4) to determine whether specific domains of cognition were protected from or vulnerable to the effects of anticholinergic medication burden in a large cohort of schizophrenia outpatients.

METHODS

Participants in the Consortium on the Genetics of Schizophrenia–2 (COGS-2) study were between 18 and 65 years old; their characteristics have been described previously (9). COGS-2 was a multisite cross-sectional study that included individuals with schizophrenia and schizoaffective disorder, depressed type, recruited at University of California, San Diego; University of California, Los Angeles; University of Washington; University of Pennsylvania; and Mount Sinai School of Medicine. Inclusion required a diagnosis of schizophrenia or schizoaffective disorder, depressed type, verified by the Structured Clinical Interview for DSM-IV. Exclusion criteria included the presence other psychiatric disorders; major medical or neurological diagnoses, including a history of head injury or stroke; a positive urine toxicology screen for recreational drug use; and a current or recent substance use disorder other than tobacco. Written consent was obtained from all participants; the study was approved by the human research protection committees at each institution, and all data were de-identified. Medication regimens were assessed from medical records obtained

from all participants as well as direct review of medications brought in by patients or their proxies at the time of enrollment and with follow-up interview of patients and/or caregivers when possible to ensure accuracy; 58% of COGS-2 participants lived in residential facilities (board and care, transitional living programs) where staff were able to provide information about medication adherence. From the initial 1,415 schizophrenia patients in COGS-2, 265 participants were excluded because of missing or incomplete medication data, and 30 participants were excluded because they were taking prescribed stimulants, opioids, or steroids. Thus, 1,120 participants were included in the analyses.

Clinical Assessments

As described by Swerdlow et al. (9), participants underwent detailed diagnostic and symptom assessments, including the Scale for the Assessment of Positive Symptoms (SAPS) (10), the Scale for the Assessment of Negative Symptoms (SANS) (11), and the Global Assessment of Functioning (GAF) (12). Chlorpromazine equivalents for antipsychotic dosages were determined as previously described (13). The demographic and clinical characteristics of participants included for analyses and the characteristics of medication classes prescribed to patients are summarized in Table 1.

Assessment of Anticholinergic Burden

Anticholinergic burden from medication regimens was calculated for each participant, using a modified version of the Anticholinergic Cognitive Burden (ACB) scale. The ACB scale is a validated expert rating scale of the anticholinergic properties of medications (4, 14–16) with established clinical utility for predicting dementia risk in large-scale longitudinal clinical outcome studies of healthy older subjects. The ACB scale assigns a dose-independent rating for each medication based on its anticholinergic properties: 1 for low/minimal activity, 2 for moderate activity, and 3 for strong/definite anticholinergic activity. ACB values assigned to various medications and their frequencies in our sample are reported in Table S1 in the online supplement. For medications for which published values were not available, we assigned scores on the basis of known structural or pharmacological similarities to medications with existing ACB scores or consensus values derived from similar scales. In this context, fluphenazine (N = 49) was given a score of 3 because of ratings of high anticholinergic burden on the Anticholinergic Risk Scale and the Anticholinergic Load Scale (17, 18) and its similarity to perphenazine. Prochlorperazine (N = 2) was given a score of 2 because of moderate anticholinergic burden as rated by the Anticholinergic Risk Scale and the Anticholinergic Load Scale. Thiothixene (N = 4) was given a score of 2 because of moderate anticholinergic burden as reported by Duran (19). Ziprasidone (N = 91) and lurasidone (N = 14) were both given a score of 1 because of ratings of either low/minimal or no anticholinergic burden (17). Although not described by the original ACB scale as having significant anticholinergic properties, citalopram (N = 47), escitalopram (N = 33), fluoxetine (N = 58), mirtazapine (N = 21), and sertraline (N = 72) were given a score of 1 because several other scales rated them as having minimal anticholinergic burden (18, 20, 21). Duloxetine (N = 18) was given a score of 1 because of its class similarity to venlafaxine. Nefazodone (N = 1) was given a score of 1 because of its structural similarity to trazodone. Because diazepam was assigned an ACB score of 1 in previous reports, alprazolam (N = 5), clonazepam (N = 59), clorazepate (N = 1),

flurazepam (N = 2), lorazepam (N = 47), oxazepam (N = 1), and temazepam (N = 10) were also given a score of 1, as was zolpidem (N = 45). Because carbamazepine was previously rated with an ACB score of 2, oxcarbazepine (N = 10) was also rated as 2. Valproic acid (N = 122) was given a score of 1, based on low/minimal anticholinergic burden as described by the Anticholinergic Drug Scale (21). Total ACB scores were generated by summing the individual ACB values from all medications for each participant, consistent with established methods (4, 8, 14, 15, 22, 23). Participants were grouped into five categories for subsequent analyses: no anticholinergic burden (ACB score = 0), low anticholinergic burden (ACB score = 1 or 2), moderate anticholinergic burden den (ACB score = 3 or 4), high anticholinergic burden (ACB score = 5 or 6), or very high anticholinergic burden (ACB score >6).

Cognitive Assessments

The Penn Computerized Neurocognitive Battery (PCNB) was used as the primary outcome measure for cognitive functioning (24). The PCNB includes accuracy and speed measures in eight domains: abstraction and mental flexibility, attention, working memory, face memory, verbal memory, spatial memory, spatial ability, and emotion processing, reported as age- and gender-corrected *z*-scores. Efficiency scores for these eight domains were obtained as the average of accuracy and speed scores, as has been previously described (24). A PCNB global cognition score was derived by averaging individual efficiency scores (24). The PCNB included additional tests of motor praxis and overall motor speed that do not contain accuracy components; these tests were analyzed separately. Aside from the PCNB, a number of other cognitive assessments were administered to COGS-2 participants, including the Continuous Performance Test-Identical Pairs Version (CPT-IP; 3- and 4-digit) (25), the Degraded-Stimulus Continuous Performance Test (DS-CPT) (26), the letter-number span (forward and reorder) (27), and the California Verbal Learning Test–II (list A trials 1–5, list A total, list B total, short-delay free and cued recall, and long-delay free and cued recall) (28).

Statistical Analysis

The impact of cumulative anticholinergic medication burden (none, low, moderate, high, or very high) on individual tests of cognition described above was examined by one-way Bonferroni-corrected analysis of variance with the initial significance threshold set to 0.05. Follow-up exploratory covariate regression analyses were conducted to determine whether relationships between ACB score (as a continuous variable, range 0–20) and cognition persisted after controlling for other important variables, including antipsychotic dosage, number of antipsychotics, positive symptom severity, negative symptom severity, duration of illness, number of hospitalizations, and cigarettes smoked per day. Lastly, we used exploratory structural equation modeling (ESEM) to determine whether relationships between ACB score (continuous variable) and cognition were specific to individual cognitive domains in the PCNB. This data reduction approach allowed us to reduce associations between ACB scores and each of the cognitive measures into associations between ACB scores and a smaller number of primary, core cognitive domains (latent cognitive domain factors). The parallel analysis function in the R *psych* package was used to determine the number of primary cognitive domains measured by the PCNB. Next, the R *lavaan* package was used to generate a latent variable measurement model that related

each of the PCNB cognitive measures to the latent cognitive domain factors. The model was identified using the reference loading approach (29). Finally, within the ESEM model, each latent cognitive domain was regressed onto ACB scores. Models were fitted to the data using maximum likelihood estimation. Model fit was evaluated using root mean square error of approximation (RMSEA) and comparative fit index (CFI) metrics. RMSEA values less than 0.06 combined with CFI values greater than 0.95 are considered evidence of good model fit (30).

RESULTS

Magnitude and Sources of Anticholinergic Burden in Schizophrenia Patients

As shown in Figure 1, the average ACB score for study subjects was 3.8 (SD = 2.9, range, 0–20). Most of the anticholinergic medication burden was attributable to antipsychotics (mean = 2.1, SD = 1.6), followed by traditional anticholinergics (benztropine, diphenhydramine, and trihexyphenidyl; mean = 0.7, SD = 1.3), antidepressants (mean = 0.5, SD = 0.8), mood stabilizers (mean = 0.4, SD = 1.0), and benzodiazepines (mean = 0.1, SD = 0.3). Among all study participants, 113 (10.1%) were not on antipsychotic therapy. Of those, 81 participants (7.2% of all included participants; 72% of those not on any antipsychotic therapy) had a medication regimen with an ACB score of 0.

The majority of schizophrenia patients were on antipsychotic monotherapy, with second-generation agents outnumbering first-generation agents by a ratio of 9:1 (see Table 1); approximately one out of five patients were on antipsychotic polypharmacy. Of those on monotherapy, ACB scores tended to be higher among those on first-generation compared with second-generation antipsychotics (total mean ACB score, 4.3 [SD = 2.5] for first-generation agents and 3.2 [SD = 2.0] for second-generation agents; F = 20.4, $p<0.001$), driven by the use of traditional anticholinergics (mean ACB scores due to anticholinergics were 1.4 [SD = 1.7] for patients taking first-generation antipsychotics and 0.4 [SD = 1.1] for those taking second-generation antipsychotics; F = 41.6, p<0.001). No other ACB score differences attributable to medication classes were detected when comparing between patients on first-generation and second-generation antipsychotic monotherapy (all other F values <1, p values >0.5). Notably, there was no difference in ACB score attributable to antipsychotics between those on first- or second-generation antipsychotic monotherapy (mean ACB scores were 2.0 [SD = 1.0] for first-generation antipsychotics and 1.8 [SD = 1.0] for second-generation antipsychotics; F = 1.5, p = 0.21). The contribution of different medication classes to cumulative ACB score over the range of ACB scores observed in participants is illustrated in Figure 2.

Association of Anticholinergic Medication Burden With Cognitive Functioning

As shown in Figure 3, ACB score was negatively associated with PCNB performance across all efficiency domains; higher anticholinergic medication burden was associated with worse cognitive performance. The PCNB global cognitive averages for none, low, average, high, and very high anticholinergic burdens were, respectively (in z values), –0.51, –0.70, –0.85, –0.96, and –1.15. Anticholinergic medication burden level was also associated with PCNB

motor speed (F=9.3, p<0.001) and motor praxis (F=11.2, p<0.001). Similar effects were seen on 15 of 16 additional cognitive tests, as shown in Table S2 in the online supplement.

Notably, when controlling for total ACB score, there were no significant differences in cognition across all PCNB domains among schizophrenia patients on second-generation antipsychotic monotherapy, first-generation antipsychotic monotherapy, or polypharmacy (F = 1.4, p = 0.256). Among those on antipsychotic monotherapy, after controlling for total ACB score, there were no significant effects of individual antipsychotics in each class across all PCNB cognitive domains (second-generation antipsychotics, F = 1.6, p = 0.093; first-generation antipsychotics, F = 0.99, p = 0.454).

The negative association between ACB score and cognitive performance remained significant after individually controlling for antipsychotic dosage, cigarettes smoked per day, positive symptoms, negative symptoms, duration of illness, age, and number of past hospitalizations at time of enrollment in COGS-2 (see Table S3 in the online supplement).

Specificity of ACB Score Effects on Cognitive Domains

Psychometric analyses identified four latent cognitive domains from the PCNB with factor structures consistent with previous studies in schizophrenia patients using a similar version of the battery (24): memory, attention and control, executive and visuospatial, and motor. The ESEM model provided an excellent fit to the data (RMSEA=0.048; CFI=0.991). Parameter estimates are reported in Figure 4. The effect of ACB score on these factors was similar, suggesting that anticholinergic medication burden effects on cognition in schizophrenia are not specific to any of the domains examined.

DISCUSSION

In this study, we characterized anticholinergic burden in a large cohort of schizophrenia outpatients. We found that many patients have medication regimens with high anticholinergic burden, with an average ACB score of 3.8. For context, an ACB score of 3 in healthy older adults is associated with cognitive dysfunction and a 50% increase in risk for developing dementia (5). In our data, the proportion of patients with an ACB score of at least 3 was 63%, with approximately 25% having an ACB score ≥6. While these numbers may be high for patients without any psychiatric illness, such scores are not difficult to achieve in routine psychiatric care. For example, a patient for whom daily olanzapine is prescribed for symptoms of psychosis would have an ACB score of 3; if hydroxyzine were also prescribed for anxiety or insomnia, the patient's ACB score would rise to 6. Since the COGS-2 study did not enroll patients with major medical illnesses, these ACB scores likely underestimate values present in the more heterogeneous population of schizophrenia patients in the community. Consistent with these prior findings in healthy subjects, anticholinergic burden was also significantly associated with generalized impairments in cognitive functioning in schizophrenia patients. Antipsychotics contributed more than half of this anticholinergic burden, while traditional anticholinergics, antidepressants, mood stabilizers, and benzodiazepines accounted for the remainder. We did not detect significant differences in ACB effects on cognitive functioning between patients on antipsychotic monotherapy with first-generation agents and with second-generation agents, between

patients taking individual antipsychotics within the two classes, or between patients on antipsychotic monotherapy and those on polypharmacy when controlling for total ACB score. The results also indicate that significant anticholinergic effects on cognition were detected across all cognitive domains with comparable magnitude. Furthermore, the ACB effects on cognition persisted even after we controlled for multiple proxies of functioning or disease severity. Our results therefore suggest that total cumulative anticholinergic burden —rather than anticholinergic burden attributable to a specific antipsychotic or psychotropic medication class—is a key contributor to cognitive impairment in schizophrenia. While larger, longitudinal studies are needed to clarify cause-effect relationships in schizophrenia patients, the results of this study are compatible with emerging findings in other psychiatric disorders (31, 32).

Psychotropic medications, especially antipsychotics, are critically important therapeutics for schizophrenia, have substantially improved the lives and outcomes for countless patients living with schizophrenia, and represent an essential staple of comprehensive treatment. The present results do not necessarily suggest that a specific psychotropic or combination of psychotropics is “better” or “worse” for cognition. The results nonetheless have several implications for current clinical practice and psychiatric research, particularly regarding procognitive therapeutic development for schizophrenia. First, important trade-offs in the treatment of patients with schizophrenia should continue to be carefully considered. While psychotropic medications with significant anticholinergic properties may be necessary to reduce symptoms and help patients achieve or maintain functional gains, they may also contribute to longer-term cognitive disability. Several studies suggest increased rates of aging-associated cognitive impairment and dementia incidence among patients with schizophrenia (33, 34). However, studies of longitudinal cognitive changes in schizophrenia have yielded mixed results (35, 36). Interestingly, recent work by Solís-Vivanco et al. (37) showed that unmedicated first-episode and unmedicated chronic schizophrenia patients have similar degrees of cognitive impairment. Thus, while it is clear that cognitive deficits are apparent even in the absence of anticholinergic medication exposure in schizophrenia, the present results suggest that anticholinergic medication burden may account for at least some of the longitudinal cognitive decline observed in some studies (35, 37).

Second, these results add to the literature that challenges assertions that second-generation antipsychotics have significantly different cognitive effects from first-generation antipsychotics. Rather, our results suggest that differences in cognitive outcomes associated with antipsychotic medications, if present, likely occur in the context of overall anticholinergic medication burden and may not necessarily reflect other complex differences in dopaminergic/serotonergic blockade or other specific pharmacologic properties of individual antipsychotics. In fact, emerging work suggests that deprescribing anticholinergic medications is associated with not only cognitive benefits but also an improved quality of life (38).

Third, given the robust differences in global cognition between schizophrenia patients in the highest ACB groups and those without any anticholinergic burden, trials of novel procognitive therapeutics in schizophrenia should consider anticholinergic load when interpreting outcomes (23, 39). Similarly, large population studies of cognitive outcomes,

or genetic studies using cognition as a disease phenotype, may benefit from considering the contribution of ACB score to their cognitive measures in schizophrenia or other patients.

Limitations

This study should be considered in the context of several limitations. First, COGS-2 used a cross-sectional design that makes it impossible to disentangle cause-effect relationships between anticholinergic burden and cognition or to determine the longitudinal impact of anticholinergic burden on cognitive functioning in schizophrenia. Since participants were not randomized to treatment in this study, other confounding factors or proxies for disease severity may account or for the association of ACB score and cognition. However, the present findings are fully compatible with results from recent large-scale longitudinal studies of anticholinergic medication burden in adults without schizophrenia.

Second, as noted above, the impact of anticholinergic medication burden on cognition in schizophrenia is likely to be *underestimated* in this study given that schizophrenia patients who had significant medical conditions were not recruited for COGS-2. Moreover, while we excluded those with major medical issues that could confound results, treatments of more “minor” medical issues were not reported (e.g., allergies, gastroesophageal reflux disease, insomnia). To the degree that intermittent medications used for treating these medical issues may have anticholinergic properties, they may have contributed to unappreciated anticholinergic burden in our sample; intermittent use of over-the-counter medications with anticholinergic properties at the time of testing could not be reliably disambiguated. Similarly, we did not formally assess for mood or motor symptoms with instruments validated for these specific illness domains. We acknowledge that there are likely independent effects of mood (particularly for those with schizoaffective disorder, depressed type) as well of the full range of extrapyramidal side effects on cognitive performance and study outcomes, which must be carefully characterized in future studies.

Third, the ACB scale, along with other similar scales, is limited by a failure to account for dose as well as previous or longitudinal exposure to medications with anticholinergic properties, and our modified ACB scale included consensus values for several medications and a novel binning strategy, which, while anchored by empirical data from previous studies, could have affected results. While further work is needed to replicate, clarify, and delineate dose and time-course effects of anticholinergic burden and cognition for schizophrenia patients, our modified ACB rating scale and other similar scales offer other advantages: they are easily deployable in routine clinical settings and can be readily incorporated into electronic medication records, as well as future or retrospective research studies.

Fourth, as with many large-scale studies investigating effects of psychotropic medications in patients with chronic psychotic disorders, it is possible that medication nonadherence may have affected our results. This is an ongoing challenge in the field, and future studies may benefit from more active methods of medication adherence surveillance.

Lastly, the COGS-2 cohort largely consisted of schizophrenia participants with chronic illness. The effects described in our analyses may not hold for clinical high risk, prodromal, or early illness populations; similarly, the relationship between ACB score and cognitive

functioning may be different during an acute decompensation or shortly after remission. Further studies are also needed to determine the longitudinal course and durability of anticholinergic burden–cognition relationships.

Recommendations

Anticholinergic medication burden associated with psychotropic medications in schizophrenia is substantial, common, and conferred by multiple medication classes, including antipsychotics. Cumulative anticholinergic medication burden should be considered when prescribing medications (psychotropic as well as nonpsychotropic) for patients with schizophrenia. Efforts to limit or avoid excessive anticholinergic medication burden—regardless of source—may have a beneficial impact on cognitive outcomes in schizophrenia. Algorithms for anticholinergic burden calculations may be deployable within electronic medical record systems to guide providers in medication choices. When deprescribing or avoiding a high–anticholinergic burden regimen may not be clinically prudent, adjuvant treatment that can reduce the negative cognitive impact of anticholinergic medication burden may be helpful. For example, we recently found that a computerized cognitive training intervention blunted some anticholinergic burden–associated cognitive deterioration in chronic schizophrenia patients in residential inpatient care (23). Studies are needed to assess the longitudinal cognitive impact of anticholinergic burden and thereby further guide and optimize prescribing practices.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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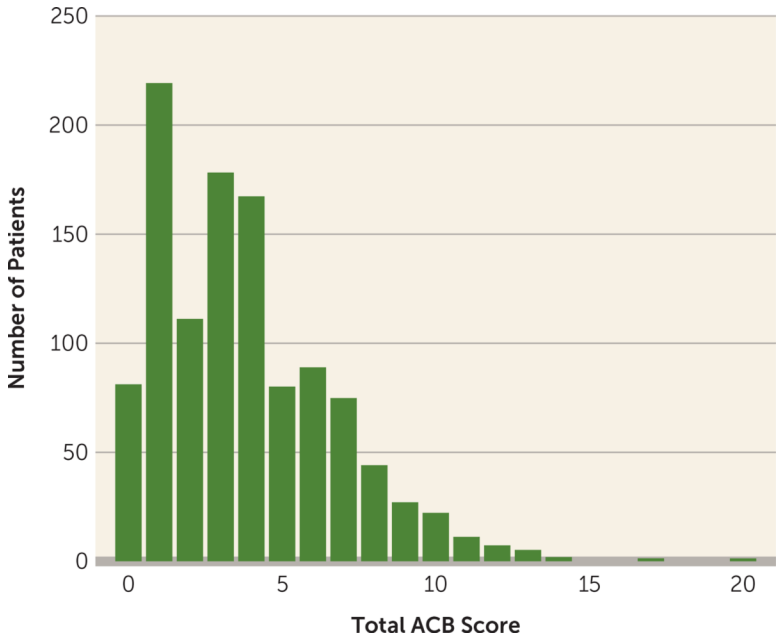


FIGURE 1.

Total Anticholinergic Cognitive Burden (ACB) scale score distribution among schizophrenia patients in COGS-2

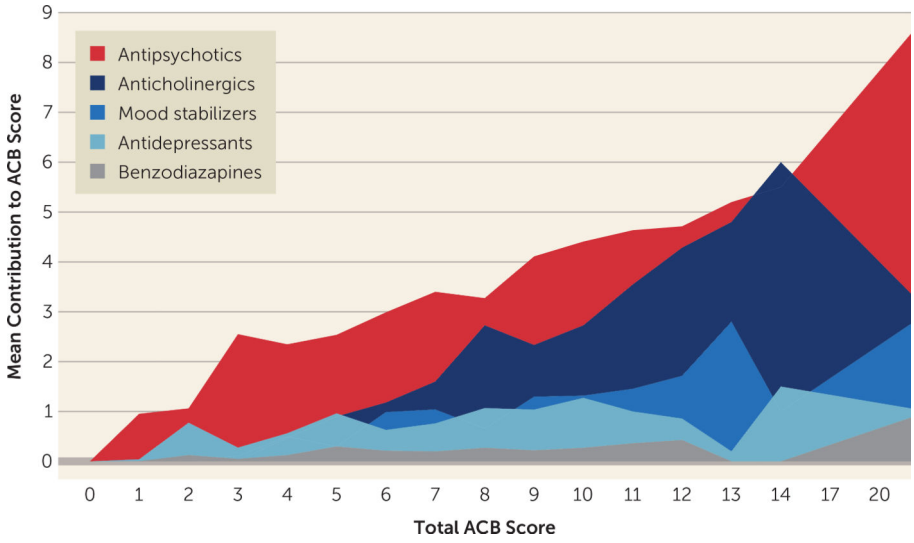
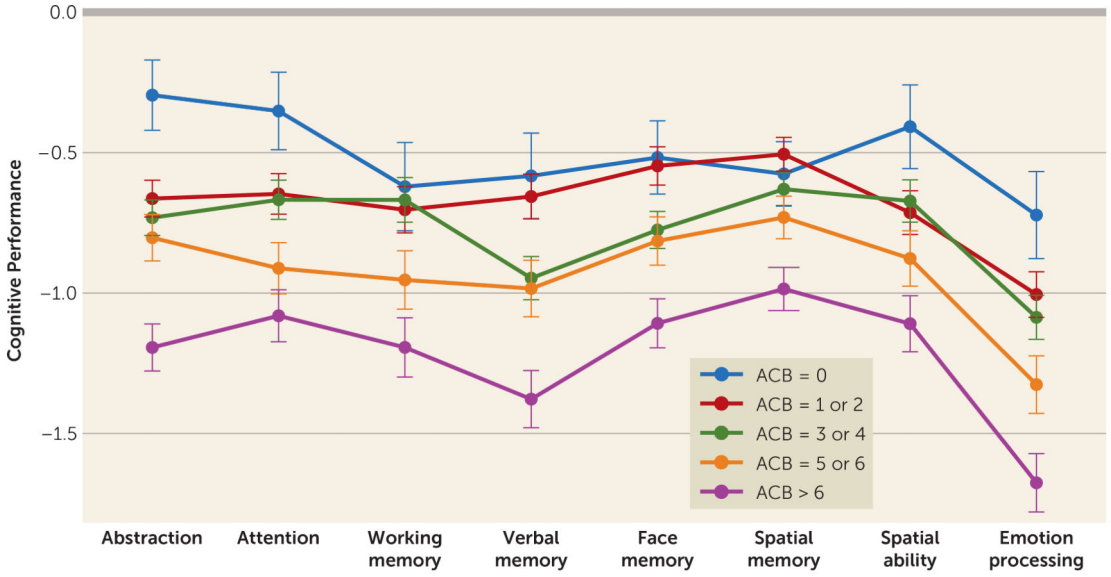


FIGURE 2.
Medication class contribution to total Anticholinergic Cognitive Burden (ACB) scale score



	ACB = 0		ACB = 1 or 2		ACB = 3 or 4		ACB = 5 or 6		ACB > 6		
PCNB Domain	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	F
Abstraction	69	−0.34 (0.66)	245	−0.68 (0.83)	268	−0.84 (1.23)	158	−0.85 (0.98)	157	−1.23 (1.28)	10.4
Attention	69	−0.31 (0.94)	247	−0.66 (0.99)	273	−0.78 (1.15)	155	−0.93 (1.14)	163	−1.24 (1.53)	10.2
Working memory	66	−0.60 (1.40)	236	−0.70 (1.16)	263	−0.70 (1.16)	151	−0.97 (1.28)	153	−0.12 (1.50)	6.3
Verbal memory	69	−0.60 (0.93)	249	−0.71 (1.00)	273	−1.06 (1.54)	158	−1.02 (1.20)	168	−1.47 (1.43)	10.6
Face memory	69	−0.52 (0.94)	250	−0.59 (0.86)	272	−0.86 (1.14)	159	−0.84 (0.93)	164	−1.14 (1.38)	8.0
Spatial memory	66	−0.58 (0.86)	245	−0.52 (0.72)	266	−0.65 (0.82)	157	−0.78 (0.77)	162	−1.01 (1.33)	7.9
Spatial ability	69	−0.45 (0.95)	248	−0.72 (1.08)	272	−0.75 (1.27)	159	−0.92 (1.31)	164	−1.18 (1.45)	5.8
Emotion processing	66	−0.72 (0.93)	243	−1.05 (1.20)	266	−1.18 (1.38)	159	−1.41 (1.24)	159	−1.82 (1.49)	12.5

FIGURE 3. Relationship between Anticholinergic Cognitive Burden (ACB) scale score and performance on Penn Computerized Neurocognitive Battery (PCNB) domains[a]

[a] Cognitive performance is reported as age- and gender-corrected z-scores. All main effects of ACB level on cognitive functioning domains were significant at p<0.001.

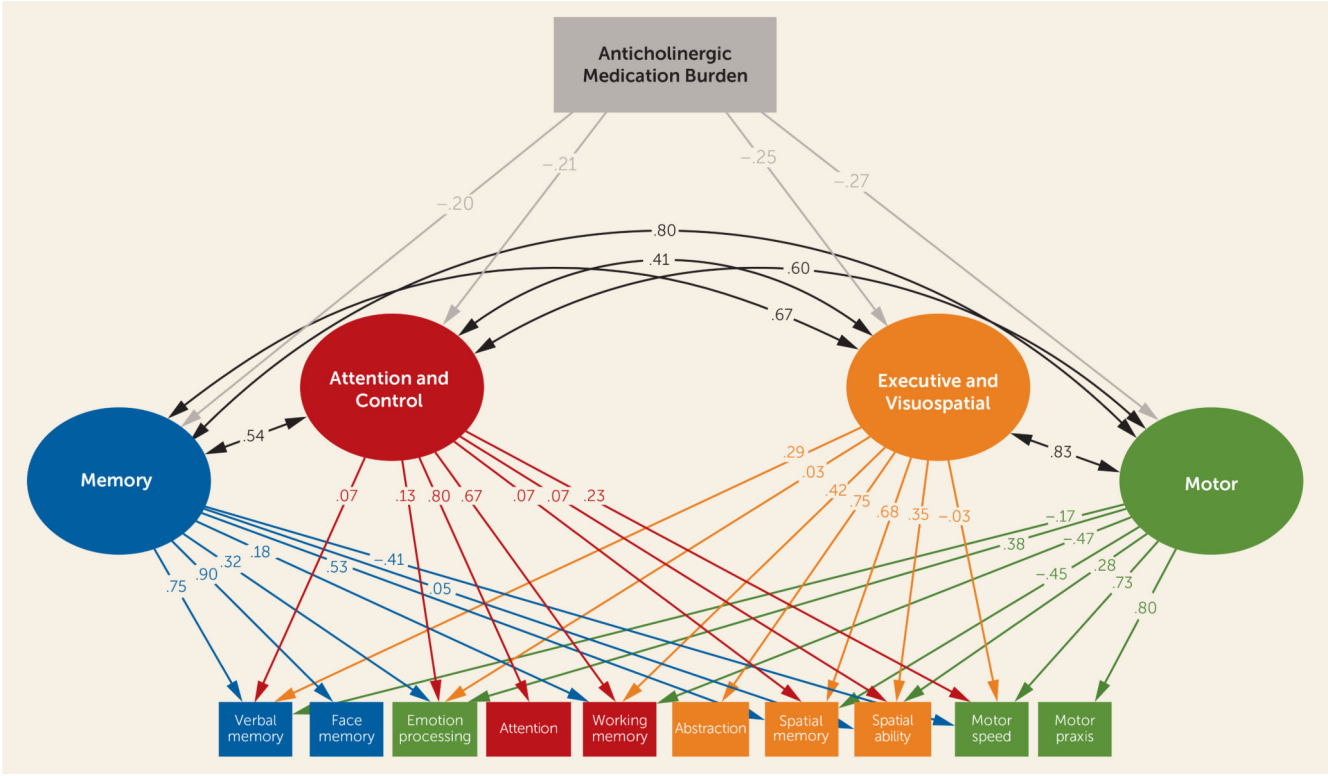


FIGURE 4. Anticholinergic medication burden effect on cognitive domains[a]

[a] Exploratory structural equation modeling identified four latent cognitive domain factors that were similarly affected by anticholinergic medication burden.

TABLE 1.

Demographic and clinical characteristics of included participants

Characteristic		
	Mean	SD
Age (years)	46.2	11.0
Age at onset (years)	22.3	6.9
Duration of illness (years)	23.8	11.4
Education (years)	12.5	2.1
Number of past hospitalizations	7.3	9.7
Global Assessment of Functioning score	43.8	8.2
Scale for the Assessment of Positive Symptoms score	6.9	4.0
Scale for the Assessment of Negative Symptoms score	11.0	5.8
Antipsychotic dosage (chlorpromazine equivalents, mg/day)	457	538
Cigarettes per day	7.8	10.0
	N	%
Female	351	31.3
Hispanic ethnicity	161	14.4
Race		
Native American	7	0.6
Asian	34	3.0
Pacific Islander	11	1.0
African American	442	39.5
Caucasian	483	43.1
More than one race	137	12.2
Not reported	6	0.5
Medication		
Antipsychotics		
None	113	10.1
One antipsychotic	783	69.9
Second-generation	708	90.4
First-generation	75	9.6
Two antipsychotics	198	17.7
Three antipsychotics	26	2.3
Anticholinergics		
One anticholinergic	225	20.1
Benztropine	147	65.3
Diphenhydramine	32	14.2
Hydroxyzine	28	12.4
Trihexyphenidyl	18	8
Two anticholinergics	20	1.8

Characteristic		
Antidepressants		
One antidepressant	418	37.3
Two antidepressants	80	7.1
Three antidepressants	5	0.4
Mood stabilizers		
One mood stabilizer	224	20
Two mood stabilizers	15	1.3
Three mood stabilizers	2	0.2
Benzodiazepines		
One benzodiazepine	167	14.9
Two benzodiazepines	14	1.3