Polypharmacotherapy and cumulative anticholinergic burden in older adults hospitalised with fall

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Abstract

Background and Purpose Polypharmacotherapy is a growing phenomenon associated with adverse effects in older adults. We assessed the potential confounding effects of cumulative anticholinergic burden (ACB) in patients who were hospitalised with falls. Methods A non-interventional, prospective cohort study of unselected, acute admissions aged [?]65 years. Data were derived from electronic patient health records. Results were analysed to determine the frequency of polypharmacotherapy and degree of ACB and their relationship to falls risk. Primary outcomes were polypharmacotherapy, defined by [?]5 medications, and ACB score. Key Results 411 consecutive subjects were included, mean age 83·8 ± 8·0 years: 40·6% male. 38·4% were admitted with fall. Incidence of polypharmacotherapy was 80·8%, (88·0% and 76·3% among those admitted with and without fall respectively). Incidence of ACB score of 0, 1, 2, [?]3 was 38*7%, 20*9%, 14*6% and 25*8% respectively. On multivariate analysis, age (OR=1*03, [1*0 ; 1*05], p= 0*0494), ACB score (OR=1.15, [1.02 ; 1.29], p= 0.0245), polypharmacotherapy (OR=2*14, [1*19 ; 3*87], p= 0*0115) but not Charlson Comorbidity Index (OR=0*92, [0*81 ; 1*04], p= 0*1723) were significantly associated with higher falls rate. Of patients admitted with fall, 29*8% had drug-related orthostatic hypotension, 24*7% had drug-related bradycardia, 37*3% were prescribed centrally acting drugs and 12*0% were taking inappropriate hypoglycaemic agents. Interpretation Polypharmacotherapy results in cumulative ACB and both are significantly associated with falls risk in older adults. The presence of polypharmacotherapy and each unit rise in ACB score have a stronger effect of increasing falls risk compared to age and comorbidities.

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Disclosures

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Competing interests

All authors understand the policy of declaration of interests. HLW, CW, LM, KOM, JD, FRA, RC, AKJM and CGM all declare that that they have no competing interests.

Contributorship

All nine authors contributed to the manuscript. All were involved in the design of the study.

HLW, CW, LM, KOM and JD collected and verified the data. HLW was responsible for the analysis. HLW, CW, LM, AKJM and CGM wrote the manuscript, and all authors were involved in the final approval of the manuscript. HLW and CW are joint first authors. AKJM and CGM are acting as guarantors of the submitted work.

Statement of ethics committee approval

As an analysis using clinically collected, non-identifiable data, this work does not fall under the remit of National Health Service Research Ethics Committees. This study was approved by our institution's Research, Quality Improvement and Audit Department with reference FXP-48. This statement is also present in the methods section of our manuscript. It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Data availability statement

Data available on request from the authors - The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

Research in context

What is already known

- Polypharmacotherapy is very common in adults over 65 and its prevalence is increasing
- It is associated with numerous adverse outcomes including hospitalisation with fall
- Many commonly prescribed medications have anticholinergic properties
- Cumulative anticholinergic burden (ACB) may explain a proportion of the poor outcomes associated with polypharmacotherapy

What this study adds

- To our knowledge, our study is the first that investigates the link between polypharmacotherapy and falls by stratifying into several plausible culprit mechanisms under the umbrella of polypharmacotherapy
- We show an increased risk of falls per unit increase of ACB score, which is previously unreported
- Patients with calculated ACB score of 3 compared to those with ACB score of 0 have a >50% higher falls risk
- Common adverse effects of polypharmacotherapy also included orthostatic hypotension, bradycardia and hypoglycaemia
- Our data demonstrate that falls are strongly associated with polypharmacotherapy rather than comorbidity, suggesting that a significant proportion of falls are iatrogenic and preventable

Clinical significance

- Structured medication review of all patients presenting with fall, with a focus on reducing ACB, is likely to reduce some of the burden of falls on the healthcare system
- Routinely calculating ACB scores in inpatients aged over 65 may assist with medication rationalisation and deprescribing
- Medical professionals at all levels would benefit from further education regarding the implications of polypharmacotherapy and the need to weigh the benefit of a new medication with the associated harms of increased medication and ACB

Abstract

Background and Purpose

Polypharmacotherapy is a growing phenomenon associated with adverse effects in older adults. We assessed the potential confounding effects of cumulative anticholinergic burden (ACB) in patients who were hospitalised with falls.

Methods

A non-interventional, prospective cohort study of unselected, acute admissions aged [?]65 years. Data were derived from electronic patient health records. Results were analysed to determine the frequency of polypharmacotherapy and degree of ACB and their relationship to falls risk. Primary outcomes were polypharmacotherapy, defined by [?]5 medications, and ACB score.

Key Results

411 consecutive subjects were included, mean age 83·8 ± 8·0 years: 40·6% male. 38·4% were admitted with fall. Incidence of polypharmacotherapy was 80·8%, (88·0% and 76·3% among those admitted with and without fall respectively). Incidence of ACB score of 0, 1, 2, [?]3 was 38*7%, 20*9%, 14*6% and 25*8% respectively. On multivariate analysis, age (OR=1*03, [1*0 ; 1*05], p= 0*0494), ACB score (OR=1.15, [1.02 ; 1.29], p= 0.0245), polypharmacotherapy (OR=2*14, [1*19 ; 3*87], p= 0*0115) but not Charlson Comorbidity Index (OR=0*92, [0*81 ; 1*04], p= 0*1723) were significantly associated with higher falls rate. Of patients admitted with fall, 29*8% had drug-related orthostatic hypotension, 24*7% had drug-related bradycardia, 37*3% were prescribed centrally acting drugs and 12*0% were taking inappropriate hypoglycaemic agents.

Interpretation

Polypharmacotherapy results in cumulative ACB and both are significantly associated with falls risk in older adults. The presence of polypharmacotherapy and each unit rise in ACB score have a stronger effect of increasing falls risk compared to age and comorbidities.

Introduction

The most widely recognised definition of polypharmacy or 'polypharmacotherapy' is the use of 5 or more medications.[1,2] The high prevalence of polypharmacotherapy is a consequence of the increasing rate of multimorbidity in the ageing population worldwide. In the United Kingdom, up to one third of 69-year-olds are prescribed polypharmacotherapy.[3] Polypharmacotherapy is associated with several negative outcomes, including adverse drug effects, non-adherence, and functional decline.[4,5]

The risk of hospitalisation with falls increases with polypharmacotherapy. Fall is one of the most common reasons for admission to hospital for older adults and are a main cause of morbidity with an in-hospital mortality rate as high as 16%.[6,7]

Polypharmacotherapy predisposes to higher anticholinergic burden (ACB), which is emerging as a risk factor for adverse events that disproportionately affect older adults, including falls, cognitive impairment and progression of neurodegenerative disease.[8–12] Many medications used to treat chronic conditions such as cardiovascular disease, hypertension, depression, urinary incontinence, pain, and allergies have weak anticholinergic properties, but the summative effects may have important implications and worse outcomes in older adults.

The aim of our study was to assess the incidence of polypharmacotherapy among older hospitalised patients and to explore the relationship between polypharmacotherapy and cumulative ACB score in these patients and risk of fall.

Methods

This was a non-interventional prospective cohort study of all elderly patients defined as aged [?]65 years admitted to an acute medical ward of a district general hospital based in southern England between September 2021 and November 2021. All patients admitted onto the ward above the age of 65 were included. Patients who were below the age of 65 and for end-of-life care were excluded. Data from consecutive patients were collected from the electronic patient health record. Data set included age, gender, past medical history, medications, documentation of falls and nursing observation charts including heart rate and postural blood pressure readings. Figure 1 shows the patient inclusion flowchart. This study was approved by our institution's Research, Quality Improvement and Audit Department with reference FXP-48.

ACB score was calculated based on each patient's regular medication prior to admission. This was ascertained using the national patient record database: NHS Summary Care Record. All regular oral medications prescribed prior to admission were included for this and polypharmacotherapy was defined as [?]5 regular medications. The ACB score was calculated using an online based ACB calculator (accessible on*http://www.acbcalc.com/*). Each medication was assigned a score of 0 for no anticholinergic properties; 1 for mild anticholinergic properties; 2 for moderate; and 3 for severe. The total ACB score was therefore the sum of scores for all regular medications on admission.

Charlson Comorbidity Index (CCI) was calculated based on each patient's past medical history as listed on their electronic patient records. Patient age and past medical history were used for CCI calculation. Aspects of past medical history used for CCI calculation included myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular accident/ transient ischaemic attack, dementia, chronic obstructive pulmonary disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, moderate to severe chronic kidney disease (CKD; stage [?]3), solid tumour, leukaemia, lymphoma and, acquired immune deficiency syndrome. An online CCI calculator was used to calculate each patient's CCI, accessible on https://www.mdcalc.com/charlson-comorbidity-index-cci.

The primary outcomes of the study were to identify the incidence of polypharmacotherapy and ACB scores, comparing this between hospitalised older adults admitted with or without a fall and to investigate the association between falls, ACB score, CCI and age. The secondary outcome of the study was to identify the incidence of drug-related orthostatic hypotension (defined as a fall in systolic blood pressure of at least 20 mmHg and/or a fall in diastolic blood pressure of at least 10 mmHg within 3 minutes of standing), drug-related bradycardia (defined as a heart rate of less than 60 beats per minute on 2 or more occasions during

the daytime [nocturnal bradycardic episodes were not deemed significant], which was reversible on cessation of negatively chronotropic agents), prescription of centrally acting and inappropriate doses or prescription of hypoglycaemic agents in patients admitted with a fall.

Statistical Analysis

Statistical analysis was performed with the online medical statistics application EasyMedStat (version 3.17; www.easymedstat.com). The data presented as mean with standard deviation, and categorical variables were shown as percentages. A multivariate logistic regression was performed to assess the relation between falls and ACB score, CCI and age. Odds ratio was adjusted for different sets of confounders and are reported with 95% confidence intervals. Data were checked for multicollinearity with the Belsley-Kuh-Welsch technique. Heteroskedasticity and normality of residuals were assessed respectively by the White test and the Shapiro-Wilk test. A p-value $< 0*05$ was considered statistically significant.

Results

A total of 411 patients were included in the study. The mean age of our patients were 83*8 +- 8*0 years, 40*6% male. Table 1 summarises patient demographics and characteristics. 38*4% of our patients were admitted with a fall. The median age was 86*0 (Q1 79*0; Q3 90*0) and 84.0 years (Q1 78*0; Q3 90*0) respectively for patients admitted with and without a fall (difference: 2*0 , p=0*125); (table 2a and 2b for univariate and bivariate analysis). Age was associated with an increased rate of patients admitted with a fall per each 1-unit rise (OR=1*03, [1*0 ; 1*05], p= 0*0494).

The mean CCI of our study group was 5*7 +- 1*7. The mean CCI in patients admitted with and without a fall was 5*65 +- 1*66 and 5*74 +- 1*76 respectively. The median CCI were respectively 5*0 (Q1 5*0; Q3 6*0) and 5.0 (Q1 5*0; Q3 7*0) for patients admitted with and without fall (difference: 0.0, p=0*549); (table 3a and 3b for univariate and bivariate analysis). CCI was not associated with the rate of patients admitted with a fall with each 1-unit rise, (OR=0*92, [0*81 ; 1*04], p= 0*1723).

Overall incidence of polypharmacotherapy of our study group was 80*8%. Polypharmacotherapy in patients admitted without and with a fall were 76*3% and 88*0% respectively. There was an association between polypharmacotherapy and an increased risk of fall (OR=2*27 [1*3;3*98],p=0*005); (table 4a and 4b for univariate and bivariate analysis of polypharmacotherapy). Table 5 lists commonly prescribed drugs (incidence of >5%) with ACB within our study group. Incidence of ACB scores of 0, 1, 2, [?]3 was 38*7%, 20*9%, 14*6% and 25*8% respectively. The median ACB scores were respectively 2*0 (Q1 0*0; Q3 3*0) and 1*0 (Q1 0*0; Q3 2*0) for patients admitted with and without fall (difference: 1*0 , p=0*009); (table 6a and 6b for univariate and bivariate analysis of ACB score). ACB score was associated with an increased rate of patients admitted with a fall per each 1-unit rise in ACB, (OR=1*15, [1*02 ; 1*29], p= 0*0245). In our linear regression model, a patient with an ACB score of 3 compared to a patient with an ACB score of 0 would have a >50% higher chance of falling.

Of the patients who were admitted with fall (38*4% of total study group), 29*8% was found to have drug-related orthostatic hypotension, 24*7% had drug-related bradycardia**,** 37*3% were taking regular centrally acting agents and 12*0% were taking inappropriate hypoglycaemic agents. Table 7 summarises the incidence of secondary outcomes in patients admitted with fall. Table 8 summarises the regression results of the study.

Discussion

Polypharmacotherapy is a common phenomenon in older adults and is associated with worse physical and cognitive outcomes which may be aggravated by the summative effect of drugs carrying ACB. Our study,

the first we are aware of, clearly demonstrates that age, ACB, polypharmacotherapy, but not comorbidity, are associated with significantly higher falls risk in older patients.

Our results demonstrate a high incidence of polypharmacotherapy in older hospitalised patients (78.3%) consistent with previous epidemiology studies (74%).[13] 88% of patients admitted with a fall were exposed to polypharmacotherapy. Our data also highlight a statistically significant positive association between polypharmacotherapy and cumulative ACB and the incidence of falls. Our data also show a higher odds ratio between polypharmacotherapy and falls compared to comorbidity. This implies that the presence of polypharmacotherapy or the increase in ACB score represents a more significant increase of falls and harm. In addition, of patients admitted with fall, 29*8% was found to have drug-related orthostatic hypotension, 24*7% had drug-related bradycardia**,** 37*3% were taking regular centrally acting agents and 12*0% were taking inappropriate hypoglycaemic agents. All these interconnected factors contribute to falls risk and play a crucial role in the progression of the cycle of frailty and has been linked to poorer outcomes for older patients in terms of maintaining independence and mortality.[14,15]

Undesirable effects of anticholinergic medications arise from their effect on G-protein coupled muscarinic receptors present in both peripheral and central nervous systems. Peripheral anti-muscarinic effects are usually associated with short term use of anticholinergics. However, many of these medications cross the blood brain barrier and affect the central nervous system directly, and this is more pronounced in older adults where age-related changes in the blood brain barrier disrupt its function.[16] By demonstrating the impact of polypharmacotherapy and cumulative ACB in older adults, particularly with respect to falls in this study, we highlight the importance of pharmacological rationalisation and deprescribing.

We found a progressive numerical decline in polypharmacotherapy and ACB without statistical significance due to numbers (Figure 2). This might be attributed to changes in physiology and drug metabolism with age such that some drugs become obsolete and/or because this population may have greater contact with healthcare professionals, either in primary or secondary care, who adjust pharmacotherapy.

Falls are often multifactorial and are both an association and cause of increased frailty. Research into interventions to reduce the risk of falls is ongoing, but even multifaceted interventions have only shown modest benefits.[17] Identifying culprit medications and drug classes with a view to develop a structured medication review for those at risk of falling could therefore improve outcomes and relieve pressure on the healthcare system.

NICE guidance on falls in older people recommends that people who have had a fall or are at increased risk of falling should have a medication review as part of a multifactorial risk assessment. It is recommended that psychotropic medications which carry a high ACB should be discontinued, if possible, to reduce their risk of falling. Despite it being well proven and understood in the literature that ACB is linked to poorer outcomes for older patients, awareness appears to remain low in clinical environments. A study conducted in 2020 showed that there is a limited understanding of the potential harms of starting regular anticholinergic medications among clinical staff.[18]Therefore, the process of due pharmacovigilance remains to be embedded into clinical practice amongst the wider medical team who care for patients above the age of 65.

Our findings clearly validate the importance of rationalising and balancing risks and benefits of starting medications with any ACB. There are several validated tools that assess the burden of anticholinergic drugs. Although there is heterogeneity in the clinical value of these scales and an absence of an established gold standard, current evidence suggests that the ACB score is of higher quality compared to other tools.[19] We therefore suggest the use of the online based ACB calculator (accessible on http://www.acbcalc.com/) in daily clinical activity to reduce potentially inappropriate medications for older patients. An ACB score [?]3 confers a heightened risk of cognitive and functional impairment, falls and mortality. As demonstrated in our study, it is also important to consider lower potential anticholinergic drugs as cumulative effects can lead to high ACB.

Falls and their complications have significant clinical and financial implications for secondary care, with an estimated cost the NHS of more than PS2.3 billion per year.[20] Therefore, falls impact quality of life, wellbeing,

and healthcare resources. With appropriate pharmacovigilance, medication rationalisation with regular review and education towards reducing the need for initiating medications with ACB, there are potentially enormous cost savings. This ranges from reduced prescription costs, to preventing acute admissions related to falls and their complications and costs associated with managing general frailty. Further study and more thorough cost benefit analysis is awaited to corroborate this.

Conclusion

There is a high incidence of polypharmacotherapy among older hospitalised adults. Our study clearly demonstrates that polypharmacotherapy and cumulative ACB score are significantly positively associated with increased incidence of falls. Furthermore, the presence of polypharmacotherapy and each unit rise in ACB score have a stronger effect of increasing falls risk when compared to age and comorbidity. ACB and polypharmacotherapy are modifiable risk factors, and our findings strongly support deprescribing when possible to prevent falls and improve outcomes in older adults.

Limitations

As a single-centre study at a district general hospital, we cannot generalise our results to other settings. Furthermore, our trust is based in southern England, where population demographics and socioeconomic status may differ from those elsewhere.

We also acknowledge that extracting information from medical notes requires second-hand interpretation and may not be representative of the full clinical picture. The Rockwood Clinical Frailty Score was not included because of the potential inconsistencies in interpretation.

Considerations were made for the utilisation of sample size calculations to ensure the study was powered appropriately. Despite achieving significant results in a number of outcomes, we acknowledge the risk of a type 2 error occurring with our experimental sample size. Therefore, we were unable to discount an association between polypharmacotherapy, ACB and those variables which did not achieve statistical significance with observed effect sizes.

Table and figures

Figure 1: Patient inclusion flowchart

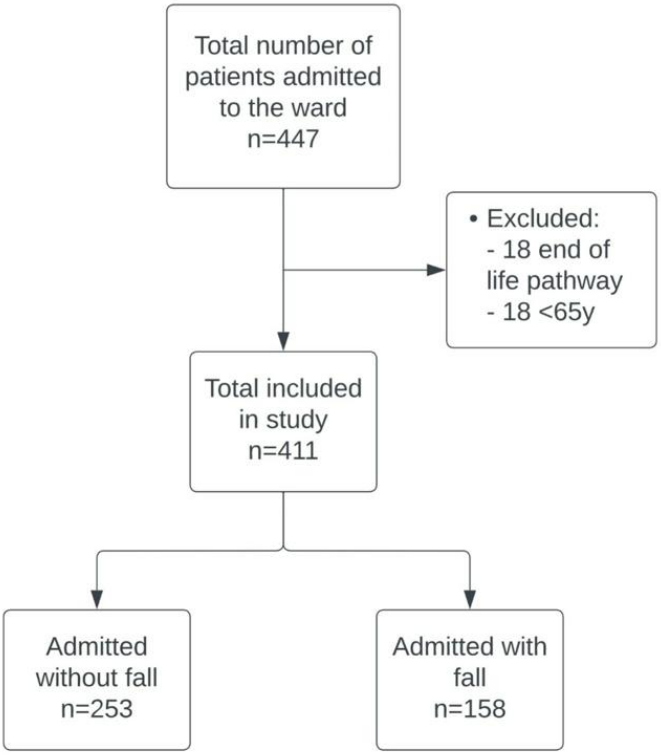


Table 1: Summary of patient demographics and characteristics

	Mean ± Standard Deviation	Percentage of total (%)
Age	83·3 ± 8·0	-
Sex (Male)	40·6	
Charlson Comorbidity Index	5·7 ± 1·7	-
Polypharmacy	-	78·3
Admitted with a fall/ History of falls	-	38·4
Past medical history		
Dementia/ Cognitive impairment		25·6
Stroke		15·1
Parkinson's Disease		5·1
Hypertension		56·9
Atrial fibrillation		34·6
Heart failure		27·3
Ischaemic heart disease		12·4
Asthma		11·2
Chronic obstructive pulmonary disease		16·3
Diabetes		27·5
Chronic kidney disease (Stage ≥3)		28·5
Cancer		18·7
Fragility fractures		12·2

Table 2a: Univariate table for age

Statistics	Age
N	411
Mean ± SD	83·83 ± 7·98
Min ; Max	66·0 ; 102·0
Median	85·0
Q1 ; Q3 (IQR)	78·0 ; 90·0 (12·0)
Unknown (%)	0 (0·0%)
Excluded (%)	0 (0·0%)

Table 2b: Bivariate table for age

Statistics	Admitted with fall	Not admitted with fall
N	158	253
Mean ± SD	84·54 ± 7·75	83·38 ± 8·1
Min ; Max	66·0 ; 98·0	66·0 ; 102·0
Median	86·0	84·0
Q1 ; Q3 (IQR)	79·0 ; 90·0 (11·0)	78·0 ; 90·0 (12·0)

Table 3a: Univariate table for CCI

Statistics	Charlson Comorbidity Index
N	411
Mean ± SD	5·7 ± 1·72
Min ; Max	2·0 ; 12·0
Median	5·0
Q1 ; Q3 (IQR)	5·0 ; 7·0 (2·0)
Unknown (%)	0 (0·0%)
Excluded (%)	0 (0·0%)

Table 3b: Bivariate table for CCI

Statistics	Admitted with fall	Not admitted with fall
N	158	253
Mean ± SD	5·65 ± 1·66	5·74 ± 1·76
Min ; Max	3·0 ; 11·0	2·0 ; 12·0
Median	5·0	5·0

Table 4a: Univariate table for polypharmacotherapy

Polypharmacotherapy	N	%
yes	332	80·78%
no	79	19·22%
Total	411	100%
Unknown values	0	
Excluded values	0	

Table 4b: Bivariate table for polypharmacotherapy

variable	Fall: no		Fall: yes		Total	
Polypharmacotherapy: no	60	75·95%	19	24·05%	79	19·22%
	23·72%	14·6%	12·03%	4·62%		
Polypharmacotherapy: yes	193	58·13%	139	41·87%	332	80·78%
	76·28%	46·96%	87·97%	33·82%		
Total	253	61·56%	158	38·44%	411	100%

Table 5: Most common (>5% incidence) medication with an ACB prescribed

Medication (ACB score)	ACB score	Incidence of use (%)
Furosemide	1	16.1
Mirtazapine	1	8.3
Digoxin	1	7.8
Sertraline	2	7.8
Codeine	1	6.6
Citalopram	1	6.3
Warfarin	1	6.1
Amitriptyline	3	5.4
Isosorbide Mononitrate	1	4.4
Morphine	1	4.1
Prednisolone	1	4.1
Olanzapine	3	3.2
Solifenacin	3	2.9
Trazodone	1	2.7
Diazepam	1	2.4
Co-Careldopa	1	2.2
Promethazine	3	1.9
Fluoxetine	1	1.7
Levomepromazine	2	1.7
Quetiapine	1	1.7
Tramadol	1	1.7
Risperidone	1	1.5
Co-codamol	1	1.2
Oxybutynin	3	1.2

Table 6a: Univariate table for ACB score

Statistics	Acetylcholine burden score
N	411
Mean ± SD	1·53 ± 1·76
Min ; Max	0·0 ; 11·0
Median	1·0
Q1 ; Q3 (IQR)	0·0 ; 3·0 (3·0)
Unknown (%)	0 (0·0%)
Excluded (%)	0 (0·0%)

Table 6b: Bivariate table for ACB score

Statistics	Admitted with fall	Admitted without fall
N	158	253
Mean ± SD	1·82 ± 1·91	1·35 ± 1·64
Min ; Max	0·0 ; 11·0	0·0 ; 8·0
Median	2·0	1·0
Q1 ; Q3 (IQR)	0·0 ; 3·0 (3·0)	0·0 ; 2·0 (2·0)

Table 7: Incidence of secondary findings in patients admitted with fall

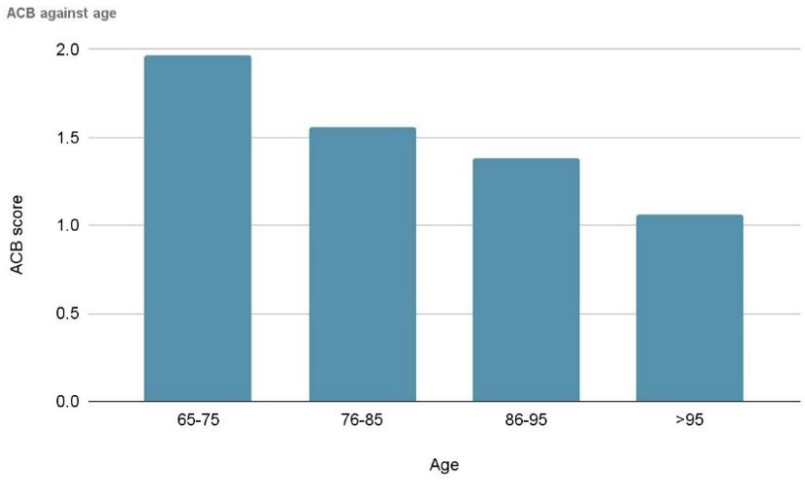
Admitted with/ history of fall with:	Percentage (%)
- Orthostatic hypotension	29·75
- Iatrogenic bradycardia	24·68
- Centrally acting agents	37·34
- Hypoglycaemic agents	12·03

Table 8: Regression results of the study

variable	modality	odds ratio	p-value
Constant/ Intercept		0·0476 [0·00473;0·479]	0·00976**
Age (Risk for each 1-unit rise)		1·03 [1·0;1·05]	0·0494*
Charlson Comorbidity Index (Risk of each 1-unit rise)		0·916 [0·807;1·04]	0·172
Polypharmacy (Y/N)		2·14 [1·19;3·87]	0·0115*
Acetylcholine burden score (Risk for each 1-unit rise)		1·15 [1·02;1·29]	0·0245*

* p<0·05 ** p<0·01

Figure 2: Mean ACB score against age



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