Comparative Associations Between Measures of Anticholinergic Burden and Adverse Clinical Outcomes

Wen-Han Hsu, *MS*[1]

Yu-Wen Wen, *PhD*[2]

Liang-Kung Chen, *MD, PhD*[3,4,5]

Fei-Yuan Hsiao, *PhD*[1,6,7]

[1]Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan

[2]Clinical Informatics and Medical Statistics Research Center, Chang Gung University, Taoyuan City, Taiwan

[3]Aging and Health Research Center, National Yang-Ming University, Taipei, Taiwan

[4]Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, Taipei, Taiwan

[5]Institute of Public Health, School of Medicine, National Yang-Ming University, Taipei, Taiwan

[6]School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan

[7]Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan

MORE ONLINE
www.annfammed.org

CORRESPONDING AUTHOR

Fei-Yuan Hsiao, PhD
Graduate Institute of Clinical Pharmacy
Room 220, 33, Linsen S Rd
College of Medicine
National Taiwan University
Taipei, Taiwan 10050
fyshsiao@ntu.edu.tw

ABSTRACT

PURPOSE No consensus has been reached regarding which anticholinergic scoring system works most effectively in clinical settings. The aim of this population-based cohort study was to examine the association between anticholinergic medication burden, as defined by different scales, and adverse clinical outcomes among older adults.

METHODS From Taiwan's Longitudinal Health Insurance Database, we retrieved data on monthly anticholinergic drug use measured by the Anticholinergic Risk Scale (ARS), the Anticholinergic Cognitive Burden Scale (ACB), and the Drug Burden Index - Anticholinergic component (DBI-Ach) for 116,043 people aged 65 years and older during a 10-year follow-up. For all 3 scales, a higher score indicates greater anticholinergic burden. We used generalized estimating equations to examine the association between anticholinergic burden (ARS and ACB: grouped from 0 to ≥4; DBI-Ach: grouped as 0, 0-0.5, and 0.5-1) and adverse outcomes, and stratified individuals by age-group (aged 65-74, 75-84, and ≥85 years).

RESULTS Compared with the ARS and DBI-Ach, the ACB showed the strongest, most consistent dose-response relationships with risks of all 4 adverse outcomes, particularly in people aged 65 to 84 years. For example, among those 65 to 74 years old, going from an ACB score of 1 to a score of 4 or greater, individuals' adjusted odds ratio increased from 1.41 to 2.25 for emergency department visits; from 1.32 to 1.92 for all-cause hospitalizations; from 1.10 to 1.71 for fracture-specific hospitalizations; and from 3.13 to 10.01 for incident dementia.

CONCLUSIONS Compared with the 2 other scales studied, the ACB shows good dose-response relationships between anticholinergic burden and a variety of adverse outcomes in older adults. For primary care and geriatrics clinicians, the ACB may be a helpful tool for identifying high-risk populations for interventions.

INTRODUCTION

Medications with anticholinergic properties are used for a variety of diseases and constitute 30% to 50% of all medications commonly prescribed to older adults.[1] The aging-related decline of acetylcholine production may increase the vulnerability of older adults to anticholinergic adverse effects,[2,3] such as blurred vision, urinary retention, tachycardia, drowsiness, and cognitive impairments.[4] The blurred vision and dizziness caused by exposure to anticholinergic agents may further result in falls and associated adverse events.[5-7] The cognitive impairment associated with exposure to these medications may lead to chronic cognitive deficits such as dementia.[4,8] The cumulative effect of multiple anticholinergic agents, the so-called anticholinergic burden, has been used as an indicator for suboptimal prescribing in older adults.[9] In recent years, several scoring systems have been developed to quantify anticholinergic burden, such as the Anticholinergic Risk Scale (ARS),[10] the Anticholinergic Cognitive Burden Scale (ACB),[8] and the Drug Burden Index - Anticholinergic component (DBI-Ach).[11]

These scales differ considerably in how they were developed, in their method of measuring anticholinergic burden, and in the results they yield. Notably, their approaches to identifying medications with anticholinergic properties to be included in their scales differ greatly. The ARS ranks the 500 most commonly prescribed drugs in a Veterans Affairs Health Care System by their dissociation constant for the cholinergic receptor,[10] while the ACB ranking was developed through a systematic literature review and expert opinions.[8] Medications were included in the DBI-Ach if they had demonstrated clinically important anticholinergic effects that were documented in country-specific drug monographs or registered product information.[11] To date, no consensus has been reached regarding which scoring system is most useful in clinical settings. Moreover, existing studies of the various scoring systems have a variety of limitations: evaluation of only a single system,[12-14] application of different cutoff values for anticholinergic burden between scoring systems, small sample sizes,[15,16] cross-sectional designs,[15,16] and short follow-up periods[17] (≤1 year). All of these limitations preclude a clear answer to this clinical question.

To address these limitations, the main aim of this study was to compare the associations between longitudinal anticholinergic burden, as defined by the different scales, and adverse clinical outcomes among older adults.

METHODS

Study Design and Data Set

We conducted a retrospective population-based cohort study using Taiwan's National Health Insurance Research Database (NHIRD).[18] Implemented in 1995,

the National Health Insurance program covers more than 99% of the total population (23 million people) in Taiwan.[19] The NHIRD contains comprehensive data about demographic information, health service use, prescriptions, and diagnoses based on the *International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)*. We used a subset of the NHIRD—the Longitudinal Health Insurance Database (LHID),[18] which contains the claims data of 2 million randomly selected beneficiaries from the NHIRD—to develop a 12-year (2000-2011) panel of claims for analysis. These individuals were sampled from the registry for beneficiaries of the NHIRD in the years 2000 (1 million) and 2005 (1 million). The age and sex distributions of the LHID do not differ significantly from those of the parent NHIRD cohort.[18]

This study was approved by the institutional review board of the National Taiwan University Hospital (National Taiwan University Hospital Research Ethics Committee No. 201401004W). Because the identification numbers of all individuals in the NHIRD were encrypted to protect their privacy, the study was exempted from full board review, and informed consents were waived.

Study Population

The study cohort consisted of individuals who were aged 65 years and older at study entry (January 1, 2001) (Figure 1). We excluded people who in the year preceding the recruitment date received a diagnosis of any of the 22 chronic diseases requiring long-term medical care and support under Taiwan's National Health Insurance system, including cancer, rheumatoid arthritis, and systemic lupus erythematosus (Supplemental Appendix 1, available at http://www.

Figure 1. Study design.

NHI = National Health Insurance.
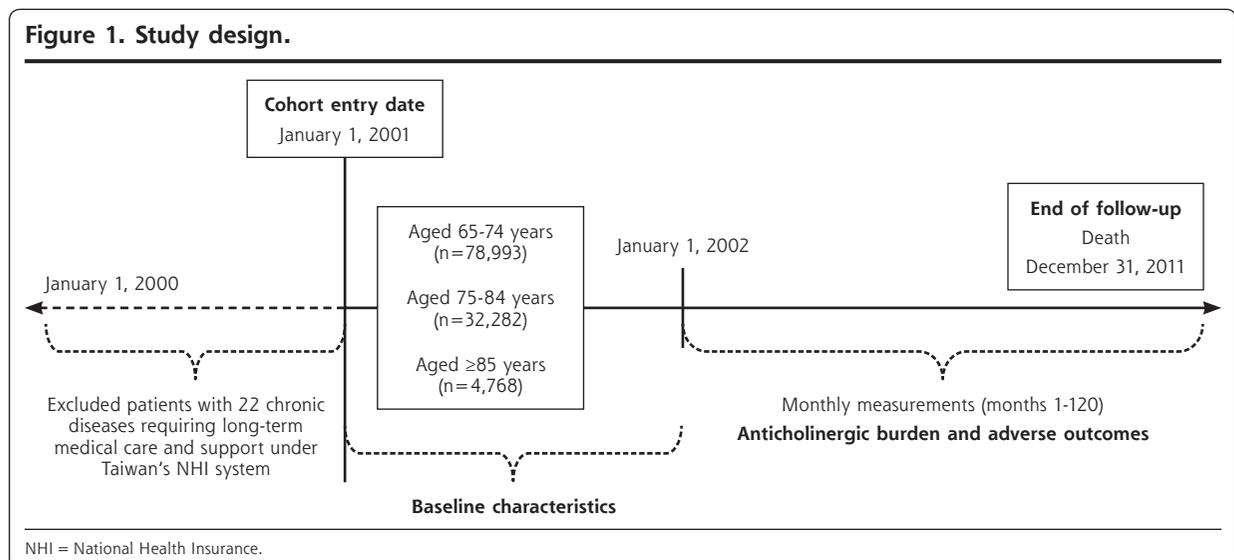
AnnFamMed.org/content/15/6/561/suppl/DC1/).[18] All eligible individuals were categorized into 3 age-groups based on their age at enrollment: aged 65 to 74 years (the so-called young-old), 75 to 84 years (middle-old), and 85 years and older (oldest-old). We examined potentially different impacts of anticholinergic burden on adverse outcomes across the 3 age-groups because we expected that drug use pattern would change with advancing age. Baseline characteristics were collected in the first year after enrollment (2001).

Anticholinergic Burden Scales

During the 10-year follow-up period, we retrieved data on longitudinal anticholinergic burden assessed monthly for 120 months as measured by the ARS (Supplemental Appendix 2, available at http://www.AnnFamMed.org/content/15/6/561/suppl/DC1/), by the ACB (Supplemental Appendix 3, available at http://www.AnnFamMed.org/content/15/6/561/suppl/DC1/), and by the DBI-Ach (Figure 1). We selected these scales to represent 3 distinct methods of identifying drug lists in clinical settings and measuring anticholinergic burden, as described in the Introduction section.

Both the ARS and ACB have 4-point scales (0, limited or none; 1, moderate; 2, strong; 3, very strong) to rank the anticholinergic activity of each medication, so a patient's score on each of these scales was calculated as the sum of the rankings for all prescribed drugs.[8,10,20] For both, a higher score indicates higher anticholinergic burden. If a patient receives a medication ranked 1 and another medication ranked 2 in the list of ARS, then the patient's ARS score is 3. There is no published consensus, however, regarding the optimal cutoff levels for ARS and ACB. We therefore grouped together individuals having scores of 4 or higher because we had relatively few with scores that high.

To calculate the DBI-Ach score, we first needed to identify country-specific medications with anticholinergic effects.[11] On the basis of our previous study,[21] we used medications listed in the ARS to calculate this score. Specifically, DBI-Ach was calculated as

$$\sum_i \left(\frac{D}{\delta + D} \right)$$

where D is the daily dose and δ is the minimum recommended daily dose as approved by the regulator; this calculation was established based on a series of assumptions made to derive a pharmacologic equation that incorporated the concept of dose-response.[11] For the DBI-Ach score, we replaced the minimum recommended daily dose used in the calculation of this score as suggested previously by Faure et al[22] with the defined daily dose. The definition of defined daily dose is the average maintenance dose per day for a

drug used for its main indication in adults as defined by the World Health Organization.[23] The DBI-Ach score ranges from 0 to 1, with 0.5 indicating that an individual is exposed to an anticholinergic medication at the minimum recommended daily dose, and higher scores indicating greater burden.

We selected only those drugs that were prescribed for more than 7 days in each month to calculate anticholinergic burden for each of the 3 scoring systems. Although drugs for short-term symptom relief such as antihistamines are often sold over the counter in other countries, they are reimbursed under Taiwan's National Health Insurance system. Including exposure to these drugs (ie, usually a 3-day supply) in our study could have resulted in overestimation of anticholinergic burden.

Adverse Outcomes

During the same 10-year period, we retrieved data on 4 adverse outcomes of interest: emergency department visits, all-cause hospitalizations, fracture-specific hospitalizations, and incident dementia. We defined a fracture-specific hospitalization as a hospital admission with a discharge diagnosis of fracture (ICD-9-CM codes 800-829).[24] Patients with incident dementia were defined as those who had at least 3 outpatient or inpatient claim records of a diagnosis of dementia (290.xx, 294.1x, 331.0, 331.2).[25] The first date of any of these diagnosis codes was considered the date of onset. We excluded patients with dementia at baseline (1 year after cohort enrollment) when analyzing the association between anticholinergic burden and incident dementia.

Statistical Analysis

We used generalized estimating equation (GEE)[26] models (SAS PROC GENMOD; SAS Institute Inc) with a logit link and first-order autoregressive correlation structure to examine the association between anticholinergic burden (measured by scores) and adverse outcomes, taking into account the repeated measurements for the same individual. The GEE models were adjusted for sex and time-varying comorbidities, annually measured by Charlson Comorbidity Index[27] (higher index indicates more comorbidities). For the ARS and ACB scales, we further adjusted the defined daily dose [23] of drugs with anticholinergic properties in the GEE models to compare the 3 scales. Separate models were fitted to each age-group and each scale. The results of all GEE models are presented as adjusted odds ratios (aORs) with 95% CIs for each of the 3 age-groups (65-74 years, 75-84 years, and ≥85 years). All statistical analyses were performed with SAS version 9.3, and a P value <.05 was considered statistically significant.

Table 1. Baseline Characteristics and Health Care Use of Study Cohort, Overall and Stratified by Age

Characteristic	Overall (N = 116,043)	Aged 65-74 Years (n = 78,993)	Aged 75-84 Years (n = 32,282)	Aged ≥85 Years (n = 4,768)
Female, No. (%)	57,523 (49.57)	38,788 (49.10)	15,933 (49.36)	2,802 (58.77)
Charlson Comorbidity Index				
Total sample, mean (SD)	1.17 (1.36)	1.13 (1.34)	1.27 (1.40)	1.16 (1.39)
Female, mean (SD)	1.13 (1.36)	1.12 (1.35)	1.19 (1.38)	1.06 (1.33)
Male, mean (SD)	1.20 (1.36)	1.14 (1.33)	1.34 (1.42)	1.30 (1.45)
Comorbidities				
Hypertension, No. (%)	44,278 (38.16)	29,692 (37.59)	12,916 (40.01)	1,670 (35.03)
Diabetes, No. (%)	20,852 (17.97)	15,017 (19.01)	5,364 (16.62)	471 (9.88)
Dyslipidemia, No. (%)	15,065 (12.98)	11,344 (14.36)	3,481 (10.78)	240 (5.03)
Coronary artery disease, No. (%)	23,475 (20.23)	15,151 (19.18)	7,378 (22.85)	946 (19.84)
Congestive heart failure, No. (%)	7,064 (6.09)	4,082 (5.17)	2,513 (7.78)	469 (9.84)
Cerebrovascular disease, No. (%)	14,915 (12.85)	8,803 (11.14)	5,255 (16.28)	857 (17.97)
Dementia, No. (%)	2,873 (2.48)	1,202 (1.52)	1,293 (4.01)	378 (7.93)
Depression, No. (%)	3,278 (2.82)	2,246 (2.84)	931 (2.88)	101 (2.12)
Psychosis/schizophrenia, No. (%)	3,185 (2.74)	1,481 (1.87)	1,331 (4.12)	373 (7.82)
Parkinson disease, No. (%)	2,491 (2.15)	1,311 (1.66)	1,012 (3.13)	168 (3.52)
Arthritis, No. (%)	32,979 (28.42)	22,147 (28.04)	9,526 (29.51)	1,306 (27.39)
Osteoporosis, No. (%)	10,217 (8.80)	6,623 (8.38)	3,086 (9.56)	508 (10.65)
Use of ambulatory care, annually				
Number of visits, mean (SD)	24.44 (19.92)	23.82 (19.41)	26.06 (20.95)	23.64 (20.60)
Use of all drugs, monthly				
Number of drugs used, mean (SD)	2.47 (2.40)	2.36 (2.35)	2.75 (2.50)	2.40 (2.33)
≥1 drug, No. (%)	74,408 (64.12)	49,260 (62.36)	22,105 (68.47)	3,043 (63.82)
≥5 drugs, No. (%)	18,178 (15.66)	11,422 (14.46)	6,040 (18.71)	716 (15.02)
≥10 drugs, No. (%)	1,005 (0.87)	630 (0.80)	344 (1.07)	31 (0.65)
Use of anticholinergic drugs				
ARS				
Score[a] per month, mean (SD)	0.26 (0.57)	0.24 (0.56)	0.29 (0.61)	0.26 (0.56)
Use of ≥1 drug per year, No. (%)	43,301 (37.31)	28,665 (36.29)	12,839 (39.77)	1,797 (37.69)
ACB				
Score[a] per month, mean (SD)	0.60 (0.92)	0.57 (0.89)	0.69 (0.97)	0.64 (0.94)
Use of ≥1 drug per year, No. (%)	69,619 (59.99)	46,024 (58.26)	20,706 (64.14)	2,889 (60.59)
DBI-Ach				
Score[b] per month, mean (SD)	0.04 (0.09)	0.04 (0.09)	0.04 (0.10)	0.04 (0.09)
Use of ≥1 drug per year, No. (%)	43,301 (37.31)	28,665 (36.29)	12,839 (39.77)	1,797 (37.69)

ACB = Anticholinergic Cognitive Burden scale; ARS = Anticholinergic Risk Scale; DBI-Ach = Drug Burden Index - Anticholinergic component.

[a] ARS and ACB scores were calculated as the sum of the rankings for all prescribed drugs, with higher scores indicating greater anticholinergic burden.

[b] DBI-Ach score ranges from 0 to 1, with 0.5 indicating that an individual is exposed to an anticholinergic drug at the minimum recommended daily dose.

RESULTS

We analyzed data from a total of 116,043 older adults: 78,993 (68.07%) aged 65 to 74 years, 32,282 (27.82%) aged 75 to 84 years, and 4,768 (4.11%) aged 85 years and older (Table 1). In the first year after cohort enrollment (baseline period), the proportion of patients who received anticholinergic agents as ascertained by the ARS, ACB, and DBI-Ach was 37.31%, 59.99%, and 37.31%, respectively. The average monthly anticholinergic burden measured by the 3 scoring systems in all older adults studied was 0.26, 0.60, and 0.04, respectively.

The mean duration of follow-up was 8.31 years. Number of events for each adverse outcome in each age-group during follow-up are provided in Tables 2 through 5.

Of the 3 scales for assessing anticholinergic burden, only the ACB and DBI-Ach showed clear dose-response relationships with increased odds of emergency department visits (Table 2) and all-cause hospitalizations (Table 3) in all age-groups.

Only the DBI-Ach showed a dose-response relationship with fracture-specific hospitalizations in all age-groups (Table 4). The ARS and ACB showed dose-

Table 2. Anticholinergic Burden and Emergency Department Visits in Older Adults

	Emergency Department Visits								
	Aged 65-74 Years (n = 287,693)			Aged 75-84 Years (n = 137,858)			Aged ≥85 Years (n = 16,830)		
Scale and Score	No.	aOR[a] (95% CI)	P Value	No.	aOR[a] (95% CI)	P Value	No.	aOR[a] (95% CI)	P Value
ARS[b]									
0 (ref)	214,635	1.00	–	101,410	1.00	–	12,926	1.00	–
1	22,426	1.90 (1.86-1.95)	<.001	13,014	1.85 (1.79-1.91)	<.001	1,590	1.61 (1.47-1.76)	<.001
2	22,753	1.55 (1.51-1.59)	<.001	10,359	1.54 (1.48-1.60)	<.001	1,047	1.34 (1.19-1.51)	<.001
3	17,616	1.65 (1.61-1.70)	<.001	8,351	1.56 (1.50-1.62)	<.001	827	1.38 (1.23-1.54)	<.001
≥4	10,263	2.04 (1.97-2.11)	<.001	4,724	1.94 (1.85-2.03)	<.001	440	1.73 (1.50-2.01)	<.001
ACB[b]									
0 (ref)	140,058	1.00	–	65,016	1.00	–	9,143	1.00	–
1	64,684	1.41 (1.37-1.45)	<.001	30,612	1.38 (1.35-1.41)	<.001	3,432	1.35 (1.28-1.44)	<.001
2	32,822	1.71 (1.66-1.75)	<.001	16,287	1.63 (1.59-1.68)	<.001	1,776	1.49 (1.38-1.61)	<.001
3	23,915	1.82 (1.78-1.87)	<.001	12,375	1.74 (1.69-1.79)	<.001	1,251	1.59 (1.46-1.74)	<.001
≥4	26,214	2.25 (2.19-2.31)	<.001	13,568	2.07 (2.00-2.14)	<.001	1,228	1.69 (1.54-1.85)	<.001
DBI-Ach[c]									
0 (ref)	214,636	1.00	–	101,411	1.00	–	12,926	1.00	–
0< score ≤0.5	56,873	1.68 (1.66-1.70)	<.001	28,900	1.60 (1.57-1.63)	<.001	3,110	1.55 (1.47-1.64)	<.001
0.5< score ≤1	16,184	2.02 (1.97-2.07)	<.001	7,547	1.87 (1.80-1.93)	<.001	794	1.98 (1.79-2.19)	<.001

aOR = adjusted odds ratio; ARS = Anticholinergic Risk Scale; ACB = Anticholinergic Cognitive Burden scale; DBI-Ach = Drug Burden Index - Anticholinergic component; ref = reference group.

Note: In multivariate generalized estimating equation models. Total sample for analysis was 442,381.

[a] Models were adjusted for sex and time-varying comorbidities (annually measured by Charlson Comorbidity Index; higher index indicates more comorbidities). For the ARS and ACB scales, we further adjusted defined daily dose of drugs with anticholinergic properties in the models to compare among the 3 scales.

[b] ARS and ACB scores were calculated as the sum of the rankings for all prescribed drugs, with higher scores indicating greater anticholinergic burden.

[c] DBI-Ach score ranges from 0 to 1, with 0.5 indicating that an individual is exposed to an anticholinergic medication at the minimum recommended daily dose.

response relationships with fracture-specific hospitalizations in individuals aged 65 to 74 years and 75 to 84 years, but not in those aged 85 years and older. The ACB showed a dose-response relationship with incident dementia in patients aged 65 to 74 years and 75 to 84 years, but not in patients aged 85 years and older (Table 5); the other scales did not show such relationships in any of the age-groups.

DISCUSSION

To the best of our knowledge, this is the first study to compare long-term associations between anticholinergic burden measured by different scales and adverse clinical outcomes, with an average follow-up period exceeding 8 years. We found that among the 3 scales, only anticholinergic burden assessed with the ACB showed a dose-response relationship with all outcomes studied—emergency department visits, all-cause hospitalizations, fracture-specific hospitalizations, and incident dementia.

Our study expands on the current knowledge of anticholinergic burden in the older population in many ways. First, by using a nationwide cohort of older adults with fairly long follow-up, our study allows head-to-head comparisons of longitudinal anticholinergic burden derived from the ARS, ACB, and DBI-Ach scales and associated clinical outcomes, which have not been previously reported in the literature. Some other studies have tried to compare the ARS and ACB, but were limited by their small sample sizes[15,28] and a 1-time cross-sectional study design.[17] Second, our study provides important insights by linking anticholinergic burden to 4 key clinical outcomes, whereas most existing studies have examined only the discrepancies between scales.[29,30] Ours is also the first to demonstrate an association between anticholinergic burden and emergency department visits, which has important clinical implications. Another aspect that distinguishes this study from previous ones is the definition of adverse outcomes considered. Although previous studies found that use of anticholinergics was associated with falls[5,6,12] and admissions due to falls[7,17] resulting from adverse effects such as blurred vision and dizziness,[31] our study used fracture-specific hospitalizations as an end point to further capture the adverse effects of anticholinergic burden. Additionally, we examined the link of anticholinergic burden with incident dementia, instead of with cognitive function as done in most of the existing studies.[32-34]

Our findings are consistent with those of previous studies[15,17] in that the proportion of patients who received anticholinergic agents measured by the ACB (59.99%) was higher than that measured by the ARS (37.31%) at the baseline assessment. This discrepancy between scoring systems may result from the different

Table 3. Anticholinergic Burden and All-Cause Hospitalizations in Older Adults

| Scale and Score | All-Cause Hospitalizations | | | | | | | | |
| | Aged 65-74 Years (n = 235,824) | | | Aged 75-84 Years (n = 118,907) | | | Aged ≥85 Years (n = 15,790) | | |
	No.	aOR (95% CI)	P Value	No.	aOR (95% CI)	P Value	No.	aOR (95% CI)	P Value
ARS									
0 (ref)	175,954	1.00	–	87,169	1.00	–	11,909	1.00	–
1	20,208	1.95 (1.91-2.00)	<.001	12,166	1.85 (1.79-1.92)	<.001	1,703	1.75 (1.59-1.93)	<.001
2	18,295	1.44 (1.40-1.48)	<.001	8,987	1.42 (1.36-1.48)	<.001	1,057	1.36 (1.21-1.53)	<.001
3	13,781	1.49 (1.45-1.53)	<.001	6,806	1.36 (1.31-1.41)	<.001	718	1.20 (1.07-1.36)	.002
≥4	7,586	1.69 (1.64-1.75)	<.001	3,779	1.62 (1.54-1.71)	<.001	403	1.58 (1.37-1.83)	<.001
ACB									
0 (ref)	115,085	1.00	–	56,126	1.00	–	8,378	1.00	–
1	53,156	1.32 (1.26-1.38)	<.001	26,370	1.31 (1.27-1.35)	<.001	3,309	1.37 (1.29-1.46)	<.001
2	27,028	1.57 (1.50-1.64)	<.001	14,574	1.59 (1.54-1.64)	<.001	1,751	1.52 (1.40-1.65)	<.001
3	20,059	1.70 (1.63-1.77)	<.001	10,565	1.61 (1.55-1.66)	<.001	1,179	1.55 (1.41-1.70)	<.001
≥4	20,496	1.92 (1.85-2.00)	<.001	11,272	1.83 (1.77-1.89)	<.001	1,173	1.66 (1.51-1.83)	<.001
DBI-Ach									
0 (ref)	175,954	1.00	–	87,173	1.00	–	11,909	1.00	–
0< score ≤0.5	47,217	1.61 (1.58-1.63)	<.001	25,312	1.56 (1.53-1.59)	<.001	3,116	1.62 (1.53-1.72)	<.001
0.5< score ≤1	12,653	1.79 (1.74-1.83)	<.001	6,422	1.74 (1.68-1.80)	<.001	765	1.95 (1.75-2.18)	<.001

aOR = adjusted odds ratio; ACB = Anticholinergic Cognitive Burden scale; ARS = Anticholinergic Risk Scale; DBI-Ach = Drug Burden Index - Anticholinergic component; ref = reference group.

Notes: In multivariate generalized estimating equation models. Total sample for analysis was 370,521. Refer to Table 2 notes for description of adjustment and scales.

Table 4. Anticholinergic Burden and Fracture-Specific Hospitalizations in Older Adults

| Scale and Score | Fracture-Specific Hospitalizations | | | | | | | | |
| | Aged 65-74 Years (n = 11,682) | | | Aged 75-84 Years (n = 6,567) | | | Aged ≥85 Years (n = 1,018) | | |
	No.	aOR (95% CI)	P Value	No.	aOR (95% CI)	P Value	No.	aOR (95% CI)	P Value
ARS									
0 (ref)	9,224	1.00	–	5,133	1.00	–	847	1.00	–
1	683	1.61 (1.47-1.76)	<.001	458	1.49 (1.33-1.66)	<.001	59	1.02 (0.75-1.39)	.88
2	832	1.64 (1.48-1.81)	<.001	443	1.56 (1.37-1.79)	<.001	47	0.99 (0.63-1.55)	.96
3	610	1.64 (1.49-1.81)	<.001	365	1.64 (1.43-1.87)	<.001	41	1.19 (0.79-1.78)	.41
≥4	333	1.96 (1.72-2.23)	<.001	168	1.73 (1.44-2.07)	<.001	24	1.65 (1.03-2.66)	.04
ACB									
0 (ref)	6,915	1.00	–	3,707	1.00	–	651	1.00	–
1	2,231	1.10 (1.02-1.18)	.009	1,310	1.17 (1.07-1.28)	<.001	164	1.00 (0.84-1.20)	.97
2	939	1.13 (1.04-1.23)	.006	575	1.18 (1.05-1.31)	.004	89	1.18 (0.94-1.48)	.16
3	756	1.34 (1.23-1.46)	<.001	474	1.37 (1.22-1.54)	<.001	62	1.28 (0.98-1.67)	.07
≥4	841	1.71 (1.57-1.86)	<.001	501	1.62 (1.45-1.82)	<.001	52	1.18 (0.89-1.58)	.25
DBI-Ach									
0 (ref)	9,224	1.00	–	5,133	1.00	–	847	1.00	–
0< score ≤0.5	1,941	1.45 (1.38-1.53)	<.001	1,171	1.43 (1.34-1.52)	<.001	134	1.13 (0.94-1.37)	.19
0.5< score ≤1	517	1.67 (1.52-1.84)	<.001	263	1.48 (1.30-1.68)	<.001	37	1.60 (1.15-2.23)	.006

aOR = adjusted odds ratio; ACB = Anticholinergic Cognitive Burden scale; ARS = Anticholinergic Risk Scale; DBI-Ach = Drug Burden Index - Anticholinergic component; ref = reference group.

Note: In multivariate generalized estimating equation models. Total sample for analysis was 19,267. Refer to Table 2 notes for description of adjustment and scales.

collections of drugs included in the scales. In our study, the commonly used anticholinergics contained in the ACB were mainly cardiovascular drugs such as dipyridamole, isosorbide mononitrate, nifedipine, atenolol, digoxin, and furosemide, whereas the commonly used anticholinergics contained in the ARS were mainly antihistamines or drugs affecting the nervous system, such as quetiapine and trazodone (data not shown). These findings are also in line with those of several previous studies.[13,15,32,35] Primary care and geriatrics clinicians should pay special attention to these medications.

Unlike the ACB score, the ARS score showed a dose-response relationship only with regard to fracture-specific hospitalizations, exhibiting a U-shaped relationship with the other adverse outcomes studied. In particular, we found that the ARS score had a U-shaped relationship with risk of incident dementia, as Pasina et al[15] have likewise reported. Our analyses showed that an ARS score of 1 was associated with a 10-fold increase in the odds of incident dementia. A potential explanation for this association is that anticholinergic drugs (particularly those contained in the ARS) may be prescribed to treat symptoms of dementia, such as insomnia or depression. The DBI-Ach score also showed a dose-response association with adverse outcomes. Calculating this score requires more effort, however, and it may not be very efficient to use it in routine daily practice.

There are some limitations to this study, mainly due to the use of claims data. First, we were not able to include drugs not reimbursed by Taiwan's National Health Insurance, nor could we consider variables not routinely recorded in the NHIRD such as body mass index, education level, and patient adherence. Second, with regard to the consistency of the study design, we did not control for a few risk factors that may affect the association between anticholinergic burden and adverse outcomes, such as osteoporosis (a risk factor for fracture) and depression and Parkinson disease (risk factors for dementia). Consistent results were still obtained, however, after adjusting for these risk factors. Third, our findings may not be generalizable to other, non-Asian populations because of different prescribing patterns. In addition, the exclusion of older adults having 22 chronic diseases requiring long-term medical care and support under Taiwan's National Health Insurance system and relatively small number of participants in the oldest-old age-group (aged ≥85 years) may limit the generalizability of our study to these patients. A large proportion of people in this age-group may be lost to follow-up over 10 years. Fourth, only drugs prescribed for 7 or more days within a 1-month period were considered in measurement of anticholinergic burden. Short-term use of anticholinergic agents, however, may also affect clinical outcomes. In addition, use of medications may represent underly-

Table 5. Anticholinergic Burden and Incident Dementia in Older Adults

| | Incident Dementia | | | | | | | | |
| | Aged 65-74 Years (n = 8,350) | | | Aged 75-84 Years (n = 5,637) | | | Aged ≥85 Years (n = 815) | | |
Scale and Score	No.	aOR (95% CI)	P Value	No.	aOR (95% CI)	P Value	No.	aOR (95% CI)	P Value
ARS									
0 (ref)	4,749	1.00	–	3,164	1.00	–	511	1.00	–
1	1,757	10.41 (9.67-11.21)	<.001	1,301	8.46 (7.76-9.22)	<.001	176	6.81 (5.30-8.76)	<.001
2	836	5.20 (4.73-5.73)	<.001	556	4.96 (4.41-5.58)	<.001	63	3.90 (2.74-5.55)	<.001
3	551	3.87 (3.51-4.27)	<.001	363	3.43 (3.05-3.87)	<.001	37	2.58 (1.78-3.75)	<.001
≥4	457	7.27 (6.48-8.16)	<.001	253	5.55 (4.76-6.46)	<.001	28	4.88 (3.08-7.74)	<.001
ACB									
0 (ref)	3,301	1.00	–	2,187	1.00	–	366	1.00	–
1	1,617	3.13 (2.89-3.39)	<.001	1,091	2.76 (2.51-3.05)	<.001	166	2.51 (1.95-3.23)	<.001
2	777	3.62 (3.27-4.00)	<.001	581	3.30 (2.92-3.72)	<.001	82	2.44 (1.78-3.35)	<.001
3	1,196	7.17 (6.55-7.85)	<.001	817	5.81 (5.21-6.48)	<.001	98	4.48 (3.30-6.08)	<.001
≥4	1,459	10.01 (9.16-10.95)	<.001	961	7.44 (6.68-8.28)	<.001	103	5.16 (3.82-6.97)	<.001
DBI-Ach									
0 (ref)	4,749	1.00	–	3,164	1.00	–	511	1.00	–
0< score ≤ 0.5	2,915	3.75 (3.57-3.93)	<.001	2,059	3.50 (3.30-3.70)	<.001	254	3.05 (2.59-3.60)	<.001
0.5< score ≤ 1	686	3.68 (3.39-3.99)	<.001	414	3.06 (2.75-3.39)	<.001	50	2.98 (2.21-4.03)	<.001

aOR = adjusted odds ratio; ARS = Anticholinergic Risk Scale; ACB = Anticholinergic Cognitive Burden scale; DBI-Ach = Drug Burden Index - Anticholinergic component; ref = reference group.

Note: In multivariate generalized estimating equation models. Total sample for analysis was 14,802. Refer to Table 2 notes for description of adjustment and scales.

ing disease; for example, many of the medications listed in the ACB are cardiovascular drugs, which may affect clinical outcomes as well. Fifth, we did not include total number of medications as a covariate in the analyses because of concerns about colinearity between this number and anticholinergic burden. A previous study has reported that patients who were prescribed 6 to 10 medications or 11 or more medications were significantly more likely to receive anticholinergic prescriptions (OR = 3.41; 95% CI, 2.23-5.22 and OR = 4.69; 95% CI, 2.99-7.34, respectively).[36] Lastly, although these scoring systems show an association between high anticholinergic burden and adverse outcomes, we could not establish causation from this observational study.

In conclusion, compared with the ARS and the DBI-Ach, the ACB consistently showed dose-response relationships with a variety of adverse outcomes. For primary care and geriatrics clinicians, the ACB may be a good tool for identifying high-risk populations for interventions.

To read or post commentaries in response to this article, see it online at http://www.AnnFamMed.org/content/15/6/561.

References

1. Chew ML, Mulsant BH, Pollock BG, et al. Anticholinergic activity of 107 medications commonly used by older adults. *J Am Geriatr Soc*. 2008;56(7):1333-1341.

2. Smith DO, Chapman MR. Acetylcholine receptor binding properties at the rat neuromuscular junction during aging. *J Neurochem*. 1987; 48(6):1834-1841.

3. Tune LE. Anticholinergic effects of medication in elderly patients. *J Clin Psychiatry*. 2001;62(Suppl 21):11-14.

4. Gerretsen P, Pollock BG. Drugs with anticholinergic properties: a current perspective on use and safety. *Expert Opin Drug Saf*. 2011; 10(5):751-765.

5. Wilson NM, Hilmer SN, March LM, et al. Associations between drug burden index and falls in older people in residential aged care. *J Am Geriatr Soc*. 2011;59(5):875-880.

6. Dauphinot V, Faure R, Omrani S, et al. Exposure to anticholinergic and sedative drugs, risk of falls, and mortality: an elderly inpatient, multicenter cohort. *J Clin Psychopharmacol*. 2014;34(5):565-570.

7. Nishtala PS, Narayan SW, Wang T, Hilmer SN. Associations of drug burden index with falls, general practitioner visits, and mortality in older people. *Pharmacoepidemiol Drug Saf*. 2014;23(7):753-758.

8. Boustani M, Campbell N, Munger S, Maidment I, Fox C. Impact of anticholinergics on the aging brain: a review and practical application. *Aging Health*. 2008;4(3):311-320.

9. Myint PK, Fox C, Kwok CS, Luben RN, Wareham NJ, Khaw KT. Total anticholinergic burden and risk of mortality and cardiovascular disease over 10 years in 21,636 middle-aged and older men and women of EPIC-Norfolk prospective population study. *Age Ageing*. 2015;44(2):219-225.

10. Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. *Arch Intern Med*. 2008;168(5):508-513.

11. Hilmer SN, Mager DE, Simonsick EM, et al. A drug burden index to define the functional burden of medications in older people. *Arch Intern Med*. 2007;167(8):781-787.

12. Landi F, Dell'Aquila G, Collamati A, et al. Anticholinergic drug use and negative outcomes among the frail elderly population living in a nursing home. *J Am Med Dir Assoc*. 2014;15(11):825-829.

13. Cai X, Campbell N, Khan B, Callahan C, Boustani M. Long-term anticholinergic use and the aging brain. *Alzheimers Dement*. 2013; 9(4):377-385.

14. Fox C, Smith T, Maidment I, et al. Effect of medications with anticholinergic properties on cognitive function, delirium, physical function and mortality: a systematic review. *Age Ageing*. 2014;43(5): 604-615.

15. Pasina L, Djade CD, Lucca U, et al. Association of anticholinergic burden with cognitive and functional status in a cohort of hospitalized elderly: comparison of the anticholinergic cognitive burden scale and anticholinergic risk scale: results from the REPOSI study. *Drugs Aging*. 2013;30(2):103-112.

16. Mangoni AA, van Munster BC, Woodman RJ, de Rooij SE. Measures of anticholinergic drug exposure, serum anticholinergic activity, and all-cause postdischarge mortality in older hospitalized patients with hip fractures. *Am J Geriatr Psychiatry*. 2013;21(8):785-793.

17. Salahudeen MS, Hilmer SN, Nishtala PS. Comparison of anticholinergic risk scales and associations with adverse health outcomes in older people. *J Am Geriatr Soc*. 2015;63(1):85-90.

18. National Health Insurance Research Database. Longitudinal Health Insurance Database (LHID). http://nhird.nhri.org.tw/en/Data_Subsets.html. Accessed Aug 30, 2015.

19. Hsiao FY, Yang CL, Huang YT, Huang WF. Using Taiwan's national health insurance research databases for pharmacoepidemiology research. *J Food Drug Anal*. 2007;15:99-108.

20. Kersten H, Wyller TB. Anticholinergic drug burden in older people's brain – how well is it measured? *Basic Clin Pharmacol Toxicol*. 2014; 114(2):151-159.

21. Lu WH, Wen YW, Chen LK, Hsiao FY. Effect of polypharmacy, potentially inappropriate medications and anticholinergic burden on clinical outcomes: a retrospective cohort study. *CMAJ*. 2015; 187(4):E130-E137.

22. Faure R, Dauphinot V, Krolak-Salmon P, Mouchoux C. A standard international version of the Drug Burden Index for cross-national comparison of the functional burden of medications in older people. *J Am Geriatr Soc*. 2013;61(7):1227-1228.

23. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD index, 2015. http://www.whocc.no/atc_ddd_index/. Accessed Jun 26, 2015.

24. Hsiao FY, Mullins CD. The association between thiazolidinediones and hospitalisation for fracture in type 2 diabetic patients: a Taiwanese population-based nested case-control study. *Diabetologia*. 2010;53(3):489-496.

25. Hsiao FY, Peng LN, Wen YW, Liang CK, Wang PN, Chen LK. Care needs and clinical outcomes of older people with dementia: a population-based propensity score-matched cohort study. *PLoS One*. 2015;10(5):e0124973.

26. Liang KY, Zeger S. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986;73(1):13-22.

27. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.

28. Lampela P, Lavikainen P, Garcia-Horsman JA, Bell JS, Huupponen R, Hartikainen S. Anticholinergic drug use, serum anticholinergic activity, and adverse drug events among older people: a population-based study. *Drugs Aging*. 2013;30(5):321-330.

29. Pont LG, Nielen JT, McLachlan AJ, et al. Measuring anticholinergic drug exposure in older community-dwelling Australian men: a comparison of four different measures. *Br J Clin Pharmacol*. 2015;80(5):1169-1175.

30. Lampela P, Taipale H, Lavikainen P, Hartikainen S. The effect of comprehensive geriatric assessment on anticholinergic exposure assessed by four ranked anticholinergic lists. *Arch Gerontol Geriatr*. 2017;68:195-201.

31. Mintzer J, Burns A. Anticholinergic side-effects of drugs in elderly people. *J R Soc Med*. 2000;93(9):457-462.

32. Fox C, Richardson K, Maidment ID, et al. Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. *J Am Geriatr Soc*. 2011;59(8):1477-1483.

33. Hilmer SN, Mager DE, Simonsick EM, et al. Drug burden index score and functional decline in older people. *Am J Med*. 2009;122(12):1142-1149, e1141-e1142.

34. Campbell NL, Boustani MA, Lane KA, et al. Use of anticholinergics and the risk of cognitive impairment in an African American population. *Neurology*. 2010;75(2):152-159.

35. West T, Pruchnicki MC, Porter K, Emptage R. Evaluation of anticholinergic burden of medications in older adults. *J Am Pharm Assoc (2003)*. 2013;53(5):496-504.

36. Lee EK, Lee YJ. Prescription patterns of anticholinergic agents and their associated factors in Korean elderly patients with dementia. *Int J Clin Pharm*. 2013;35(5):711-718.