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The Impact of Anticholinergic Burden on the Development of Mild Behavioral Impairment

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ABSTRACT

Objective: *Mild behavioral impairment (MBI) is a syndrome of late-life-onset persistent neuropsychiatric symptoms. Anticholinergic medication is commonly prescribed in older adults. Both MBI and anticholinergic exposure are associated with increased dementia risk. We sought to understand the association of anticholinergic burden (ACB) with MBI.* ***Design, Setting, Participants:*** *We mapped ratings on the Neuropsychiatric Inventory Questionnaire to the MBI checklist (MBI-C) using an established algorithm to define MBI status in cognitively unimpaired individuals in the National Alzheimer's Coordinating Center database. We then assessed the association between time-varying ACB ratings and risk of incident MBI.* ***Results:*** *4865 participants met inclusion criteria and were followed for a mean (SD) of 5.64 (3.92) years. ACB scores ranged from 0 to 11. 63.3% of participants had a score of 0, 27.7% had a score of 1–2, and 9% had a score of ≥3. Higher maximum total ACB score was associated with a higher likelihood of developing MBI ($p \leq 0.001$). When assessed as a time varying covariate, ACB score was associated with incident MBI (HR 1.07, 95% CI 1.02–1.14, $p = 0.010$). This association remained significant when adjusted for 10-year mortality risk, age, sex, education, and race.* ***Conclusions:*** *MBI risk should be considered when prescribing anticholinergic medication in older adults.* (Am J Geriatr Psychiatry 2026; 34:1019–1030)

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Highlights

- **What is the primary question addressed by this study?**
  The association of anticholinergic burden (ACB) with mild behavioral impairment (MBI).
- **What is the main finding of this study?**
  Anticholinergic exposure was associated with risk of incident MBI when adjusting for age, gender, education, race and 10-year mortality risk. This increase in risk was dose dependent.
- **What is the meaning of the finding?**
  Anticholinergic medication use was found to be associated with incident MBI, we advise that MBI risk be considered when prescribing anticholinergic medication in older adults.

OBJECTIVE

Mild behavioral impairment (MBI) is a relatively new construct described by the International Society to Advance Alzheimer's Research and Treatment (ISTAART) as "persistent neuropsychiatric symptoms (NPS) that emerge, *de novo*, in advance of or concurrent with mild cognitive impairment (MCI)."[1] MBI symptoms can occur in ≥1 more of the following 5 domains: decreased motivation, emotional dysregulation, impulse dyscontrol, social inappropriateness, and abnormal perception or thought content.[1,2] These domains have been quantified in the MBI Checklist (MBI-C), developed to more clearly characterize MBI symptoms and domains, as well as quantify MBI severity, thus better enabling clinicians and researchers to identify a group of patients in a "predementia" state.[3]

MBI affects a significant proportion of older adults. A study of community dwelling, cognitively unimpaired (CU) older adults reported an MBI prevalence of 10%.[4] A memory clinic study found an MBI prevalence of 37% in patients with subjective cognitive decline, and 54% in MCI.[5] MBI can be a prodrome for cognitive decline, MCI or dementia.[4,6] We reported that NPS and other behavioral symptoms precede cognitive manifestations of dementia in as many as 55% of participants.[6] Others reported a 2.76-fold greater incidence rate of dementia in individuals with MBI when compared to those with no NPS.[7] Individuals with MCI and concurrent MBI have lower reversion rates to CU and higher rates of progression to dementia.[8]

Alzheimer's Dementia (AD) is predicted to affect 13.9 million Americans >65 years of age in 2060, with a 2025 cost burden of $781 billion in the USA. It is important to identify reversible risk factors for AD.[9,10] Identifying variables linked to greater MBI risk may allow earlier recognition of individuals at higher risk for dementia as well as facilitate earlier interventions.

Medications with anticholinergic effects are recognized by the Beers Criteria as potentially inappropriate to use in older adults due to links with greater risk of side effects such as confusion, constipation, orthostasis, falls, and dry mouth.[11,12] Anticholinergic medications are commonly prescribed to the elderly, with 9.1%−52.7% of individuals >65 years of age exposed to such medications.[13,14] Anticholinergic prescribing is increasing: in >220,000 UK Biobank participants assessed between 1990 and 2015, anticholinergic burden, calculated by a 'meta-scale' combining nine different anticholinergic ratings, increased nine-fold over that 15 year period.[15]

Long-term anticholinergic exposure is linked to greater dementia risk.[16,17] A large, nested case-control study by Coupland et al.[16] studied 284,343 General Practice patients in England ≥55 years of age. Compared to no anticholinergic drug prescriptions in the preceding 1−11 years, adjusted OR for dementia was 1.06 (95% CI 1.03−1.09) in the lowest anticholinergic exposure category versus 1.49 (95% CI 1.44−1.54) in the highest. This is supported by a case−control study of 395,397 Japanese individuals ≥65 years of age. Exposure to anticholinergic drugs led to significantly higher risk of developing dementia (adjusted OR 1.50, 95% CI 1.47−1.54).[17]

This analysis aimed to assess the association between anticholinergic medication and development of MBI in CU subjects. We are aware of no studies to date assessing the association. This analysis did not

assess the direct association between anticholinergic burden or MBI with dementia risk but, given we know that long-term anticholinergic exposure has been linked to greater dementia risk, and MBI can be a prodrome of dementia, establishing any impact of these medications on the onset of MBI could have a real-world impact on prescribing practices and guide future prospective studies.

METHODS

Participants

Participants were volunteers with normal cognition recruited and then followed up approximately annually at Alzheimer's Disease Research Centers (ADRCs), funded by the National Institute on Aging and located across the United States. The National Alzheimer's Coordinating Center (NACC) maintains a database of ADRC participants' neuropathologic and clinical data.[18] To be included, individuals had to be age 65 and over, CU at baseline, and have a Neuropsychiatric Inventory Questionnaire (NPI-Q) score of 0 at their first and second ADRC visits.[19] Those with a history of bipolar disorder, schizophrenia, and posttraumatic stress disorder were excluded, as were those with a remote history of depression (>2 years prior to their initial ADRC visit). We included those with a depression diagnosis within 2 years of initial ADRC visit as depressive symptoms overlap with MBI criteria and may indicate the development of MBI. Those with neurodegenerative disorders (Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple system atrophy and progressive supranuclear palsy), developmental neuropsychiatric disorders (e.g., autism spectrum disorder, attention-deficit hyperactivity disorder, and dyslexia), or Down Syndrome were excluded. Written informed consent was obtained from all participants at each ADRC and overseen by local IRBs.

Data collected by ADRCs accrue by NACC comprising a Uniform Data Set (UDS) which includes demographics, health history, medications, behavioral assessment, and neuropsychological battery.[20,21] We examined data collected from ADRC visits between May 2005 and February 2020.

Measures

Neuropsychiatric inventory questionnaire

The NPS assessment tool in the NACC database is the Neuropsychiatric Inventory questionnaire (NPI-Q). This is a widely used, validated, informant-based, self-report that evaluates the presence or absence of 12 NPS domains with a 0−3 rating of severity: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, night-time behaviors, and change in appetite/eating.[19]

MBI diagnosis

To map the NPI-Q to the MBI-C we used the method of cross-walking described by Sheikh et al.[22] shown in Table 1. A score of ≥1 in any NPI-Q domain resulted in a score in its corresponding MBI domain. To meet criteria for a diagnosis of MBI, a participant had to score ≥1 in any corresponding MBI domain, and their symptoms had to be persistent over a 6-month period. However, as the NPI-Q assesses symptoms over only the prior 1-month period, we used the TCV (two consecutive visits) MBI operational case definition. This considers MBI to be present if there is persistence of symptoms on the NPI-Q over two successive annual NACC visits.[23]

TABLE 1. Mapping NPI-Q to MBI

MBI Domains	Decreased Motivation	Emotional/Affective Dysregulation	Impulse Dyscontrol	Social Inappropriateness	Abnormal Perception or Thought Content
NPI-Q domains	Apathy/Indifference	Depression/Dysphoria anxiety elation/euphoria	Agitation/Aggression irritability/liability aberrant motor behavior	Disinhibition	Delusions hallucinations

MBI: mild behavioral impairment; NPI-Q: neuropsychiatric inventory questionnaire.

MCI and dementia diagnoses

Diagnoses were made by a consensus panel or an individual clinical assessment using all available UDS data.[24] Modified Petersen criteria were used to diagnose MCI.[25,26] NINCSD/ADRDA criteria were used to diagnose AD, the NINDS/AIREN criteria were used to diagnose vascular dementia, the Dementia with Lewy bodies (DLB) consortium criteria were used to diagnose DLB, and consensus criteria as described in Neary et al. was used to diagnose frontotemporal dementia.[27–30]

Anticholinergic cognitive burden scale

Individual anticholinergic medication exposure information was obtained from the NACC database, where each participant's current medication list, including both prescribed and over the counter medication, is documented at their initial and each follow-up visit. To quantify anticholinergic exposure, we used the updated Anticholinergic Cognitive Burden (ACB) scale.[31] The ACB scale was developed in 2008 by researchers at the Indiana University Center for Aging and Regenstrief Institute for use as a tool to optimize geriatric pharmacotherapy by reducing anticholinergic burden. It was updated in 2012 with additional medications reviewed and added.[32] Though multiple similar scales exist, the ACB was chosen as it lends itself to use in datasets such as the NACC, and has been widely used in other peer reviewed studies looking at anticholinergic burden.[33,34]

The ACB scale categorizes medications with a score of 1 ("evidence from in vitro data that chemical entity has antagonist activity at muscarinic receptor"), 2 ("evidence from literature, prescriber's information, or expert opinion of clinical anticholinergic effect"), or 3 ("evidence from literature, expert opinion, or prescriber's information that medication may cause delirium").[32] If an individual was taking no anticholinergic medication, they received a score of 0. For a full list of medications and their ACB scores see Supplemental Table 1.

Charlson Comorbidity Index

The Charlson Comorbidity Index (CCI) calculates 10 year mortality risk by allocating a score to age and the following comorbidities: history of myocardial infarction, peripheral vascular disease, congestive heart failure, cerebrovascular disease, hemiplegia, chronic pulmonary disease, dementia, connective tissue disease, liver disease, peptic ulcer disease, diabetes, renal disease, tumor with or without metastases, leukemia, lymphoma, and AIDS.[35] We included CCI in our multivariate model as a marker of participant morbidity.

Statistical Methods

We categorized cognitive status as "CU," "impaired but not MCI," "MCI," or "dementia." Participants who developed MCI were not censored as MCI can be concurrently diagnosed with MBI.[1] As described by Wise et al., a diagnosis of MCI or dementia was considered "sticky," i.e., once a participant was diagnosed with dementia they were considered to have that diagnosis at subsequent visits and, once a participant was diagnosed with MCI they were considered to have that diagnosis at subsequent visits until they were diagnosed with dementia.[6] Participants who developed dementia were censored at the time of their diagnosis. Participants who died during follow-up were censored at their time of death.

To generate a Kaplan-Meier curve, each participant's maximum ACB score across all visits was used.

To assess individual participant's change in ACB score, we calculated the maximum difference in each participant's ACB score across all visits, i.e., if a participant's maximum difference was 0, their ACB score remained consistent from their first to last ADC visit. We then separated participants into groups based on their baseline ACB score and generated spaghetti plots looking at each participant's ACB scores over time.

In the primary analysis, ACB score was a time-varying covariate with participant scores calculated by adding together the ACB score of each medication they were taking at each ADRC visit during the study period. We fit a series of separate Cox proportional hazard models with site clustering and competing risks for hazard of MBI, with ACB score, non-aspirin NSAIDs, opioids, benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), non-SSRI antidepressants, antipsychotics, aspirin, diphenhydramine, and oxybutynin as time-varying predictors. Death was treated as a competing risk using the STATA

command stcrreg, this model was implemented as described by Fine and Gray.[36] Psychoactive medication classes were chosen to assess for protopathic bias. In addition, there is some evidence to suggest that SSRIs may be neuroprotective.[37] Benadryl and oxybutynin were chosen as they are commonly used medications with strong anticholinergic activity. Aspirin was chosen as a proxy marker of cardiovascular risk. We completed unadjusted models as well as models adjusting for age at baseline, sex, race, years of education, and CCI. We tested the assumption of proportional hazards via Schonfeld residuals.[38]

RESULTS

4,865 participants met inclusion criteria. Table 2 shows their baseline characteristics. Most participants were white (77.3%), female (64.9%), with a mean education time of 16.14 years, and a mean age of 73.48 years at their first visit. Participants were followed for up to 16 years, for a mean of 5.64 years. Mean CCI score was low, with most participants having ≤1 comorbidity. 440 individuals developed MBI, 651 developed MCI and 230 developed dementia (see Supplemental Figure 1). 514 participants died during the follow-up period.

Figure 1 displays the distribution of baseline ACB scores. These ranged from 0 to 11. 63.3% of participants had a score of 0. Of those taking anticholinergic medication, 21.0% had a score of 1, 6.7% had a score of 2, and 9% had a score of 3 or greater.

We found that the majority of participant's ACB scores did not change over time, with 51.0% of participants having a maximum ACB score difference of 0 across all their visits, with another 24.0% with a maximum score difference of 1 (Table 3). When separating participants by their baseline ACB score, we found that participants who had an ACB score of 0 at baseline, 63.6% stayed at 0 across all visits, and another 19.0% increased to a maximum ACB score difference of 1 (Supplemental Table 2, supplemental Figures 2–12).

To examine the impact of ACB score on the development of MBI, we plotted MBI-free survival probability in those with max ACB scores of 0, 1, 2, and 3 or greater (Figure 2). Unlike in the Cox models, we used a participant's maximum ACB score to create the Kaplan-Meier plot because it was not possible to display a survival curve with ACB as a time-varying predictor. Of 440 individuals who developed MBI, 106 (3.44%) had a maximum ACB score of 0, 105 (10.6%) had a maximum score of 1, 55 (17.0%) had a maximum score of 2, and 174 (39.8%) had a maximum score of 3 or more. A log rank test comparing the four groups was statistically significant (p ≤0.001),

FIGURE 1. Breakdown of baseline ACB scores. The figure above each bar represents the percentage of total participants with the corresponding baseline ACB score. ACB: anticholinergic cognitive burden.

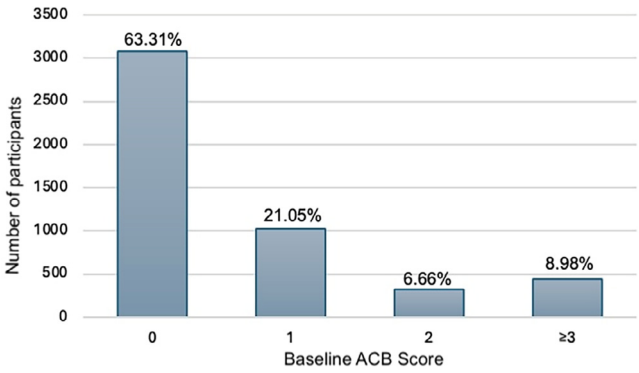

TABLE 2. Baseline Characteristics of Participants

Characteristic	N Total = 4,865
Age at first visit, mean (SD)	73.48 (7.00)
Female, n (%)	3,157 (64.9%)
Race, n (%)	
White	3,761 (77.3%)
Black/African American	1,072 (22.0%)
Other	32 (0.7%)
Years of education, mean (SD)	16.14 (5.32)
Years of follow-up, mean (SD)	5.64 (3.92)
Mean CCI score (SD)	0.28 (0.70)

N: number; SD: standard deviation; CCI: Charlson Comorbidity Index.

TABLE 3. Maximum Change in ACB Score Across All visits

Max Difference in ACB Score	N (%)
0	2,481 (51.0%)
1	1,168 (24.0%)
2	351 (7.2%)
3	482 (9.91%)
≥4	383 (7.9%)

ACB: anticholinergic cognitive burden.

FIGURE 2. Kaplan-Meier plot of MBI-free survival. Maximum ACB score was used to facilitate the production of a Kaplan−Meier plot. A log rank test comparing the four groups was statistically significant (p ≤0.001). ACB: anticholinergic cognitive burden.

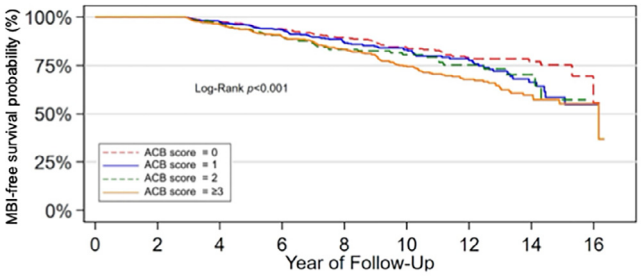

TABLE 4. Number of Participants Who Reported Taking Selected Medication and Medication Classes at baseline

Drug Class	Reported Taking (%)
Non-aspirin NSAIDs	772 (15.9%)
Opioids	89 (1.8%)
Benzodiazepines	99 (2.0%)
SSRIs	169 (3.5%)
Non-SSRI antidepressants	169 (3.5%)
Typical antipsychotics	6 (0.1%)
Atypical antipsychotics	9 (0.2%)
Individual Drug	**Reported taking (%)**
Aspirin	1,420 (29.2%)
Diphenhydramine	53 (1.1%)
Oxybutynin	73 (1.5%)

NSAIDs: nonsteroidal anti-inflammatory drugs; SSRI: selective serotonin reuptake inhibitor.

indicating that a higher maximum total ACB score was significantly associated with a higher likelihood of developing MBI.

Table 4 shows the number of participants who reported taking selected medication and medication classes at baseline. This table includes all medications in each class that participants reported taking at baseline, not only those listed in the ACB scale. 338 (7.0%) reported taking antidepressants, those included in the ACB scale are: bupropion, fluvoxamine, trazodone, venlafaxine, amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, paroxetine. 15 (0.3%) reported taking antipsychotics, those included in the ACB scale are: aripiprazole, asenapine, haloperidol, iloperidone, paliperidone, loxapine, risperidone, methotrimeprazine, molindone, pimozide, chlorpromazine, clozapine, olanzapine, perphenazine, quetiapine, trifluoperazine and thioridazine. 99 (2.0%) reported taking benzodiazepines, those included in the ACB scale are: diazepam, alprazolam and clorazepate. 89 (1.8%) reported taking opiates, those included in the ACB scale are: codeine, fentanyl, meperidine, and morphine. 53 (1.1%) reported taking diphenhydramine, and 73 (1.5%) reported taking oxybutynin, both medications having an ACB score of 3. 772 (15.9%) reported taking non-aspirin NSAIDs, and 1,420 (29.2%) reported taking aspirin.

Table 5 shows the hazard ratios for incident MBI. In both unadjusted and adjusted models ACB was

TABLE 5. Impact ACB Score on the Development of MBI

Variable	Unadjusted Model			Adjusted for Baseline Age, Sex, Education, Race			Adjusted for Baseline Age, Sex, Education, Race, CCI		
	HR	95% CI	p-Value	HR	95% CI	p-Value	HR	95% CI	p-Value
ACB score	1.07	1.02−1.14	0.010	1.07	1.02−1.13	0.012	1.07	1.01−1.13	0.019

Unadjusted and adjusted Cox proportional hazard models with co-variates are included. ACB score was treated as a time-varying predictor. ACB: anticholinergic cognitive burden; HR: hazard ratio; CI: confidence interval; CCI: Charlson Comorbidity Index.

TABLE 6. Association of Drug Classes and Individual Drugs with Development of MBI

Drug Class									
Variable	**Unadjusted Model**			**Adjusted for Baseline Age, Sex, Education, Race**			**Adjusted for Baseline Age, Sex, Education, Race, CCI**		
	HR	**95% CI**	**p-Value**	**HR**	**95% CI**	**p-Value**	**HR**	**95% CI**	**p-Value**
Non-aspirin NSAIDs	0.87	0.69–1.09	0.218	0.87	0.70–1.09	0.222	0.87	0.69–1.09	0.216
Opioids	**1.79**	**1.26–2.54**	**0.001**	**1.80**	**1.27–2.56**	**0.001**	**1.78**	**1.26–2.51**	**0.001**
Benzodiazepines	**2.17**	**1.39–3.40**	**0.001**	**2.16**	**1.41–3.29**	**<0.001**	**2.14**	**1.40–3.28**	**<0.001**
SSRIs	**2.24**	**1.64–3.06**	**<0.001**	**2.21**	**1.58–3.10**	**<0.001**	**2.21**	**1.58–3.08**	**<0.001**
Non-SSRI antidepressants	1.37	0.87–2.13	0.171	1.37	0.88–2.13	0.163	1.36	0.87–2.12	0.177
Typical antipsychotics	1.17	0.16–8.53	0.875	1.14	0.15–8.47	0.900	1.01	0.15–6.84	0.995
Atypical antipsychotics	**2.39×10^{-19}**	**7.71×10^{-20} -7.39×10^{-19}**	**<0.001**	**5.64×10^{-8}**	**1.63×10^{-8} -1.95×10^{-7}**	**<0.001**	**5.63×10^{-8}**	**1.62×10^{-8} -1.96×10^{-7}**	**<0.001**
Individual drug									
Variable	**Unadjusted Model**			**Adjusted for Baseline Age, Sex, Education, Race**			**Adjusted for Baseline Age, Sex, Education, Race, CCI**		
	HR	**95% CI**	**p-Value**	**HR**	**95% CI**	**p-Value**	**HR**	**95% CI**	**p-Value**
Aspirin	1.29	1.12–1.47	<0.001	1.26	1.11–1.43	<0.001	1.27	1.12–1.44	<0.001
Diphenhydramine	1.01	0.59–1.72	0.971	1.04	0.61–1.78	0.878	1.04	0.61–1.78	0.884
Oxybutynin	1.55	0.88–2.76	0.132	1.60	0.91–2.78	0.098	1.59	0.90–2.80	0.108

Unadjusted and adjusted Cox proportional hazard models with co-variates are included. Medications and medication classes were treated as a time-varying predictors. Bolded figures represent statistically significant findings (p=<0.05). ACB: anticholinergic cognitive burden: HR: hazard ratio; CI: confidence interval; CCI: Charlson Comorbidity Index; NSAIDs: nonsteroidal anti-inflammatory drugs; SSRI: selective serotonin reuptake inhibitor.

included as a time-varying covariate. In the unadjusted model, ACB score was significantly associated with greater hazard of incident MBI (HR 1.07, 95% CI 1.02−1.14, p = 0.010). This association remained significant when adjusted for age, sex, education, and race (HR 1.07, 95% CI 1.02−1.13, p = 0.012), as well as CCI score (HR 1.07, 95% CI 1.01−1.13, p = 0.019). For all model parameter estimates for each covariate see Supplemental Table 3.

Table 6 shows the hazard ratios of taking different drugs from specific classes, or selected individual medications, as time-varying covariates regarding risk of incident MBI. Drug classes with anticholinergic activity, opioids (HR 1.79, 95% CI 1.26−2.54, p = 0.001), SSRIs (HR 2.24, 95% CI 1.64−3.06, p ≤0.001) and benzodiazepines (HR 2.17, 95% CI 1.39 −3.40, p = 0.001) were associated with a significantly increased hazard of incident MBI in the univariate model. Atypical antipsychotics were associated with a significantly decreased hazard of incident MBI (HR 2.39×10^{-19}, 95% CI 7.71×10^{-20}−7.39×10^{-19}, p ≤0.001). Opioids, SSRIs, atypical antipsychotics, and benzodiazepines remained significantly associated with development of MBI in both multivariate models. Non-SSRI antidepressants and typical antipsychotics were not associated with incident MBI. The only individual medication significantly associated with risk of incident MBI was aspirin (HR 1.29, 95% CI 1.12−1.47, p ≤0.001), this significance persisted when adjusted for baseline age, sex, education, race, and CCI score.

CONCLUSIONS

To our knowledge, this is the first study to examine the impact of anticholinergic medication exposure on the development of MBI in CU individuals. Anticholinergic exposure, as measured by the ACB scale, was significantly associated with an increased hazard of MBI in models adjusted for baseline age, sex, education, race and 10-year mortality risk. The association was dose dependent, with increasing ACB ratings associated with increasing likelihood of developing MBI.

One possible mechanism for this is the cholinergic anti-inflammatory pathway, in which the vagus nerve modulates inflammation through the parasympathetic nervous system. Acetylcholine is thought to down-regulate inflammation by reducing the production of pro-inflammatory cytokines.[39] There have recently been significant advances in the use of muscarinic receptor agonists, coupled with a peripheral muscarinic receptor antagonist, in the management of psychotic symptoms in schizophrenia, as well as an increasing interest in studying how the anti-inflammatory effect of cholinergic agents may improve neuropsychiatric symptoms of dementia.[40,41]

When looking at anticholinergic drug classes, SSRIs were associated with an increased risk of developing MBI, while non-SSRIs were not. This conflicts with evidence that SSRIs are neuroprotective as they are associated with delayed progression from MCI to AD in individuals with depressive symptoms, and fewer amyloid plaques in mouse models and humans.[37,42] A more recent observational study of patients with dementia reported several antidepressants including SSRIs and non-SSRIs were associated with faster cognitive decline. They addressed the issue of indication bias by performing a repeat analysis limited to only those with no history of depression.[43] If participants were prescribed antidepressants to treat pre-existing NPS, it is possible that protopathic bias (i.e., when a medication is prescribed to treat symptoms of a disease before the disease is diagnosed, leading to an incorrect interpretation that the medication itself caused the disease in question) strengthened the association of SSRIs with risk of MBI. Given both SSRIs and non-SSRIs share clinical indications, these findings go against the argument that SSRIs may be associated with increased MBI risk as a result of protopathic bias. However, non-SSRIs also have distinct nonpsychiatric indications, namely insomnia, decreased appetite, pain, and smoking cessation. As we do not know the indications for which each medication was prescribed, it is difficult to draw firm conclusions on the impact of protopathic bias on the relationship of antidepressants to MBI risk.

Atypical antipsychotics were associated with a lower risk of developing MBI. However, there were only nine individuals who reported taking this medication class at baseline, and the parameter estimates were extremely small suggesting a very low incidence of MBI in this group, as well as instability of the estimates. Similarly, only 53 participants were taking

diphenhydramine, and only 73 were taking oxybutynin at baseline, with neither of these medications associated with the development of MBI. These findings are most likely due to a lack of statistical power and are not consistent with prior studies looking at dementia risk in those taking these medications.[16,34,44] In this setting, statistical significance should be interpreted with caution.

Opioids were associated with an increased risk of MBI. The association between opiates and dementia risk is controversial, with studies showing conflicting results.[45,46] The impact of opioids may be exaggerated as some of the side effects of opiates can mimic NPS, namely mood and perceptual disturbances.

Though benzodiazepines are not generally thought of as anticholinergic medications, alprazolam and diazepam are both included in the ACB scale (Supplemental Table 1). Benzodiazepines were associated with greater hazard of MBI. This may partly explain the results of prior studies examining the impact of benzodiazepine use on dementia risk, though these studies have shown mixed results. Billioti de Gage et al. found benzodiazepines associated with an increased risk of AD, while Imfield et al. found no association.[47,48]

Study strengths include the large sample size, systematic assessment of medications and diagnoses, systematic follow-up, use of a well-validated measure of anticholinergic burden, and a mean duration of 5.64 years follow-up. ACB was examined as a time-varying covariate in the Cox models, allowing us to more accurately capture the effect of a participant's cumulative anticholinergic burden.

Several limitations are notable. As with any longitudinal study, some participants were lost to follow-up and as a result we may have not captured all cases of MBI that developed. We did not directly assess for MBI, but mapped NPI-Q to the MBI-C using a previously described method and therefore may not be accurately capturing MBI. Not all MBI-C items are reflected in the NPI-Q, making it likely that we are under-capturing MBI. NPI-Q assesses symptoms in the past 30 days whereas NPS must be persistent over a 6-month period to meet MBI criteria. To mitigate this, we only considered MBI to be present if there was persistence of symptoms on the NPI-Q over two successive annual visits. Given this, we may both be over-capturing MBI if symptoms are not persistent for 6 months between visits, and under-capturing MBI as we are doubling the time a participant is required to experience NPS from 6 months to 12. As we did not directly assess for MBI, we determined binary MBI status. Thus, we did not perform a sub-analysis to establish if specific MBI symptom domains are driving the association of ACB with MBI. NACC has now begun assessing MBI directly, allowing sub-domains to be analyzed in future studies. In terms of medication data, current medication is captured but not past medication use. We also don't capture aspects of actual medication use (e.g., regular or *as needed*), and there is no assessment of adherence. Some medications in the ACB are over the counter and, as a result, may not be as accurately reported. This may have affected our findings as our results indicate that MBI risk increases in a dose-dependent manner. The ACB scale was last updated in 2012, 8 years prior to the end of our data collection, as a result, we may not be capturing anticholinergic exposures to newer medications. By using the ACB, which encompasses medications with multiple indications, we endeavored to reduce the effect of certain medications being prescribed to treat pre-existing neuropsychiatric symptoms (i.e., antidepressants, antipsychotics), however protopathic bias cannot be completely mitigated given these medications are included in the ACB scale. That these medications had mixed effects on the likelihood of developing MBI, suggests the effect of protopathic bias may be limited, though we are unable to conclusively determine this. ADRC participants are not a true representation of the general population. They are overall more educated, and healthier (as evidenced by the relatively low percentage of participants taking antidepressants or benzodiazepines), and there is a lower proportion of non-White participants. As a result, participants may have a different anticholinergic burden and risk of cognitive impairment. Though our overall sample size was large, some sample sizes were much smaller in our sub-analyses of medication class or individual medications, reducing statistical power. Survivorship bias may have affected our findings, with 10.6% of participants dying during the follow-up period. We have addressed this

by treating death as a competing risk, though survivorship bias cannot be fully eliminated.

We report that anticholinergic exposure is associated with the development of MBI, a known precursor to dementia. Future prospective studies should be done to look at how cumulative anticholinergic exposure impacts the incidence of MBI, and should include how long prior to the development of MBI the medication was started, how long each medication was taken, at what dose. Anticholinergic medication prescription is a modifiable risk factor, and we suggest that MBI risk may warrant consideration when weighing up the use of anticholinergic medication in older adults.

AUTHOR CONTRIBUTIONS

CEF, JML, CGL, and PBR conceptualized the project. CEF drafted the manuscript. CEF drafted the tables and Figure 1. JML performed the statistical analysis and drafted Figure 2. JML, CGL, PBR, and ZI edited the manuscript and approved the final version.

DATA STATEMENT

A limited portion of this data was previously presented orally by Dr. Leoutsakos on 1/20/2024 in a talk entitled "Trajectories of neuropsychiatric symptoms across normal elders, MCI, and dementia." Speaker Series, University College, London, UK. Host: Claudia Cooper, MBBS.

DISCLOSURES

PBR has received honoraria from Lilly, GLG, Leerink, Acadia, Medalink, Novo Nordisk, Noble Insights, TwoLabs, Otsuka, Lundbeck, Acadia, MedaCorp, ExpertConnect, HMP Global, Sinaptica, Worldwide Clinical Trials, Medscape, and Neurology Week. CGL has served as paid consultant or advisor for Astra-Zeneca, Glaxo-Smith Kline, Eisai, Novartis, Forest, Supernus, Adlyfe, Takeda, Wyeth, Lundbeck, Merz, Lilly, Pfizer, Genentech, Elan, NFL Players Association, NFL Benefits Office, Zinfandel, BMS, Abvie, Janssen, Orion, Servier, Astellas, SVB Leerink, Roche, Avanir, Karuna, Maplight, Axsome, GIA, GW Research Limited, Merck, EXCIVA GmbH, Otsuka, Intra-Cellular Therapies, Medesis, BMS, Abbvie. ZI has served as advisor/consultant for the Canadian Agency for Drugs and Technology in Health, Eisai, Lilly, Lundbeck/Otsuka, Novo Nordisk, and Roche. CEF and JML have no conflicts of interest to declare.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jagp.2026.05.008.

References

1. Ismail Z, Smith EE, Geda Y, et al: Neuropsychiatric symptoms as early manifestations of emergent dementia: provisional diagnostic criteria for mild behavioral impairment. Alzheimers Dement 2016; 12(2):195–202;doi:10.1016/j.jalz.2015.05.017 https://www.clinicalkey.es/playcontent/1-s2.0-S1552526015002150
2. Taragano FE, Allegri RF, Krupitzki H, et al: Mild behavioral impairment and risk of dementia: a prospective cohort study of 358 patients. J Clin Psychiatry 2009; 70(4):584–592; doi:10.4088/JCP.08m04181 https://www.ncbi.nlm.nih.gov/pubmed/19323967
3. Ismail Z, Agüera-Ortiz L, Brodaty H, et al: The mild behavioral impairment checklist (MBI-C): a rating scale for neuropsychiatric symptoms in pre-dementia populations. J Alzheimers Dis 2017; 56(3):929–938;doi:10.3233/jad-160979
4. Creese B, Brooker H, Ismail Z, et al: Mild behavioral impairment as a marker of cognitive decline in cognitively normal older adults. Am J of Geriatric Psychiatry 2019; 27(8):823–834; doi:10.1016/j.jagp.2019.01.215
5. Hu S, Patten S, Charlton A, et al: Validating the mild behavioral impairment checklist in a cognitive clinic: comparisons with the neuropsychiatric inventory questionnaire. J Geriatr Psychiatry Neurol 2023; 36(2):107–120;doi:10.1177/08919887221093353 https://journals.sagepub.com/doi/full/10.1177/08919887221093353
6. Wise EA, Rosenberg PB, Lyketsos CG, et al: Time course of neuropsychiatric symptoms and cognitive diagnosis in national Alzheimer's coordinating centers volunteers. Alzheimers Dement (Amst) 2019; 11(1):333–339;doi:10.1016/j.dadm.2019.02.006
7. Ghahremani M, Smith EE, Ismail Z: Improving dementia prognostication in cognitively normal older adults: conventional versus novel approaches to modelling risk associated with neuropsychiatric symptoms. Br J Psychiatry 2025; 226(3):129–136; doi:10.1192/bjp.2024.136 https://www.cambridge.org/core/product/identifier/S0007125024001363/type/journal_article
8. McGirr A, Nathan S, Ghahremani M, et al: Progression to dementia or reversion to normal cognition in mild cognitive impairment as a function of late-onset neuropsychiatric symptoms. Neurology 2022; 98(21):e2132–e2139;doi:10.1212/wnl.0000000000200256 https://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=n&CSC=Y&PAGE=fulltext&D=ovft&AN=00006114-202205240-00006
9. Matthews KA, Xu W, Gaglioti AH, et al: Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015−2060) in adults aged ≥65 years. Alzheimers Dement 2019; 15(1):17–24;doi:10.1016/j.jalz.2018.06.3063
10. USC Schaeffer Center for Health Policy & Economics: The cost of dementia in 2025. https://schaeffer.usc.edu/wp-content/uploads/2025/04/The-Cost-of-Dementia-in-2025.pdf; 2025 Accessed June 4, 2025
11. Fick DM, Semla TP, Steinman M, et al: American geriatrics society 2019 updated AGS beers criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2019; 67(4):674–694;doi:10.1111/jgs.15767 https://onlinelibrary.wiley.com/doi/abs/10.1111/jgs.15767
12. Green AR, Reifler LM, Bayliss EA, et al: Drugs contributing to anticholinergic burden and risk of fall or fall-related injury among older adults with mild cognitive impairment, dementia and multiple chronic conditions: a retrospective cohort study. Drugs Aging 2019; 36(3):289–297;doi:10.1007/s40266-018-00630-z https://link.springer.com/article/10.1007/s40266-018-00630-z
13. Machado-Alba JE, Castro-Rodríguez A, Álzate-Piedrahita JA, et al: Anticholinergic risk and frequency of anticholinergic drug prescriptions in a population older than 65. J Am Med Dir Assoc 2016; 17(3):275.e1–275.e4;doi:10.1016/j.jamda.2015.12.003 https://www.clinicalkey.es/playcontent/1-s2.0-S1525861015007525
14. Narayan SW, Hilmer SN, Horsburgh S, et al: Anticholinergic component of the drug burden index and the anticholinergic drug scale as measures of anticholinergic exposure in older people in New Zealand: a population-level study. Drugs Aging 2013; 30(11):927–934;doi:10.1007/s40266-013-0111-y https://link.springer.com/article/10.1007/s40266-013-0111-y
15. Mur J, Cox SR, Marioni RE, et al: Increase in anticholinergic burden from 1990 to 2015: age-period-cohort analysis in UK biobank. Br J Clin Pharmacol 2022; 88(3):983–993;doi:10.1111/bcp.15045 https://onlinelibrary.wiley.com/doi/abs/10.1111%2Fbcp.15045
16. Coupland C, Hill T, Dening T, et al: Anticholinergic drug exposure and the risk of dementia. JAMA Intern Med 2019; 179(8):1084;doi:10.1001/jamainternmed.2019.0677 https://jamanetwork.com/journals/jamainternalmedicine/articlepdf/2736353/jamainternal_coupland_2019_oi_190025.pdf
17. Okita Y, Kitamura T, Komukai S, et al: Association of anticholinergic drug exposure with the risk of dementia among older adults in Japan: the LIFE study. Int J Geriatr Psychiatry 2023; 38(12);doi:10.1002/gps.6029
18. Beekly DL, Ramos EM, Lee WW, et al: The national Alzheimer's coordinating center (NACC) database: the uniform data set. Alzheimer Dis Assoc Disord 2007; 21(3):249–258;doi:10.1097/wad.0b013e318142774e https://www.ncbi.nlm.nih.gov/pubmed/17804958
19. Kaufer DI, Cummings JL, Ketchel P, et al: Validation of the NPI-Q, a brief clinical form of the neuropsychiatric inventory. J Neuropsychiatry Clin Neurosci 2000; 12(2):233–239;doi:10.1176/jnp.12.2.233
20. Morris JC, Weintraub S, Chui HC, et al: The uniform data set (UDS): clinical and cognitive variables and descriptive data from Alzheimer disease centers. Alzheimer Dis Assoc Disord 2006; 20(4):210–216;doi:10.1097/01.wad.0000213865.09806.92 https://www.ncbi.nlm.nih.gov/pubmed/17132964
21. Beekly DL, Ramos EM, Van Belle G, et al: The national Alzheimer's coordinating center (NACC) database: an Alzheimer disease database. Alzheimer Dis Assoc Disord 2004; 18(4):270–277 https://www.ncbi.nlm.nih.gov/pubmed/15592144

22. Sheikh F, Ismail Z, Mortby ME, et al: Prevalence of mild behavioral impairment in mild cognitive impairment and subjective cognitive decline, and its association with caregiver burden. Int Psychogeriatr 2018; 30(2):233–244;doi:10.1017/S1041610217001511
23. Guan DX, Smith EE, Pike GB, et al: Persistence of neuropsychiatric symptoms and dementia prognostication: a comparison of three operational case definitions of mild behavioral impairment. Alzheimers Dement (Amst) 2023; 15(4):e12483—n/a; doi:10.1002/dad2.12483 https://onlinelibrary.wiley.com/doi/abs/10.1002%2Fdad2.12483
24. Morris JC, Kukull WA: NACC Uniform Data Set Coding Guidebook for Follow-up Visit Packet. Seattle: University of Washington, 2015 Version 3.0 Ed
25. Petersen RC, Smith GE, Waring SC, et al: Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999; 56(3):303–308;doi:10.1001/archneur.56.3.303
26. Winblad B, Palmer K, Kivipelto M, et al: Mild cognitive impairment − beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment. J Intern Med 2004; 256(3):240–246;doi:10.1111/j.1365-2796.2004.01380.x https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2796.2004.01380.x
27. McKhann G, Drachman D, Folstein M, et al: Report of the NINCDS-ADRDA work group* under the auspices of department of health and human services. Neurology 1984; 34(7):939–944
28. Roman GC, Tatemichi TK, Moody DM, et al: Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN international workshop. Neurology 1993; 43(2):250–260; doi:10.1212/wnl.43.2.250 https://www.ncbi.nlm.nih.gov/pubmed/8094895
29. McKeith IG, Dickson DW, Lowe J, et al: Diagnosis and management of dementia with lewy bodies: third report of the DLB consortium. Neurology 2005; 65(12):1863;doi:10.1212/01.wnl.0000187889.17253.b1 https://www.ncbi.nlm.nih.gov/pubmed/16237129
30. Neary D, Snowden JS, Gustafson L, et al: Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998; 51(6):1546–1554
31. Boustani M, Campbell N, Munger S, et al: Impact of anticholinergics on the aging brain: a review and practical application. Aging Health 2008; 4(3):311–320;doi:10.2217/1745509X.4.3.311
32. Regenstrief Institute. Anticholinergic Cognitive Burden Scale 2012 Update. Aging Brain Care Web site. https://www.idhca.org/wp-content/uploads/2018/02/DESAI_ACB_scale_-_Legal_size_paper.pdf. Accessed May 19, 2024.
33. Lozano-Ortega G, Johnston KM, Cheung A, et al: A review of published anticholinergic scales and measures and their applicability in database analyses. Arch Gerontol Geriatr 2020; 87:103885; doi:10.1016/j.archger.2019.05.010
34. Richardson K, Fox C, Maidment I, et al: Anticholinergic drugs and risk of dementia: case-control study. BMJ 2018; 361:k1315; doi:10.1136/bmj.k1315 https://bmj.com/content/361/bmj.k1315.full
35. Charlson ME, Pompei P, Ales KL, et al: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40(5):373–383;doi:10.1016/0021-9681(87)90171-8
36. Fine JP, Gray RJ: A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999; 94(446):496–509;doi:10.1080/01621459.1999.10474144 https://www.tandfonline.com/doi/abs/10.1080/01621459.1999.10474144
37. Bartels C, Wagner M, Wolfsgruber S, et al: Impact of SSRI therapy on risk of conversion from mild cognitive impairment to Alzheimer's dementia in individuals with previous depression. Am J Psychiatry 2018; 175(3):232–241;doi:10.1176/appi.ajp.2017.17040404
38. Schoenfeld DA: Sample-size formula for the proportional-hazards regression model. Biometrics 1983; 39(2):499–503;doi:10.2307/2531021 https://www.jstor.org/stable/2531021
39. Alen NV: The cholinergic anti-inflammatory pathway in humans: state-of-the-art review and future directions. Neurosci Biobehav Rev 2022; 136:104622;doi:10.1016/j.neubiorev.2022.104622
40. Kaul I, Sawchak S, Walling DP, et al: Efficacy and safety of xanomeline-trospium chloride in schizophrenia: a randomized clinical trial. JAMA Psychiatry 2024; 81(8):749–756;doi:10.1001/jamapsychiatry.2024.0785
41. Nowrangi MA, Outen JD, Kim J, et al: Neuropsychiatric symptoms of Alzheimer's disease: an anatomic-genetic framework for treatment development. J Alzheimer's Dis 2023; 95(1):53–68; doi:10.3233/JAD-221247 https://journals.sagepub.com/doi/full/10.3233/JAD-221247
42. Cirrito JR, Disabato BM, Restivo JL, et al: Serotonin signaling is associated with lower amyloid-β levels and plaques in transgenic mice and humans. Proc Natl Acad Sci U S A 2011; 108(36):14968–14973;doi:10.1073/pnas.1107411108 https://www.jstor.org/stable/27979410
43. Mo M, Abzhandadze T, Hoang MT, et al: Antidepressant use and cognitive decline in patients with dementia: a national cohort study. BMC Med 2025; 23(1);doi:10.1186/s12916-025-03851-3, https://www.ncbi.nlm.nih.gov/pubmed/39994788 82—15
44. Yang C, Chien W, Chung C, et al: The usage of histamine type 1 receptor antagonist and risk of dementia in the elderly: a nationwide cohort study. Front Aging Neurosci 2022; 14:811494; doi:10.3389/fnagi.2022.811494 https://www.ncbi.nlm.nih.gov/pubmed/35370616
45. Sun M, Chen W, Wu S, et al: Long-term opioid use and dementia risk in patients with chronic pain. J Am Med Dir Assoc 2023; 24(9):1420–1426.e2;doi:10.1016/j.jamda.2023.06.035
46. Taipale H, Hamina A, Lampela P, et al: Is Alzheimer's disease associated with previous opioid use? Pain Med 2018; 19(11):2115–2121;doi:10.1093/pm/pnx210 https://www.ncbi.nlm.nih.gov/pubmed/29025166
47. Billioti De Gage S, Moride Y, Ducruet T, et al: Benzodiazepine use and risk of Alzheimer's disease: case-control study. BMJ 2014; 349:g5205;doi:10.1136/bmj.g5205
48. Imfeld P, Bodmer M, Jick SS, et al: Benzodiazepine use and risk of developing Alzheimer's disease or vascular dementia: a case−control analysis. Drug Saf 2015; 38(10):909–919;doi:10.1007/s40264-015-0319-3 https://link.springer.com/article/10.1007/s40264-015-0319-3