A Five-Year Prospective Evaluation of Anticholinergic Cognitive Burden and Falls in the Malaysian Elders Longitudinal Research (MELoR) study

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Abstract

Background

While anticholinergic use is associated with stroke, dementia and mortality, few have evaluated its potential link with falls. To determine the relationship between anticholinergic cognitive burden (ACB) and falls over five years using the Malaysian Elders Longitudinal Research (MELoR).

Methods

Community-dwelling adults aged 55 years and over were recruited through electoral roll sampling. Data obtained at baseline and follow-up (FU) at two and five years were included. Falls in the preceding 12 months were recorded.

Results

Of the 1499 individuals (mean (SD) age= 68.9(7.5) yrs and 53.3% female) with information on baseline ACB exposure, 575(38.4%) had ACB scores of 1-2 and 117(7.8%) had ACB scores ≥ 3. Differences in age, ethnicity, smoking status, diabetes, hypertension, cardiovascular disease, arthritis and education existed between ACB groups. Fall occurrence differed between ACB groups at recruitment (p=0.004) and 2-year FU (p=0.001) but not at 5-year FU (p=0.053). Logistic regression revealed an independent association between ACB 1-2 and falls at baseline (odds ratio, OR (95% confidence interval, CI) =1.412(1.035-1.926)) and ACB$\geq$ 3 and falls at 2-yr FU (OR (95%CI) =2.098(1.032-4.263)) following adjustment for confounders.

Conclusion

Low level exposure to drugs with anticholinergic properties was associated cross-sectionally with falls, while exposure to higher levels were prospectively associated with falls at 2-year but not at 5-year FU. Future studies should determine whether avoidance of drugs with anticholinergic effects will lead to reduction in falls.

Keywords: anticholinergic cognitive burden, falls, elders, longitudinal, Malaysia.

1. Introduction

One in four community-dwelling individuals aged 65 years and over fall at least once a year (Alex et al. 2018) Falls often leads to injuries, such as fractures and intracranial bleed, which adversely affects the quality of life of the older adult as well as increases healthcare costs and mortality (Tan et al. 2016). Numerous risk factors for falls exist, including muscle weakness, visual impairment, environmental hazards, cardiovascular disease and medications(Alex et al. 2020).

Increasing age is associated with the presence of comorbidities (Calcagno et al. 2016), which then leads to the unavoidable increase in medication burden (Nobili, Garattini, and Mannucci 2011). The risk of adverse events from medication use also increases with ageing, and this is amplified by drug-drug interactions with the use of multiple medications. The relationship between falls and medication use is influenced by the use of various drug classes though the actual drug groups which comprise falls risk increasing drugs remain unclear, with drug classes such as opioids and antiepileptics as well as polypharmacy in general featuring as prominent medication related falls risk factors (Maximos, Chang, and Patel 2017).

The presence of polypharmacy has been found to be associated with increased use of medications with anticholinergic properties (Lu et al. 2015). The relationship between medications with anticholinergic properties, which include antipsychotics and antispasmodics, with increased risk of confusion in older adults has long been established. Cumulative exposure to anticholinergic medications has been linked to increased risk of dementia in a study which evaluated length of exposure to anticholinergics over a 10-year period among over 3400 individuals aged 65 years and over (Gray et al. 2015). Other common anticholinergic side effects of medications include, muscle weakness, urinary retention, dry eyes, dry mouth, blurred vision in addition to mental confusion(Collamati et al. 2016). A longitudinal cohort study has, in fact demonstrated the link between anticholinergic use and recurrent falls over 12 months (Marcum et al. 2015) while a long-term follow-up study had demonstrated the relationship between baseline anticholinergic exposure and falls hospitalization over 20 years (Weichert et al. 2018).

The objective of this study was, therefore, to determine the longitudinal relationship between falls and anticholinergic cognitive burden (ACB). Few studies have been able to evaluate the link between falls at multiple time-points following exposure to drugs with anticholinergic effects. Such a study will provide more in depth understanding on the long-term effects of anticholinergic medication use which will be of major consequence to a rapidly expanding older population globally.

2. Methods

2.1. Sample population

Participants were drawn from the Malaysian Elders Longitudinal Research (MELoR) study, which involved community-dwelling individuals aged 55 to 97 were recruited based on the official retirement age in Malaysia in 2013 and taking into account the life expectancy of Malaysians (Effendi-Tenang et al. 2020). Eligible participants for the MELoR study were selected through simple randomization from the electoral rolls of three parliamentary constituencies in the Klang Valley of Malaysia, stratified by age deciles and the three ethnic

groups of Malays, Chinese and Indians. Ethnic stratification was determined based on the population composition of Malaysia whereby the three main ethnic groups were the ethnic Malays (67.9%), Chinese (24.0%) and Indians (7.2%) (Department of Statiscics Malaysia 2015). The database recorded basic information about participants as well as their medications and fall history. This study was approved by the University of Malaya Medical Centre Medical Research Ethics Committee (MED-ID 20191231-8121).

2.2. Data collection

Baseline data were obtained during computer assisted interviews conducted face-to-face by trained researchers at participants' homes. Detailed information on participants' socio-demographic, economic status, living environment, psychological status, quality of life as well as medical history were obtained during this initial encounter which occurred between 2013 to 2015. The first follow-up then occurred in 2015-2016 when researchers returned to participants' homes and administered a similar version of the original questionnaire. Due to funding limitations, follow-up visits ceased abruptly after 770 participants were interviewed. The second follow-up occurred in 2019 through a brief telephone interview where key outcomes, including falls occurrence were established. Falls were determined through retrospective recall of any fall occurrence in the past 12 months. Further information about fall frequency, injuries and hospitalization were then obtained if the participants reported the presence of at least one fall in the previous 12 months (Figure 1).

2.3. Medications

The database contains participants' disease history and medication history. Information on medications were established by asking participants to show all their medications during the baseline home visits. Researchers then copied the proprietary or generic names of the drugs as stated in the packaging. The information obtained were then evaluated by a trained pharmacist, who classified the medications according to the ATC Classification (Lim et al. 2017). The researcher then reviewed both the information on the ATC Classification as well as the actual drug names and ATC Classification. Drugs with anticholinergic effects were identified and assigned a score according to the Ageing Brain Care 2012 Anticholinergic Cognitive Burden (ACB scale)(Campbell et al. 2013). ACB scale was devised to establish a list of drugs with anticholinergic activity by identification of medications with measured serum anticholinergic activity (SAA) or in vitro affinity to muscarinic receptors and through expert opinion. Individual drugs were assigned zero points if they contained nonanticholinergic effects), one point for possible anticholinergic effects, two for presence of anticholinergic effects and three for strong anticholinergic effects. The total anticholinergic burden score was then calculated using the formula:

$$Total\ ACB\ Score = [(No.ACB1\ drugs \times 1) + ((No.ACB2\ drugs \times 2) + (No.ACB3\ drugs \times 3)]$$

Total ACB scores were then further classified into the three categories of total ACB score of zero (Group 1), total ACB scores of one to two (Group 2) and total ACB scores of three or more with higher scores implying greater anticholinergic exposure.

As the Ageing Brain Care ACB scale was last updated in 2012, it was unclear whether newer drugs of a similar drug class as the drug named in the scale would contain anticholinergic property. Newer drugs of similar classes to those identified with ACB in the scale were first classified separately. Sensitivity analyses were conducted with and without the inclusion of these drugs in the analysis which revealed similar results with and without the inclusion of the newer drugs. For instance, amlodipine was the calcium channel blocker commonly used by participants in the study for the treatment of hypertension. Amlodipine does not appear in the ACB scale, but a different, older, calcium channel blocker, Nifedipine does. Amlodipine was first classified separately as of unclear ACB property but was then incorporated in the final analysis following sensitivity analysis. Subsequent analyses, therefore, included these newer drugs based on the presence of their older class counterparts within the ACB scale.

2.4. Data analysis

Statistical analyses were conducted using the Statistical Package for Social Science version 26.0 (IBM^{TM}, USA). Descriptive data were presented for baseline characteristics and ACB scores, including participants' demographic and lifestyle characteristics (age, sex, race, smoking, alcohol consumption, education, etc.) and medical history (diabetes, hypertension, etc.). The analysis of variance was utilized for continuous data (e.g. age), and the Chi-squared test used for categorical variables for comparisons between the three ACB groups. Comparisons between ACB groups and falls occurrence at baseline and subsequent follow-ups were conducted using logistic regression analysis with dummy variables. The total ACB=0 group was considered the reference category. Additional comparisons were then made for those with fall recurrence and fracture occurrence using similar statistical methods. Variables were then selected from the basic characteristics table based on the presence of significant differences and clinical judgement, stepwise adjustments were conducted and presented within the tables to avoid overadjustment. Fall occurrences at baseline, first and second follow-up were included in separate models. Models for falls detected at the follow-up visit or telephone call included adjustments for falls at baseline.

3. Results

3.1 Baseline characteristics

A total of 1,705 individuals, mean age (SD)= 68.94 (7.54) years, were recruited to the MELoR study. Data on ACB drug classification were obtainable for 1600 individuals. 908 (56.8%) were not on any ACB drugs, 575 (35.9%) had a total ACB score of one to two, while 117 (7.3%) had a total ACB score of three or greater (Appendix 1. List of anticholinergic medications within each ACB category). Age, ethnicity, smoking status, and education level varied between ACB categories. The presence of diabetes, hypertension, cardiovascular disease, and arthritis were different between groups (Table 1).

Table 1. Basic Characteristics Based on Total Anticholinergic Cognitive Burden Score Categories

	N	Total ACB score			P-value
		0 (n=908)	1-2 (n=575)	≥3 (n=117)	
Age (Yrs), mean (SD)	1532	68.11 (7.36)	69.60 (7.72)	71.44 (7.34)	*<0.001*
Female, n (%)	1529	497(57.9)	308(55.1)	55 (49.1)	0.165
Ethnicity, n (%)	1523	853 (56.0)	558(36.6)	112 (7.4)	*<0.001*
Malay	523	294 (56.2)	198(37.9)	31 (5.9)	
Chinese	494	337 (68.2)	131(26.5)	26 (5.3)	
Indian	499	219 (43.9)	225(45.1)	55 (11.0)	
Others	7	3 (42.9)	4 (57.1)	0	
Smoking, n (%)	1483	72 (9.0)	39 (6.9)	13 (11.3)	*0.003*
Alcohol, n (%)	1516	172 (20.8)	123 (21.5)	21 (18.1)	0.156
Living alone, n (%)	1526	55 (6.4)	29 (5.2)	11 (9.8)	0.169
Married, n (%)	1520	618 (73.9)	408 (73.1)	81 (72.3)	0.499
>6 Years of Education, n (%)	1519	630 (74.2)	390 (69.9)	69 (61.6)	*0.010*
Medical history, n (%)					
Diabetes, n (%)	1515	108 (13.1)	298 (51.8)	67 (57.3)	*<0.001*
Hypertension, n (%)	1515	325 (39.5)	428 (74.4)	82 (70.1)	*<0.001*
Visual impairment, n (%)	1511	697 (84.9)	490 (85.4)	92 (79.3)	0.245
Cardiovascular disease, n (%)	1515	499 (60.6)	516 (89.7)	100 (85.5)	*<0.001*
Hearing impairment, n (%)	1510	175 (21.4)	135 (23.5)	34 (29.3)	0.142
Cancer, n (%)	1515	42 (5.1)	38 (6.6)	7 (6.0)	0.489
Arthritis, n (%)	1515	104 (12.6)	119 (20.7)	26 (22.2)	*<0.001*

*Chi-squared test unless otherwise indicated (t-test for age)

3.2 Falls and Anticholinergic Cognitive Burden

3.2.1. Fall occurrence

Of the 1499 individuals who had the presence or absence of falls recorded at baseline, 339 (22.6%) reported at least one fall in the 12 months prior to the initial interview. Data on presence or absence of falls were available for 761 participants at the first follow-up visit. Of these, 155 (20.4%) reported at least one fall in the preceding 12 months. Data on presence or absence of falls were available for 836 individuals at the second follow-up conducted via telephone interviews. Of these 183 (21.9%) reported the presence of at least one fall in the preceding 12 months. Univariate analysis using analysis of variance detected differences in fall occurrence between the three ACB categories for any falls at baseline ($p=0.004$) and first follow-up ($p=0.001$). No significant difference in fall occurrence was detected between ACB categories at the second follow-up (Table 2).

3.2.2. Recurrent Falls and Fractures

Of the 339 individuals who reported the presence of falls in the last 12 months at baseline, 114 (33.6%) had experience two or more falls, while 28 (8.3%) had fractures. At the first follow-up visit, 48 (31.0%) of all individuals who reported falls had two or more falls, with 12 (7.7%) reporting fractures. At the second follow-up interview, 69 (37.7%) had two or more falls while 34 (18.6%) had fractures. Among fallers, recurrent falls and fracture occurrence differed between ACB groups at baseline, and recurrent falls differed between ACB groups at first follow-up (Table 2).

Table 2. Falls Outcomes Based on Total Anticholinergic Cognitive Burden Score Categories

	N	Total ACB Score			p-value
		0	1-2	≥3	
Falls at Baseline(n=1499)					
Any fall on past 12 months, n (%)	339	159(19.3)	149(26.4)	31(27.4)	*0.004*
Recurrent Falls, n (%)	114	46(5.6)	50(9.0)	19(16.8)	*<0.001*
Fractures, n (%)	28	9(1.3)	16(3.7)	3(3.5)	0.030
Falls at 2–3-year Follow-Up (n=761)					
Any fall on past 12 months, n (%)	155	74(17.2)	59(21.6)	22(37.9)	*0.001*
Recurrent Falls, n (%)	48	21(4.9)	17(6.2)	10(17.2)	*0.001*
Fractures, n (%)	12	5(1.2)	5(1.8)	2(3.4)	0.597
Falls at 5-year Follow-Up (n=836)					
Any fall on past 12 months, n (%)	183	93(19.1)	74(24.9)	16 (30.2)	0.053
Recurrent Falls, n (%)	69	32(6.6)	29(9.8)	8 (15.1)	0.051
Fractures, n (%)	34	20(4.1)	11 (3.7)	3 (5.7)	0.799

3.3. Logistic Regression

The odds ratios (OR) with 95% confidence intervals (CI) for unadjusted models and four adjusted models for ACB groups with total ACB=0 (Group 1) as the reference group with fall occurrence at baseline (Models 1-4), first follow-up (Models 5-8) and second follow-up (Models 9-12) as dependent variables are summarized in Table 3. Cross-sectional analysis of baseline data revealed an independent association between fall occurrence at baseline with ACB=1-2 (Group 2) compared to ACB=0 (Group 1) following adjustment for age, sex, ethnicity, education, smoking, alcohol, diabetes, hypertension, cardiovascular disease, hearing impairment and arthritis (OR= 1.412; 95%CI= 1.035 to 1.926). There was no significant difference in fall occurrence between the total ACB=1-2 group compared to the total ACB=0 at first or second follow-ups. Individuals with ACB≥3 (Group 3) were significantly more likely to report fall occurrence at first follow-up after adjustment for age, sex, ethnicity, education, smoking, alcohol, diabetes, hypertension, cardiovascular disease, hearing impairment, arthritis and any fall at baseline (OR=2.098; 95%CI= 1.032-4.263) compared to the ACB=0 group (Group 1). The significant increase risk of falls a baseline in the ACB≥3 group compared to those with the ACB=0 group during unadjusted analysis (OR=1.576; 95%CI=1.007 to 2.467) was attenuated by adjustment for age, sex, ethnicity and education differences (OR=1.266; 95%CI=0.792 to 2.024). ACB≥3 (Group 3) was not associated with any difference in fall occurrence at second follow-up compared to ACB=0 (Group 1).

Table 3 Logistic Regression of Falls Outcomes vs. Anticholinergic Cognitive Burden

	Odds Ratio (95%Confidence Interval)		
	ACB SCORE=0	ACB SCORE=1-2	ACB SCORE≥3
		Baseline	
Unadjusted	Ref	*1.497 (1.160-1.932)*	*1.576 (1.007-2.467)*
Model 1*	Ref	*1.350(1.036-1.760)*	1.266(0.792-2.024)
Model 2**	Ref	*1.394(1.063-1.827)*	1.286(0.797-2.074)
Model 3π	Ref	*1.489(1.116-1.987)*	1.346(0.830-2.185)
Model 4ϕ	Ref	*1.412(1.035-1.926)*	1.245(0.752-2.061)
		Falls at 2–3-year Follow-Up	
Unadjusted	Ref	1.326(0.905-1.943)	*2.940(1.635-5.285)*
Model 5*	Ref	1.223(0.810-1.847)	*2.535(1.321-4.864)*
Model 6**	Ref	1.167(0.763-1.786)	*2.498(1.282-4.869)*
Model 7π	Ref	1.063(0.676-1.671)	*2.317(1.174-4.576)*
Model 8ϕ	Ref	1.037(0.641-1.678)	*2.098(1.032-4.263)*
		Falls at 5-year Follow-Up	
Unadjusted	Ref	1.402 (0.991-1.983)	1.827 (0.975-3.426)
Model 9*	Ref	1.220(0.843-1.766)	1.603(0.815-3.154)
Model 10**	Ref	1.317(0.902-1.923)	1.721(0.852-3.476)
Model 11π	Ref	1.487(0.985-2.247)	1.954(0.946-4.033)
Model 12ϕ	Ref	1.247(0.798-1.951)	1.548(0.721-3.324)

*Adjusted for age and sex, ethnicity, education, falls at wave1 (falls excluded for baseline comparisons)

**Adjusted for age, sex, ethnicity, education, smoking, alcohol, falls at wave1. (falls excluded for baseline comparisons)

π Adjusted for age, sex, ethnicity, education, smoking, alcohol, hypertension, CVD, falls at wave 1. (falls excluded for baseline comparisons)

ϕ Adjusted for age, sex, ethnicity, education, smoking, alcohol, diabetes, hypertension, CVD, hearing impairment, arthritis, falls at wave1. (falls excluded for baseline comparisons)

Italicized indicates statistical significance

4. Discussion

Within our study population, the exposure to medications with mild to strong anticholinergic properties at baseline was associated with an increased risk of falls cross-sectionally and prospectively, with individuals with total ACB scores of 1-2 associated with increased risk of falls at baseline, while those with ACB scores of ≥3 were significantly more likely to report falls at the first follow-up at two to three years compared to individuals with no anticholinergic exposure at baseline. The relationship between baseline ACB exposure and falls in the preceding 12 months was no longer present in the second follow-up at five years. Our findings, therefore, confirm the concerns highlighted by previous studies with regard to potential longer-term effects of baseline exposure to medications with anticholinergic properties, but also suggests that the relationship is diluted by other competing factors beyond five years.

Squire et al (Squires et al. 2020) reported the presence of a strong association between those using medications with anticholinergic properties and mobility disability outcomes and injurious falls when compared to those not using these medications. Using the drug burden index, a study involving 602 residents of residential aged care facilities found a significant increased incidence in falls with over a 12-month period for those with low and high anticholinergic and sedative drug exposure (N.M. et al. 2011). Szabo et al (Szabo et al. 2019) showed that higher levels of anticholinergic burden are associated with higher rates of falls and fractures. The dose response relationship between ACB and falls in this study was not apparent at baseline, with similar parameter estimates for both groups with ACB scores of one to two and ACB score of three and above compared to those without no ACB exposure. However, the relationship between ACB scores of three or more and fall occurrence at two to three year follow-up existed. Thirty six percent of our study population had a total ACB score of one to two while seven percent had a score of three and above at baseline. Therefore, the lack of dose response relationship may be attributable to the smaller number of individuals with higher total ACB burden. However, the longer-term effect of ACB scores of three or greater was apparent at follow-up. Our findings, therefore, suggest that the use of drugs with possible or mild anticholinergic properties is associated with a risk of falls cross-sectionally, but a longitudinal relationship exists in those with a high cumulative ACB exposure at baseline and falls. The lack of association between ACB and falls at five-years may have occurred as the result of changes made to the medications which had not been documented in this study.

In the univariate analyses, differences in the occurrence of falls and fall recurrence at the baseline and first follow-up visits differed significantly according to total ACB score categories which was in concordance with the findings of the case-control study conducted by Zia et al (Zia et al. 2016). The association between ACB and falls was, however, only established cross-sectionally within this previous study which had compared individuals with recurrent and injurious falls against community controls with no falls. The presence of any exposure to anticholinergic medications at baseline, also determined using the ACB scale, was associated with an increased incidence of hospitalization due to falls and fractures over a median follow-up period of 19 years (Weichert et al. 2018). The latter study reported hospitalization from falls rather than fall occurrence or the presence of recurrent falls(Lamb et al. 2011). Marcum et al found no significant relationship between anticholinergic use and recurrent falls in a study involving nearly 3000 participants with anticholinergic use established as self-reported use at each annual assessment conducted over six years(Marcum et al. 2015). Richardson et al reported a significant relationship between anticholinergic exposure at baseline with injurious falls at two years' follow-up among 1500 individuals recruited from a primary care

registry(Richardson et al. 2015). The last two studies only evaluated self-reported anticholinergic use rather than anticholinergic burden. The handful of remaining studies which evaluated falls and anticholinergic use were conducted amongst disease specific populations including those with psychiatric disorders (Aizenberg et al. 2002) and overactive bladder(Suehs et al. 2019; Szabo et al. 2019). Our study was, therefore, unique in evaluating the occurrence of falls in a longitudinal cohort study involving a community-dwelling, general, older population.

While the relationship between ACB and falls was not significant statistically at five-year follow-up, the parameter estimates or odds ratios appeared to be of similar in order of magnitude to baseline and first follow-ups. The lack of significance may be attributable to the large confidence intervals, which in turn may be due to loss to follow-up and fluctuations in health status over the five-year period, which had not been evaluated in this study. While falls at baseline are more likely to be associated with the immediate side-effects that are well-established, the long term side-effects of anticholinergic use remain unclear. Cumulative anticholinergic use has been found to increase the risk of incident dementia(Gray et al. 2015). In addition to long term cognitive effects, anticholinergic effects also include muscle weakness which could lead to sarcopenia and balance impairment(Phillips et al. 2019).

Medications were only obtained at one timepoint in this study. Unfortunately, due to limitations in resources, medications lists were not obtained at follow-up encounters. At the point of writing, reliable records of medication use and changes in prescription were not obtainable as no centralised prescribing records existed. While medication databases did exist within some primary and secondary care centers, our participants accessed healthcare through a large variety of portals, and it was not feasible to consolidate this information at the time the study was conducted. Future research should include establishment of potential changes in medications over time and also to identify mechanisms which explain the increased risk of falls associated with ACB. While a large number of sociodemographic and medical variables have been included in our analysis, the dataset obtained had not included cognition and function ability which would be important areas to considered in future studies. Our findings also have implications on public policy and medical practice since doctors are well aware of drugs with a high level of anticholinergic activity and avoid these, but they may be less aware of drugs with lower anticholinergic activity, and continue to prescribe these long terms.

5. Conclusion

The use of medications with anticholinergic properties is associated cross-sectionally and prospectively with both the occurrence of falls as well as fall recurrence, though this relationship was no longer significant at five-year follow-up. At baseline, low to moderate anticholinergic exposure was independently associated with falls. At two to three year follow-up, only a high level of anticholinergic exposure at baseline was independently associated with the occurrence of falls. The longitudinal relationship between fall occurrence and a high level of anticholinergic exposure should be further evaluated with more detailed information on prescription changes in future studies, in addition to intervention studies to determine appropriate strategies of reducing fall risk with de-prescribing medications with anticholinergic properties in older adults.

CRediT authorship contribution statement

Xiang Jiang Xu: **Data analysis, manuscript writing.** Phyo Kyaw Myint: **Conceptualization, analysis, review & editing.** Kioh Sheng Hui: **Study design, data**

collection, review & editing. Sumaiyah Mat: **Study design, data curation, data analysis, review & editing.** Reena Rajasuriar: **Conceptualization, data analysis, review & editing.** Shahrul Bahyah Kamaruzzaman: **Grant application, conceptualization, study design, review & editing.** Maw Pin Tan: Grant application, conceptualization, study design, supervision, review & editing.

Ethics Statement

The study was conducted according to ethical standards at university of Malaya. Formal ethical approval was obtained from the research ethics committee of the university of Malaya.

Declaration of Conflict Interest

The authors declare no conflict of interest.

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Appendix 1. List of medications within each anticholinergic cognitive burden category

Anticholinergic Cognitive Burden Score			
ACB=1		ACB=2	ACB=3
Alverine	Indapamine	Carbamazepine	Amitriptyline
Alprazolam	Dexamethasone		Chlorpheniramine
Aripiprazole	Escitalopram		Dimenhydrinate
Atenolol	Fluoxetine		Diphenhydramine
Captopril	Mirtazapine		Hydroxyzine
Cetirizine	Sertraline		Olanzapine
Colchicine	Sumatriptan		Orphenadrine
Desloratadine	Tramadol		Quetiapine
Digoxin	Celecoxib		Solifenacin
Fluvoxamine	Diltiazem		Trifluoperazine
Hydrocortisone	Carbidopa		Trihexyphenidyl
Isosorbide	Domperidone		
Loperamide	Metoclopramide		
Loratadine	Prochlorperazine		
Metoprolol	Levodopa		
Nifedipine	Famotidine		
Ranitidine	Cephalexin,		
Risperidone	Ipratropium		
Theophylline	Timolol		
Warfarin	Dosulepin		
Rivaroxaban	Tiotropium		
Clonazepam	Bromazepam		
Lorazepam	Tenoxicam		
Pramipexole	Flupentixol		
Methotrexate	Moclobemide		
Azathioprine	Piribedil		
Bisacodyl	Cinnarizine		
Metformin	Omeprazole		
Salmeterol	Serotonin		

ACB=Anticholinergic cognitive burden

Figure 1. Baseline and Follow-up of Participants in Malaysian Elders Longitudinal Research.