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Anticholinergic Medication Burden and its Effects on Memory Impairment

By

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Abstract

This study investigates the optimal way to calculate anticholinergic burden using two calculators known as the Anticholinergic Cognitive Burden Scale and the Anticholinergic Loading Scale. The first aim of the study was to replicate extant literature that has suggested a significant, deleterious impact of anticholinergic burden on cognitive performance (Taylor-Rowan et al., 2022). It aims to find the more optimal calculator to see which one is a better predictor of cognitive performance, and specifically, cognitive impairment, as research has shown an association between anticholinergic burden and cognitive decline. This study aims to provide an optimal calculator to be used as a tool for physicians in their prescribing practices to most accurately predict the potential cognitive impact of medications with anticholinergic properties. Archival data was used from the Department of Psychiatry in the University of Chicago Medical Center to find each individual patient's anticholinergic burden score, separately calculated using the Anticholinergic Cognitive Burden Scale and Anticholinergic Loading Scale protocols. The analysis showed no significant differences between burden and no burden groups and there were no correlations between anticholinergic burden and test scores on neuropsychological tests. We did not find a way to best predict cognitive performance. Future research should focus on longitudinal designs and moderating factors.

Keywords: Anticholinergic burden, ACB, ALS, cognitive performance, cognitive impairment, association, archival data, acetylcholine, dementia, t-tests, correlation

Anticholinergic Burden and its Effects on Memory Impairment

In the United States, approximately 20-50% of older adults take prescription drugs with anticholinergic effects (Hilmer & Gnjidic, 2022). Anticholinergic medications inhibit or block the neurotransmitter acetylcholine in the peripheral or central nervous system (Bell & Avery, 2021). Acetylcholine is a neurotransmitter responsible for numerous functions, including cognition, behavior, and emotion (Taylor-Rowan et al., 2022). Medications with anticholinergic effects treat a myriad of conditions such as Parkinson's disease, overactive bladder, Chronic Obstructive Pulmonary Disease, and dizziness (NHS, 2022). These medications are associated with adverse drug reactions such as cognitive impairment (ACB calculator, 2024). As people age, it is common for individuals to increase the dosage of drugs with anticholinergic effects, leading to a buildup known as anticholinergic burden. The anticholinergic burden is the negative impact of an accumulation of drugs with anticholinergic properties dependent on the duration of the medications, dose, and the number of anticholinergics taken (NHS, 2022). One way anticholinergic burden can be measured is through serum radioreceptor anticholinergic activity assay (SAA) (Taylor-Rowan et al., 2022). In addition to such direct measurement techniques, this burden can be estimated in many ways with different scales. Most scales rank medications on a scale of 0 (no anticholinergic effects) to 3 (high levels of anticholinergic activity) (ACB calculator, 2024). These scales were developed to quantify the effects of these anticholinergics and to give clinicians a tool for understanding potential anticholinergic effects when prescribing medications to older adults (ACB calculator, 2024). This raises the question: is there an optimal way to calculate anticholinergic burden?

Research has shown an association between this burden and cognitive impairment or even dementia in older adults, given that they are more likely to be affected by multiple conditions and therefore are prescribed several medications (ACB calculator, 2024). Dementia, a common form of cognitive impairment, is "a syndrome of decline in cognitive function beyond

what is expected from normal aging to an extent that interferes with usual functioning" (Taylor-Rowan et al., 2022, p. 1). This interference can affect memory, thinking, comprehension, learning, language, and judgment (Taylor-Rowan et al., 2022). Dementia is considered a major public health issue as there are now more than 40 million people in the world with dementia and this number is expected to continue increasing over time (Taylor-Rowan et al., 2022). When cognitive functioning declines, people's independence is progressively diminished, increasing caregiver burden, healthcare support requirements, and institutionalization (Taylor-Rowan et al., 2022). Another issue is the neuropsychiatric disturbances that occur in response to declining cognition and dementia. Research has shown that up to 90% of Alzheimer's patients experience symptoms such as mood disturbance, depression, agitation, anxiety, sleep disorders, psychosis, hallucinations, and delusions (Taylor-Rowan et al., 2022). According to Risacher et al. (2016), the use of anticholinergic medications with high or medium anticholinergic effects was associated with poorer cognition, whole-brain atrophy, and clinical decline, suggesting that anticholinergic medications may be dangerous for brain structure and function in addition to cognition. This problem may only become worse. Gildengers et al. (2023) discovered that any anticholinergic drug use was associated with risk of development of mild cognitive impairment.

The role of the central cholinergic system in cognitive impairment is well-known. Many studies done over the years have shown that numerous problems in the central cholinergic system lead to cognitive symptoms (Boustani et al., 2008). Cholinergic system abnormalities include changes in choline transport, acetylcholine release, muscarinic-receptor expression, and axonal transport (Boustani et al., 2008). Dysfunction of cholinergic neurons in the forebrain pathways leads to low levels of the neurotransmitter acetylcholine which has a substantial impact on cognitive impairment and behavioral symptoms of patients with Alzheimer's disease, vascular dementia, and delirium (Boustani et al., 2008). Lesions that damage cholinergic input to the

neocortex from the basal forebrain lead to the same cognitive impairment done by anticholinergics (Boustani et al., 2008).

According to Boustani et al. (2008), there are three methods to determine the anticholinergic properties of medications. There is SAA, in vitro measurement of drug affinity to muscarinic receptors, and expert-based lists of medications with anticholinergic activity (Boustani et al., 2008). The first method, known as serum radioreceptor anticholinergic activity assay (SAA), quantifies a person's anticholinergic burden caused by all drugs and their metabolites, using tritiated quinuclidinyl benzilate, "a high and specific affinity agent that competes with other anticholinergics for the muscarinic receptors" (Boustani et al. 2008, p. 3). SAA measures the cumulative anticholinergic effect of all prescribed and over-the-counter medications taken by someone but reflects a transitional state outside the brain (Boustani et al., 2008). The second is a similar method to SAA but performed in an in vitro sample, measuring "the binding of a medication into a specific muscarinic receptor, and quantifies the antagonistic properties with a comparative cholinergic agonist, leading to a measurement of the direct anticholinergic effect" (Boustani et al., 2008, p. 3). Finally, the third method is most clinically relevant, and based on the opinions of clinicians, pharmacists, and pharmacology researchers who "combine their expertise with drug information available in the literature" to determine anticholinergic properties of medications (Boustani et al., 2008, p. 3).

Objective and Current Study

This study aims to replicate past research that has suggested that anticholinergic burden has a deleterious effect on cognition. Moreover, the study aims to investigate the optimal way to calculate anticholinergic burden to better understand the consequences of such burden on cognitive performance. Taking several anticholinergic medications can increase one's anticholinergic burden which, in turn, has been demonstrated to have a significant impact on cognition. The higher the burden, or number of medications taken, the higher the likelihood that

someone will develop memory and learning deficits. Notably, in individuals aged 65 or older, a high degree of anticholinergic burden can even exacerbate the effects of cognitive decline related to an independent neurodegenerative process. Knowing the best way to calculate an individual's level of anticholinergic burden can have significant clinical utility. Namely, this may assist providers in better tailoring a patient's medication regimen such that their physical and/or psychiatric complaints are treated while also reducing the risk of negatively impacting their cognitive functioning. I hypothesize that the ACB calculator will be more predictive of cognitive performance because it has more medications and uses more methods (e.g. SAA, in vitro measurement of drug affinity to muscarinic receptors, and an expert list of medications with anticholinergic activity) to find anticholinergic medications than the ALS. These two calculators were selected for comparison for reasons that will be elucidated below. This paper will start with a review of relevant literature, describe the methods used to collect and analyze the data, and present and discuss the investigation results.

Literature Review

There are several scales used to estimate anticholinergic burden. For example, in Bell and Avery's (2021) investigation, six scales were determined to be suitable for the quantification of anticholinergic exposure, and each scale varies in how scores are assigned, suggesting nonuniversal agreement about anticholinergic burden and its impact. The Anticholinergic Cognitive Burden (ACB) scale and the Anticholinergic Drug Scale (ADS) are two commonly used scales that contain the largest number of relevant medicines and use the average daily dose to calculate anticholinergic burden (Bell & Avery, 2021). The ACB also considers anticholinergic potency. The ACB calculator is one of the calculators used in the present study.

Notably, there is a strong relationship between memory impairment and use of anticholinergic drugs (Pieper et al., 2020). Uusvaara et al (2013) recruited 400 people aged 75 to 90 years old with a questionnaire that asked about their health, current use of prescription drugs,

and their social relationships. Participants were tested with the CERAD test battery and other tests of aspects such as verbal fluency, wordlist recall, and wordlist recognition (Uusvaara et al., 2013). There was a statistically significant association between use of anticholinergic drugs and low scores on verbal fluency, naming, and MMSE tests; however, there were no differences between people who do and do not take anticholinergic drugs on tests such as wordlist recall, recognition, tests of episodic memory (Uusvaara et al., 2013). These results would suggest that use of anticholinergic drugs may be associated with cognitive decline in specific cognitive domains such as executive functioning, semantic memory, and visuospatial reasoning (Uusvaara et al., 2013).

Similarly, Ancelin et al. (2006) sought to find whether anticholinergic burden is associated with cognitive dysfunction. There were 372 participants that were interviewed about their health and prescription drug use before undergoing a neuropsychological exam that tests cognitive constructs such as reasoning, attention, memory, and language. Subjects who took the anticholinergic drugs were found to have specific cognitive deficits in areas like psychomotor speed, recall, visuospatial memory compared to nonusers (Ancelin et al., 2006).

Taylor-Rowan et al. (2022) gathered several studies on anticholinergic burden and its relationship to neuropsychiatric outcomes. They found that 40% of the studies included found that there was a significantly increased risk of greater long-term cognitive decline for participants with an anticholinergic burden when compared to those who had no anticholinergic burden (Taylor-Rowan et al., 2022). They also found that one study suggested a significant association with physical function between participants who had an anticholinergic burden and those who did not have one (Taylor-Rowan et al., 2022). Interestingly, six out of ten studies found a significantly increased risk of mortality for those with an anticholinergic burden compared to those with no burden or even minimal burden (Taylor-Rowan et al., 2022). Overall, the authors found that anticholinergic medications may increase the risk of death in older adults

with dementia (Taylor-Rowan et al., 2022). There was a 15% higher risk of death for those taking anticholinergic medications compared to those who were not taking anticholinergic medication (Taylor-Rowan et al., 2022).

As mentioned earlier, there are different scales that can be used to calculate anticholinergic burden. Two anticholinergic medication scales will be used in the current study, the ACB and the Anticholinergic Loading Scale (ALS). To create the ACB scale, researchers searched the Medline database from 1966 to 2007 for studies on anticholinergic medications and how those medications can impact cognitive performance (Boustani et al., 2008). They then used the same methods as those studies and built a list of drugs with anticholinergic properties before presenting the list to a team of geriatricians, geriatric pharmacists, geriatric psychiatrists, general physicians, geriatric nurses, and aging brain researchers (Boustani et al., 2008). The team separated the list into three categories of mild, moderate, and severe cognitive anticholinergic effects while also establishing a scoring system—drugs with possible anticholinergic effects given a score of 1 and drugs with clinically relevant cognitive anticholinergic effects were given a score of 2 or 3 based on the blood brain barrier permeability and its association with delirium (Boustani et al., 2008). Drugs were said to have anticholinergic effects based on the SAA and the in vitro affinity to muscarinic receptors (Boustani et al., 2008). On the other hand, to create the ALS, researchers used SAA and clinician-rated scores (Sittironnarit et al., 2011). They used previously published scores for medications when possible with an ordinal scale of 0 (no effect) to 3 (strong effect), but when it was not possible to use already scored medications, they applied a loading based on ratings by a geriatrician, psychiatrist, and a clinical pharmacologist (Sittironnarit et al., 2011).

The ALS and ACB calculators were used in the present investigation as the methods used to develop the scales were readily accessible to the public.

Methods

Participants

The participants included 136 men and 211 women all at or above the age of 65 years. There were 144 Caucasian participants, 179 African American participants, 7 Hispanic participants, and 10 Asian participants. The majority of the participants were right-handed with 245 being right-handed and 20 being left-handed. There were 127 participants who had less than 13 years of education, 18 participants who graduated from high school with no further education, and 198 participants who continued education past high school. One participant completed 22 years of education.

This study used archival data collected by the University of Chicago Medical Center, Department of Psychiatry. These data were collected as part of clinical neuropsychological evaluations on patients referred to the Neuropsychology Service, typically due to known or suspected cognitive problems, These data were stored in a secure database managed by the clinic manager. The 347 participants identified in the present investigation were selected from the database of archival data collected by the University of Chicago Medical Center, Department of Psychiatry, based on study inclusionary criteria described below. Archival data were collected and made into a new database with demographic information, participants codes (i.e. "neuropsych number [NP number]"), referral information, and test scores. While 347 participants were selected to go into the database, only 265 participants' data were used as some patients did not show up in the hospital's electronic health system, Epic, when searched for, which did not allow for the collection of detailed medication regimen information. The subjects were drawn from the database if they met the following criteria: (1) participants and/or their caregiver/loved one must have expressed a complaint of subjective cognitive impairment; (2) participants must have been administered the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Mini Mental Status Exam (MMSE), and the Hopkins Verbal Learning Test Revised (HVLT-R) and the Wide Range Achievement Test (WRAT); (3) participants must take at least

one prescription medication; and (4) participants must have been at least 65 years old at the time of their neuropsychological evaluation. Participants were excluded from the study if they were under the age of 65 years as a diagnosis of dementia is less common in younger (i.e., < age 65 years) adults, or if they were not taking at least one prescription medication.

Materials

Four tests considered in the present study were administered to patients at some point during their neuropsychological evaluations. First, is the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): The RBANS is a standardized screening tool used to measure neuropsychological status in people aged 20 to 89. It measures immediate memory, visuospatial skills, attention, language, and delayed memory. It consists of 12 subtests that produce 5 scores, one for each of the domains previously listed. The current study specifically examined verbal learning and memory subtests (i.e., list learning/list recall and story memory/story recall). Second, is the Mini Mental Status Exam (MMSE): The MMSE is a 30 point cognitive screening measure questionnaire used to measure cognitive impairment. It examines registration, attention, executive functioning, visuospatial functioning, calculation, delayed memory/recall, language, one's ability to follow simple commands, and orientation. It also tests basic motor skills. A score of 24 or above indicates normal cognition while a score less than 9 indicates severe cognitive impairment. Third, is the Hopkins Verbal Learning Test Revised (HVLT-R): The HVLT-R assesses acquisition and delayed recall. It is a list learning test which consists of 12 nouns within 3 semantic groups. There are 3 acquisition trials where the person attempts to immediately recall as many of the words from the list as they can. Delayed recall trials have the person retrieve as many words from before as they can. Following the delayed recall trial is a recognition trial wherein the person discriminates between items that were presented on the list from those that were not presented on the list. Fourth, is the Wide Range Achievement Test (WRAT). The WRAT measures reading, spelling, and math for anyone

between the ages of 5 and 85+. The WRAT subtest used in this study was the Word Reading subtest. Word reading measures letter and word decoding through letter identification and word recognition.

According to Cheng et al. (2011), to test the reliability of the RBANS, Cronbach's alpha was calculated, and the RBANS total score showed strong internal consistency with an R-value of 0.806. In addition, delayed memory, immediate memory, and visuospatial indices showed strong internal reliability (Cheng et al., 2011). To test the validity of the RBANS, correlations between the RBANS subtests and MMSE subtests were conducted, and strong correlations were demonstrated for most of the subtests, especially the immediate memory, delayed memory, and attention indices of the RBANS (Cheng et al., 2011). The internal reliability of the MMSE, using Cronbach's alpha, is high, and the validity is solid as well (Baek et al., 2016). The internal consistency reliability of the HVLT-R, using Cronbach's alpha, is 0.94 and the split-half reliability was 0.96, indicating good internal consistency reliability (Jiang et al., 2023). Moreover, the validity was assessed by calculating the correlation coefficients of the HVLT-R and the Hong Kong Brief Cognitive Test (HKBC) and the Brief Visuospatial Memory Test Revised (BVMT-R), and the Logical Memory Test (LM) (Jiang et al., 2023). There were strong correlations found, indicating good validity of the HVLT-R (Jiang et al., 2023). The WRAT is reliable according to studies of its internal consistency, immediate and delayed retest stability, and standard score confidence intervals (Ivypanda, 2024)). The range is from 0.87 to 0.96 (Ivypanda, 2024). The test is also valid because "content and development of the subtests increase in mean subtest scores in successive age levels" and there are intercorrelations between subtests (Ivypanda, 2024).

Data Collection

This study used archival data. The data were collected through the years from patients who came into the University of Chicago Medical Center to be tested and examined for cognitive

complaints. Cognitive outcome data were collected from the RBANS, MMSE, WRAT, and the HVLT-R tests. Whether there was a statistically significant difference in mean performances between burden vs. no burden groups was evaluated where presence vs. absence of anticholinergic burden represented the independent variables and performance on each cognitive measure represented the dependent variables. Whether there was an association between any of the aforementioned variables was also evaluated. Data analysis is further delineated in the *Statistical Analysis* section below.

Procedure

This study was aligned with IRB-approved procedures. The first goal was to find the MRN numbers that corresponded with the NP numbers of each patient. Once this was completed, I needed to find all the medications each patient was taking. To do this, I used the electronic medical record system program known as Epic with UChicago Medicine. I typed the patient's MRN number into Epic's database to search for the matching patient. Once I found and confirmed the correct patient name and MRN number, I went to the patient's profile. On their profile, I found the "Neuropsychology Final Report" for the patient. Next, I looked for the medication list in the report, and I wrote down all prescription medications the report said they were taking at the time of the neuropsychological assessment, into the Excel spreadsheet next to the patient's name. Anticholinergic burden (i.e. 0-, 1, 2, 3) for each medication was established using the ACB scale and ALS. Burden scores as calculated by both scales were recorded. If a medication was not in either scale's database, it was given a score of zero. Total ACB and ALS burden scores for each patient were also recorded. For the test data (i.e. select performance on the RBANS, MMSE, WRAT, and HVLT-R measures), I converted scaled scores or standard scores to z-scores and t-scores. This was a descriptive, observational study that used archival data. The data analysis that was done was a between-subjects design.

Once this data had all been collected, there were a few things to do to clean it up. Mainly, any patients with no prescription medications, invalid test scores, and those patients who did not come up when searched for, or who were under the age of 65 were all removed from the spreadsheet. This left us with 265 participants whose data was valid, clear, and fit the inclusionary criteria of the study.

Statistical Analysis

This study used two-quantitative analysis techniques to evaluate study aims. The first aim of the study was to replicate extant literature that has suggested a significant deleterious impact of anticholinergic burden on cognitive performance (Taylor-Rowan et al., 2022). As such in the current investigation, several independent two-sample t-tests were conducted to determine whether there was a significant difference in mean performance across cognitive measures between burden (i.e. anticholinergic load > 1) vs. no burden groups (i.e. anticholinergic load = 0). For example, we ran an independent two-sample t-test to compare MMSE raw score performance between burden vs no burden groups. This was done in order to identify whether there is an association between anticholinergic burden and cognitive test performance. The second aim of the study was to evaluate which of the two anticholinergic burden calculators used in the study was a better predictor of cognitive performance. A linear regression model was initially identified as the analysis of choice; however, as several assumptions of the analytic method were violated, this method was not considered a viable option. Instead, Pearson bivariate correlations were conducted to identify whether there were any statistically significant linear relationships between each anticholinergic burden calculator (i.e. ACB calculator vs, ALS calculator) and performance on each cognitive measure. These measures include MMSE raw scores, WRAT z-scores, RBANS story memory z-scores RBANS story recall z-scores, HVLT total learning z-scores, HVLT delayed recall z-scores, and HVLT discriminability z-scores.

Results

An independent two-sample t-test was used to compare neuropsychological measures scores between burden and no burden groups. Of these, only HVLT-R Delayed Recall differed significantly between groups (burden ($M = -1.96$, $SD = 1.05$) and no burden ($M = -1.56$, $SD = 3.64$); $t(65) = -0.865$, $p < .001$)). There were no significant differences for WRAT, MMSE, and RBANS. Please see Table 1 for results.

Table 1. Comparison of Neuropsychological Test Performance Between Burden and No Burden Groups

This table presents the results of a series of two-sample t-tests comparing the performance of participants in burden and no burden groups on various neuropsychological measures. The tests examined differences in raw scores, z-scores, and discriminability across domains such as global cognition, academic achievement, memory, and learning. Overall, the findings indicate no significant differences between groups, with the exception of a small but significant effect on delayed recall memory.

Test	Condition	Mean	Standard Deviation	T-statistic	p-value
MMSE Raw Score	Burden	25.26	4.10	1.293	0.197
	No Burden	24.29	4.71	1.293	0.197
WRAT Z-Score	Burden	0.00	1.01	0.612	0.541
	No Burden	-0.09	1.01	0.612	0.541
RBANS Story Memory Z-Score	Burden	-1.16	1.33	0.741	0.459
	No Burden	-1.32	1.44	0.741	0.459

RBANS Story Recall Z-Score	Burden No Burden	-1.44 -1.9	1.35 1.33	1.705 1.705	0.089 0.089
HVLT-R Total Learning Z-score	Burden No Burden	-1.53 -1.59	0.98 1.05	-1.536 -1.536	0.125 0.125
HVLT-R Delayed Recall Z-Score	Burden No Burden	-1.96 -1.56	1.05 3.64	-0.865 -0.865	< .001 < .001
HVLT-R Discriminability Z-Score	Burden No Burden	-1.60 -1.86	1.35 1.43	1.319 1.319	0.188 0.188

Bivariate Pearson correlations were completed to identify whether there was a statistically significant linear relationship between ACB calculator Total Burden score and each neuropsychological measure. Results demonstrated no statistically significant correlation between ACB Total Burden Score and: MMSE Raw Score (r = 0.066, p = 0.232), WRAT Z-Score (r = -0.009, p = 0.876), RBANS Story Memory Z-Score (r = 0.034, p = 0.577), RBANS Story Delayed Recall Z-Score (r = 0.106, p = 0.079), HVLT-R Total Learning Z-Score (r = -0.044, p = 0.429), HVLT-R Delayed Recall Z-Score (r = -0.025, p = 0.652), or HVLT-R Discriminability Z-Score (r = 0.070, p = 0.217).

Bivariate Pearson correlations were also completed to identify whether there were any statistically significant linear relationships between ALS calculator Total Burden score and each neuropsychological measure. Results demonstrated no statistically significant correlation between ALS Total Burden Score and: MMSE Raw Score (r = 0.094, p = 0.089), WRAT Z-Score (r =

0.037, p = 0.510), RBANS Story Memory Z-Score (*r* = 0.018, p = 0.771), RBANS Story Delayed Recall Z-Score (*r* = 0.040, p = 0.509), HVLT-R Total Learning Z-Score (*r* = -0.053, p = 0.347), HVLT-R Delayed Recall Z-Score (*r* = -0.071, p = 0.202), or HVLT-R Discriminability Z-Score (*r* = 0.067, p = 0.238).

Finally, a bivariate Pearson correlation was completed to evaluate whether there was a statistically significant linear relationship between ACB calculator and ALS calculator Total Burden scores. Results demonstrated a statistically significant relationship between the two (*r* = 0.661, p <0.001, Table 2).

Correlations

Correlations

		ACBTotalBurden	ALSTotalBurden	MMSERaw	WRATZscore	RBANSStoryMem Zscore	RBANSStoryRecall Zscore	HVLTTotalLearn Zscore	HVLTDelayZscore	HVLTDiscrimZscore
ACBTotalBurden	Pearson Correlation	1	.661**	.066	-.009	.034	.106	-.044	-.025	.070
	Sig. (2-tailed)		<.001	.232	.876	.577	.079	.429	.652	.217
	N	327	327	327	319	277	275	322	323	312
ALSTotalBurden	Pearson Correlation	.661**	1	.094	.037	.018	.040	-.053	-.071	.067
	Sig. (2-tailed)	<.001		.089	.510	.771	.509	.347	.202	.238
	N	327	327	327	319	277	275	322	323	312
MMSERaw	Pearson Correlation	.066	.094	1	.428**	.510**	.491**	.487**	.260**	.373**
	Sig. (2-tailed)	.232	.089		<.001	<.001	<.001	<.001	<.001	<.001
	N	327	327	327	319	277	275	322	323	312
WRATZscore	Pearson Correlation	-.009	.037	.428**	1	.375**	.240**	.224**	.159**	.182**
	Sig. (2-tailed)	.876	.510	<.001		<.001	<.001	<.001	.005	.001
	N	319	319	319	319	270	267	315	316	305
RBANSStoryMem Zscore	Pearson Correlation	.034	.018	.510**	.375**	1	.678**	.536**	.408**	.263**
	Sig. (2-tailed)	.577	.771	<.001	<.001		<.001	<.001	<.001	<.001
	N	277	277	277	270	277	273	273	273	263
RBANSStoryRecall Zscore	Pearson Correlation	.106	.040	.491**	.240**	.678**	1	.531**	.529**	.399**
	Sig. (2-tailed)	.079	.509	<.001	<.001	<.001		<.001	<.001	<.001
	N	275	275	275	267	273	275	271	271	261
HVLTTotalLearn Zscore	Pearson Correlation	-.044	-.053	.487**	.224**	.536**	.531**	1	.471**	.509**
	Sig. (2-tailed)	.429	.347	<.001	<.001	<.001	<.001		<.001	<.001
	N	322	322	322	315	273	271	322	321	309
HVLTDelayZscore	Pearson Correlation	-.025	-.071	.260**	.159**	.408**	.529**	.471**	1	.418**
	Sig. (2-tailed)	.652	.202	<.001	.005	<.001	<.001	<.001		<.001
	N	323	323	323	316	273	271	321	323	310
HVLTDiscrimZscore	Pearson Correlation	.070	.067	.373**	.182**	.263**	.399**	.509**	.418**	1
	Sig. (2-tailed)	.217	.238	<.001	.001	<.001	<.001	<.001	<.001	
	N	312	312	312	305	263	261	309	310	312

**. Correlation is significant at the 0.01 level (2-tailed).

Table 2. Correlation Matrix of Neuropsychological Test Scores

This table presents the Pearson correlation coefficients among various neuropsychological test scores, including measures of global cognition (MMSE), academic achievement (WRAT), memory (RBANS, HVLT-R), and learning (HVLT-R). The correlations are shown for participants with and without a cognitive burden, with significance levels indicated. This

correlation matrix provides insight into the relationships between different cognitive domains assessed by the test battery.

Discussion

This study aimed to (1) replicate extant literature which has suggested a significant, deleterious impact of anticholinergic burden on cognitive performance and (2) identify which of the two anticholinergic burden calculators (ACB vs. ALS) used in the study was a better predictor of cognitive performance; however, as early noted, as several assumptions of the linear regression were violated, this method was not considered to be a viable option. Instead the study aimed to evaluate whether there were any significant associations between performance on identified cognitive measures and anticholinergic burden as calculated by (1) the ALS measure and (2) the ACB measure, and finally, whether there were any significant correlations between the two anticholinergic calculators themselves.

Overall, the results of the study were largely inconsistent with the hypothesis of the first study aim such that the anticholinergic burden group did not perform any worse on the cognitive measures compared to the no burden group, except in one instance. As such, these results do not lend strong support to the claims that anticholinergic burden is associated with impaired performance on cognitive tests as has previously been demonstrated (Taylor-Rowan et al., 2022; Risacher et al., 2016, Usuvaara et al., 2013). However, there was one instance that did not align with study predictions. That is, upon evaluating HVLT-R Delayed Recall Z-Score performances, there was a significant difference between the two groups, such that the burden group performed worse than the no burden group, and there was a small effect; this is consistent with study predictions. That we observed this finding on a delayed recall measure makes sense upon considering the mechanism behind anticholinergic medications. That is, these medications block the action of acetylcholine which has been demonstrated to play a crucial role in memory

formation and retrieval, and may also have a more pronounced effect on delayed recall, which relies on the hippocampus and associated memory processes (Haam & Yakel, 2018).

The results of the study were also inconsistent with the hypothesis of the second study aim such that there were no significant relationships between the ACB or ALS calculators and performances on any of the neuropsychological measures. The two calculators did have a statistically significant relationship between each other and this was expected. In summary, the groups with an anticholinergic burden did not do any better or worse on the cognitive measures when compared to the group with no anticholinergic burden except in one instance. As such, these results do not lend strong support that the claims that anticholinergic burden is associated with impaired performance on cognitive tests as previously demonstrated (Taylor-Rowan et al., 2022; Risacher et al., 2016; Uusvaara et al., 2013).

The results challenge current and past literature on the topic. This may be the case for a few different reasons. First, there may be confounding factors such as medication use, comorbidities, and lifestyle factors that all influence cognition and may mask the effect of the anticholinergic burden. The different medications a person is on, how many they take, and how high their burden is may also have an effect on someone's cognition and scores on cognitive tests, so this may be a reason why these results do not support the literature. Lifestyle factors such as sleep, exercise, diet, and any other differences can also impact cognitive capabilities, so that may have masked the effects of anticholinergic burden on their performances. Another issue may be the smaller sample size. It may have been too small to detect a significant effect. Perhaps a more suitable sample size would be something larger. Finally, the sample may have differences in cognitive impairment among patients. With some patients having an underlying neurodegenerative disease while others maybe only have mild cognitive impairment. This can be

impacted by anticholinergic burden as well, so the effects of the medications may not be as heavily felt in someone with less cognitive impairment.

As results of the current investigation do not support the extant literature, it is necessary to consider limitations of the study. For one, the sample size is smaller compared to other similar studies. If we had a bigger sample size, then perhaps we would see a bigger effect of anticholinergic burden on cognitive performance. This attempt may have a limited ability to adequately produce results like those of other studies. The sample may not be generalizable to other populations since it is smaller and only representative of a population that goes to UChicago Hospitals to get evaluated for neuropsychological concerns. Perhaps the study's age group was too broad. Had we included those older than 70 or even 80 years, would the results be any different? Maybe the number of people closer to 65 outweighs the number closer to 100 and this impacted the results. This is a correlational study, so no causal relationships can be concluded. Maybe a longitudinal instead of a cross-sectional design would have allowed for more accurate results and been better for tracking the long-term effects of anticholinergic burden on cognitive abilities. The measures of anticholinergic burden used may not have been comprehensive or sensitive enough to capture the full spectrum of anticholinergic effects. More detailed assessments of medication use, different calculators, and measures of anticholinergic burden may be needed. The assessment of cognition may not have been sufficiently comprehensive, focusing on specific domains rather than a broader cognitive battery. Maybe different tests besides the MMSE, RBANS, WRAT, and HVLT-R should have been used to better assess the impact of anticholinergic burden on cognition. Another limitation of the study is that the two calculators used were developed in fairly similar ways. As evaluating which calculator was the more optimal predictor of cognitive impairment was not possible within the scope of the study, given linear regression assumption violations, that the calculators were

developed similarly likely did not threaten the validity of the findings. Future studies should examine other calculators that were developed in different ways to see if there is a better predictor of impairment.

A linear regression was initially thought appropriate, but after doing the Pearson's bivariate correlation tests, it was clear that there were no linear relationships in the data. Thus, we were not able in the confines of this investigation to assess one of our aims i.e. which anticholinergic model was the best predictor of cognitive performance.

There are a few future directions for this study. One, it could be done as a longitudinal study that follows participants over an extended period to examine the long-term effects of anticholinergic burden on cognitive decline and the development of cognitive impairment. This would allow for the examination of the temporal relationship and the potential cumulative impact of anticholinergic burden on cognition. Next, it would be important to explore moderating factors. Investigating factors such as age, education, comorbidities, and other lifestyle factors would be crucial for their influence on the relationship between anticholinergic burden and cognitive outcomes.

Conclusion

Research shows that anticholinergic burden may negatively impact cognition, and this burden can be measured using several different calculators. Results of the current investigation challenged extant literature as there were no significant differences between burden and no burden groups except for one instance. Moreover, there were no significant correlations between anticholinergic burden and cognitive test scores. Future research should focus on longitudinal work and how moderating factors may influence cognition. For the sake of physicians' prescribing practices, anticholinergic burden must continue to be calculated properly.

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