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Analysis of anticholinergic and sedative medicine effects on physical function, cognitive function, appetite and frailty: a cross-sectional study in Australia

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ABSTRACT

Objective To test the association between use of medicines with anticholinergic or sedative properties and physical function, cognitive function, appetite and frailty.

Design, setting and participants This cross-sectional study analysed baseline data collected as part of the Australian Longitudinal Study of Ageing, a population-based cohort of 2087 participants aged 65 years or over living in South Australia.

Main outcome measures Physical function was measured at baseline using measures including hand grip strength, walking speed, chair stands, activities of daily living and instrumental activities of daily living (IADL). Cognitive function was measured using Mini-Mental State Examination. Appetite was measured using Center for Epidemiologic Studies Depression question 2. Frailty was measured using frailty index. The association between use of anticholinergics or sedatives and physical or cognitive function, appetite, or frailty was assessed using analysis of covariance and ordinal or binary logistic regression.

Results Almost half of the population were using anticholinergics or sedatives (n=954, 45.7%). Use of anticholinergics was significantly associated with poorer grip strength, slower walking speed, poorer IADL and poorer appetite. Use of sedatives was significantly associated with poorer grip strength, slower walking speed and poorer IADL. We found no significant association between medicine use and cognitive function. Users of anticholinergics or sedatives were significantly more likely to be frail compared with non-users.

Conclusion Use of medicines with anticholinergic or sedative properties is significantly associated with poorer physical function, poorer appetite and increased frailty. Early identification of signs and symptoms of deterioration associated with medicine use is particularly important in older people so that worsening frailty and subsequent adverse events are prevented.

Strengths and limitations of this study

- ► Our findings on the association between use of anticholinergics and poorer appetite contribute uniquely to the literature.
- ► We analysed the association between medicines with anticholinergic or sedative properties and grip strength based on sex, which previous studies have not done.
- ► The outcome measures chosen were both objective and clinically relevant.
- ► The study is limited by its cross-sectional design.
- ► It is not possible to identify a cause–effect relationship between use of medicines with anticholinergic or sedative properties and reduced physical function or poorer appetite using this study design.

INTRODUCTION

Medicines with anticholinergic or sedative properties are commonly prescribed to older people,[1] with prevalence estimates ranging from 13% to 42% for medicines with sedative properties[2 3] and from 8% to 36% for medicines with anticholinergic properties.[3 4] Adverse effects of these medicines, like falls and confusion, are detrimental to older people. This risk is increased due to age-related changes in pharmacokinetics and pharmacodynamics, the presence of multiple comorbidities and the use of multiple medicines with subsequent increased probability of drug interactions.[5 6] The cumulative medication burden of anticholinergic and sedative medicines is often unintentional and compounded by the fact that many medicines with anticholinergic properties also have sedative properties.[5]

Use of medicines can directly lead to adverse events[5] which are easily recognised and potentially rectifiable. Use of medicines with anticholinergic or sedative properties has also been associated with frailty,[7] and frailty may contribute to an increased risk of adverse events.[8] However, medicines with anticholinergic or sedative properties often have what might be considered 'minor side effects' which are difficult to detect and frequently unrecognised. These side effects, which we describe as medicine-induced deterioration,

particularly if the cumulative effect builds slowly over time, are often misattributed as geriatric syndromes, frailty or simply changes due to ageing. Medicine-induced deterioration may include decline in physical function, decline in cognitive function and loss of appetite. While these same symptoms may occur independently due to ageing, medicines with anticholinergic or sedative properties have side effect profiles that also contribute to these declines. The lack of recognition of these signs and symptoms as medicine induced may subsequently contribute to increased risk of frailty and subsequent increased risk of adverse events such as falls and fractures.

There are several pharmacological pathways by which medicines with anticholinergic or sedative properties may contribute to medicine-induced deterioration. Medicines with sedative properties enhance the effects of the neurotransmitter gamma-aminobutyric acid (GABA) at the $GABA_A$ receptor in the central nervous system, causing sedative and muscle relaxant effects.[9] The side effects related to the sedative and muscle-relaxing actions may cause a decline in both cognitive and physical function. Additionally, some medicines with sedative properties may cause a decline in cognitive function by blocking the dopamine D_2 receptors in the central nervous system. Similarly, use of medicines with anticholinergic properties may lead to medicine-induced deterioration via several pathways. As some medicines with anticholinergic properties have sedative properties, these medicines may directly lead to a decline in physical function due to the sedative side effects. Medicines with anticholinergic properties may affect cognitive function by blocking the muscarinic receptors in the central nervous system which regulates learning and memory.[10] Medicines with anticholinergic properties block the effects of acetylcholine at the M3 muscarinic receptors of the salivary glands causing dry mouth, which may lead to loss of appetite.

We have created a model of the relationship between medicine use, medicine-induced deterioration and frailty

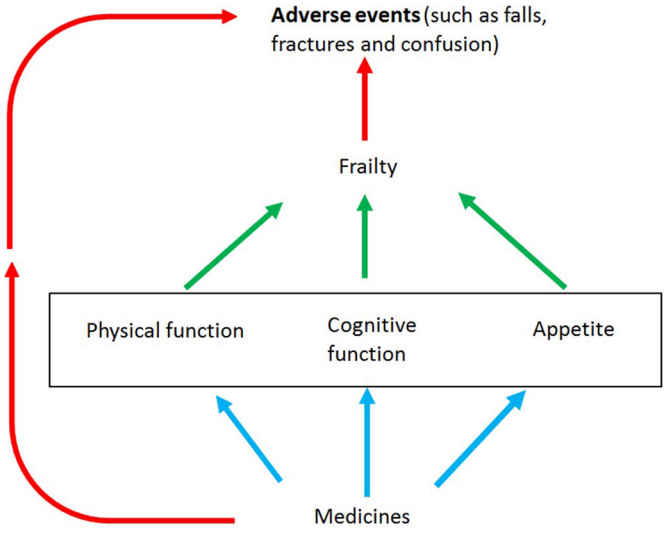

Figure 1 The hypothesised relationship between medicines, medicine-induced deterioration, frailty and adverse events.

(figure 1). If anticholinergic or sedative medicine-induced deterioration was monitored for and detected in practice, this would provide an opportunity for healthcare professionals to prevent deterioration by moderating medicine use, mitigating progression to frailty and potentially avoiding subsequent adverse events (figure 1). Using data from the Australian Longitudinal Study of Ageing (ALSA),[11] the study aims to assess (1) the association between use of medicines with anticholinergic or sedative properties and medicine-induced deterioration (physical function, cognitive function, appetite) and (2) the association between use of medicines with anticholinergic or sedative properties and frailty. We hypothesised that use of medicines with anticholinergic or sedative properties is associated with decline in physical function and decline in cognitive function for anticholinergics or sedatives, poorer appetite for anticholinergics and increased frailty.

METHODS

Study population and data collection

This study analysed baseline data collected as part of the ALSA, a population based cohort of 2087 participants aged 65 years or over at baseline (1992) living in South Australia.[11] Both community-dwelling and people living in residential care were eligible and were recruited by stratified random sampling from the South Australian electoral roll. At baseline, 93% of participants lived in the community and 6% lived in residential care.[11] Data collection was undertaken by comprehensive personal interviews, self-completed questionnaires and clinical assessments on physical function.

Medicines with anticholinergic or sedative properties

We identified medicines with anticholinergic properties using Duran's scale[12] with the addition of other anticholinergic medicines used in Australia based on the lists used in previous Australian studies.[1 13] Medicines with sedative properties were identified from the Australian Pharmaceutical Formulary and Handbook. Medicines with sedative properties were defined as those which cause sedation, and which are required by legislation to be dispensed with a specific sedation warning on the pharmacy label. Participants were stratified into one of four groups: (1) non-users, (2) users of medicines with anticholinergic properties only, (3) users of medicines with sedative properties only, or (4) users of medicines with sedative and anticholinergic properties.

Measures of physical function, cognitive function, appetite and frailty

As part of baseline assessments in ALSA,[11] participants had their physical function objectively assessed using hand grip strength, a timed 8-feet (2.4 m) walk at a normal pace and repeated chair stands. Hand grip strength was assessed using a handheld dynamometer in the dominant hand.[14] The maximum grip strength (kg) was recorded based on the best of two trials. Walking speed was

calculated using distance in metres and time in seconds. Participants were instructed to walk at normal pace from a standing start over a distance of 8 feet. Repeated chair stands were conducted by asking participants to rise unassisted from a chair five times. Functional status was subjectively assessed by interviewers using activities of daily living (ADL) and instrumental activities of daily living (IADL) scores. The ADL includes walking, bathing, personal grooming, dressing, eating, using the toilet and getting from bed to chair.[15] The IADL encompasses the following tasks: housekeeping, meal preparation, telephone use, handling finances, use of transportation and shopping.[16] Cognitive function was measured using the Mini-Mental State Examination (MMSE) questionnaire (range 0–30).[17] Appetite was measured using the Center for Epidemiologic Studies Depression (CES-D) question 2, 'I did not feel like eating; my appetite was poor', with scores of 0=rarely or none of the time, 1=some or a little of the time, 2=occasionally or a moderate amount of time, and 3=most or all of the time. The frailty index,[8] a multidimensional assessment which included physical, medical, psychological and social factors, was used to measure frailty. The frailty index, which has been validated in the Australian setting,[18 19] included 39 variables with a total score range of between 0 and 1. A higher frailty index indicates worse frailty status. The subjective functional status (ADL and IADL) formed part of the frailty index while the objective physical function (grip strength, walking speed, chair stands), cognitive function (MMSE) and appetite (CES-D question 2) were not directly measured in the frailty index.

Covariates

Univariate analysis was performed to determine which measures were significantly associated with use of anticholinergics or sedatives. The final analyses were adjusted for age, body mass index, residential status, smoking status, cognitive impairment, depressive symptoms and number of comorbidities using the functional comorbidity index. The functional comorbidity index contains a list of diseases reported to be associated with function in older populations.[20] We excluded depressive symptoms from the functional comorbidity index when we used it as a covariate for adjustment as depression was assessed independently. We did not adjust for covariates for the frailty analysis because it is unclear how the covariates such as age and comorbidities affect the relationship between medicine use and frailty.[21]

Statistical analysis

Descriptive statistics were used to report the baseline characteristics of the study population. The one-way analysis of variance was used to compare continuous variables including age, body mass index, functional comorbidity index, MMSE and CES-D, while the χ^2 test was used to compare categorical variables including sex, smoking, presence of cognitive impairment and presence of depression. The prevalence of use of medicines was grouped by Anatomical Therapeutic Chemical class.[22]

Unadjusted analysis of variance and adjusted analysis of covariance were performed to compare differences in physical or cognitive function between users and non-users. Given that hand grip strength has been shown to be significantly different between men and women with distinct sex-specific cut-off points,[23] this performance measure was analysed separately based on sex. All other analyses were not stratified by sex. Ordinal logistic regression was used to compare differences in appetite between users and non-users. Binary logistic regression was used to compare differences in frailty between users and non-users. Analysis was performed using SAS V.9.4 for Windows (SAS Institute). A priori, a p value <0.05 was considered statistically significant.

Patient and public involvement

There was no direct participant involvement in the present study. We use data collected as part of the ALSA study.[11]

RESULTS

Characteristics of study population

Table 1 shows the baseline characteristics of study participants. The mean age±SD of participants was 78±7 years old; 94% were community-dwelling participants and 6% lived in residential care. Nearly half of the population were using medicines with anticholinergic or sedative properties (n=954, 45.7%); 18.3% were using medicines with anticholinergic properties only, 11.3% were using medicines with sedative properties only and 16.1% were using medicines with sedative and anticholinergic properties. The most commonly used medicines with sedative properties were benzodiazepines, antidepressants and antihistamines (table 2). The most frequently used medicines with anticholinergic properties were frusemide, H2 receptor antagonists and digoxin (table 2).

Use of medicines with anticholinergic or sedative properties and physical function

In the unadjusted analyses, users of medicines with anticholinergic properties only, medicines with sedative properties only, or medicines with sedative and anticholinergic properties had significantly poorer function in all physical function measures (p<0.05).

After adjusting for covariates, use of medicines with anticholinergic properties only was significantly associated with poorer grip strength (women only, mean difference M_{diff} −1.43, 95% CI −2.56 to 0.31), poorer performance on chair stands (M_{diff} 0.90, 95% CI 0.13 to 1.68), slower walking speed (M_{diff} −0.05, 95% CI −0.09 to 0.02) and poorer IADL score (M_{diff} 0.22, 95% CI 0.04 to 0.41) (table 3). After adjusting for covariates, use of medicines with sedative properties only was significantly associated with poorer grip strength (men only, M_{diff} −1.92, 95% CI −3.54 to 0.30), slower walking speed (M_{diff} −0.05,

Table 1 Baseline characteristics of users and non-users of medicines with anticholinergic or sedative properties

Baseline characteristics	Total (n=2087)	Use of anticholinergics (n=383, 18.3%)	Use of sedatives (n=235, 11.3%)	Use of anticholinergics and sedatives (n=336, 16.1%)	Non-users (n=1133, 54.3%)	P value
Age, mean (SD), years	78.2 (6.7)	80.3 (6.6)	79.1 (6.1)	78.5 (6.9)	77.2 (6.6)	<0.001
Sex (male), n (%)	1056 (50.5)	235 (61.36)	109 (46.4)	128 (38.1)	584 (51.5)	<0.001
Body mass index, mean (SD), kg/m^2	26.1 (4.1)	26.2 (4.3)	26.2 (3.7)	26.1 (4.4)	26.0 (4)	0.852
Community living, n (%)	1961 (93.9)	356 (93)	222 (94.5)	293 (87.2)	1090 (96.2)	<0.001
Current smoker, n (%)	176 (8.4)	24 (6.3)	23 (9.8)	34 (10.2)	95 (8.4)	0.441
MMSE score, mean (SD)	26.9 (4.2)	26.4 (4.5)	26.5 (4.7)	26.4 (4.8)	27.2 (3.7)	<0.001
Presence of cognitive impairment, n (%)*	325 (15.6)	70 (18.3)	39 (16.6)	63 (18.8)	153 (13.5)	0.035
CES-D score, mean (SD)	8.2 (7.4)	9.1 (7.5)	9.7 (7.4)	11.7 (8.7)	6.6 (6.5)	<0.001
Presence of depressive symptoms, n (%)†	295 (14.1)	63 (16.5)	36 (15.3)	87 (25.9)	109 (9.6)	<0.001
Functional comorbidity index, mean (SD)	2.2 (1.6)	2.9 (1.7)	2.2 (1.5)	2.9 (1.7)	1.7 (1.4)	<0.001

*Presence of cognitive impairment was defined as MMSE score of less than 24.
†Presence of depressive symptoms was defined as CES-D score of 16 or more.
CES-D, Center for Epidemiologic Studies Depression; MMSE, Mini-Mental State Examination.

95% CI −0.10 to 0.01) and poorer IADL score (M_{diff} 0.23, 95% CI 0.01 to 0.45) (table 3). After adjusting for covariates, use of medicines with anticholinergic and sedative properties was significantly associated with slower walking speed (M_{diff} −0.08, 95% CI −0.11 to 0.04) and poorer IADL score (M_{diff} 0.42, 95% CI 0.22 to 0.61) (table 3).

Use of medicines with anticholinergic or sedative properties and cognitive function

Use of medicines with anticholinergic or sedative properties was significantly associated with poorer cognitive function in the unadjusted analysis (p<0.05), but the associations were not significant after adjusting for covariates (p>0.05) (table 3).

Use of medicines with anticholinergic properties and appetite

Use of medicines with anticholinergic properties was significantly associated with poorer appetite in both the unadjusted (OR 2.25, 95% CI 1.79 to 2.82) and adjusted analysis (OR 1.77, 95% CI 1.27 to 2.45).

Use of medicines with anticholinergic or sedative properties and frailty

Participants who used anticholinergics or sedatives had three times or more the odds of being frail compared with non-users (anticholinergics only: OR 3.9, 95% CI 2.9 to 5.3; sedatives only: OR 3.3, 95% CI 2.3 to 4.8; sedatives and anticholinergics: OR 6.2, 95% CI 4.6 to 8.5).

DISCUSSION

Our results showed that use of medicines with anticholinergic or sedative properties was significantly associated with poorer physical function and poorer appetite. In addition, we found that participants who used medicines with anticholinergic or sedative properties were significantly more likely to be frail. We have previously demonstrated using a longitudinal design in the same study population that frail older people (as identified by the frailty index) were more likely to have adverse events at follow-up including an increased risk of mortality (OR 3.2, 95% CI 2.4 to 4.1), hospitalisation (OR 2.3, 95% CI 1.7 to 3.0), nursing home admission (OR 3.3, 95% CI 1.6 to 7.0) and fall (OR 3.4, 95% CI 2.7 to 4.3).[8] Collectively, our results support the hypothesis that use of medicines with anticholinergic or sedative properties may contribute to frailty via the intermediary pathways of deterioration associated with medicine use or may directly contribute to frailty, leading to an increased risk of adverse events (figure 1).

Table 2 List of medicines with anticholinergic or sedative properties included in the study

Drug group (ATC code)	Anticholinergic or sedative	Frequency (%)
Benzodiazepines (N05BA, N05CD)		
Temazepam (N05CD07)	Sedative	88 (4.2)
Oxazepam (N05BA04)	Sedative	84 (4.0)
Nitrazepam (N05CD02)	Sedative	76 (3.6)
Diazepam (N05BA01)	Sedative	51 (2.4)
Flunitrazepam (N05CD03)	Sedative	11 (0.5)
Bromazepam (N05BA08)	Sedative	1 (0.05)
Flurazepam (N05CD01)	Sedative	1 (0.05)
Diuretics (C03)		
Frusemide (C03CA01)	Anticholinergic	287 (13.8)
H2 receptor antagonists (A02BA)		
Ranitidine (A02BA02)	Anticholinergic	114 (5.5)
Cimetidine (A02BA01)	Anticholinergic	87 (4.2)
Antidepressants (N06A)		
Doxepin (N06AA12)	Sedative, anticholinergic	48 (2.3)
Amitriptyline (N06AA09)	Sedative, anticholinergic	28 (1.3)
Dothiepin (N06AA16)	Sedative, anticholinergic	24 (1.1)
Imipramine (N06AA02)	Sedative, anticholinergic	22 (1.1)
Mianserin (N06A×03)	Sedative	6 (0.3)
Fluoxetine (N06AB03)	Sedative, anticholinergic	3 (0.1)
Nortriptyline (N06AA10)	Sedative, anticholinergic	3 (0.1)
Moclobemide (N06AG02)	Sedative	2 (0.1)
Clomipramine (N06AA04)	Sedative, anticholinergic	1 (0.05)
Tranylcypromine (N06AF04)	Sedative	1 (0.05)
Cardiac glycosides (C01A)		
Digoxin (C01AA05)	Anticholinergic	179 (8.6)
Drugs for obstructive airway diseases (R03)		
Theophylline (R03DA04)	Anticholinergic	52 (2.5)
Ipratropium (R03BB01)	Anticholinergic	13 (0.6)
Antihistamines (R06A)		
Promethazine (R06AD02)	Sedative, anticholinergic	17 (0.8)
Astemizole (R06A×11)	Sedative	10 (0.5)
Dexchlorpheniramine (R06AB02)	Sedative, anticholinergic	9 (0.4)
Terfenadine (R06A×12)	Sedative	7 (0.3)
Diphenhydramine (R06AA02)	Sedative, anticholinergic	5 (0.2)
Loratadine (R06A×13)	Anticholinergic	4 (0.2)
Methdilazine (R06AD04)	Sedative	4 (0.2)
Azatadine (R06A×09)	Sedative	4 (0.2)
Chlorphenamine, combinations (R06AB54)	Sedative	2 (0.1)
Cyproheptadine (R06A×02)	Sedative, anticholinergic	1 (0.05)
Diphenylpyraline (R06AA07)	Sedative	1 (0.05)
Dexchlorpheniramine, combinations (R06AB52)	Sedative	1 (0.05)
Thiethylperazine (R06AD03)	Sedative	1 (0.05)
Promethazine, combinations (R06AD52)	Sedative	1 (0.05)
Hydroxyzine (R06AE)	Sedative	1 (0.05)
Antipsychotics (N05A)		
Prochlorperazine (N05AB04)	Sedative, anticholinergic	37 (1.8)
Thioridazine (N05AC02)	Sedative, anticholinergic	7 (0.3)
Trifluoperazine (N05AB06)	Sedative, anticholinergic	4 (0.2)
Pericyazine (N05AC01)	Sedative, anticholinergic	4 (0.2)
Fluphenazine (N05AB02)	Sedative, anticholinergic	1 (0.05)
Haloperidol (N05AD01)	Sedative, anticholinergic	1 (0.05)
Antihypertensives (C02)		
Methyldopa (C02AB01)	Sedative	47 (2.3)
Clonidine (C02AC01)	Sedative	6 (0.3)
Opioids (N02A)		
Codeine/paracetamol (N02AA59)	Sedative	30 (1.4)

Table 2 Continued

Drug group (ATC code)	Anticholinergic or sedative	Frequency (%)
Dextropropoxyphene (N02AC04)	Sedative	19 (0.9)
Morphine (N02AA01)	Sedative	4 (0.2)
Antiepileptics (N03A)		
Phenytoin (N03AB02)	Sedative	22 (1.1)
Carbamazepine (N03AF01)	Sedative, anticholinergic	5 (0.2)
Clonazepam (N03AE01)	Sedative	4 (0.2)
Phenobarbital (N03AA02)	Sedative	3 (0.1)
Valproate (N03AG01)	Sedative	2 (0.1)
Drugs for functional gastrointestinal disorders (A03)		
Belladonna alkaloids (A03BA04)	Anticholinergic	14 (0.7)
Domperidone (A03FA03)	Anticholinergic	6 (0.3)
Metoclopramide (A03FA01)	Anticholinergic	4 (0.2)
Antigout preparations (M04A)		
Colchicine (M04AC01)	Anticholinergic	15 (0.7)
Antiparkinson drugs (N04)		
Bromocriptine (N04BC01)	Anticholinergic	3 (0.1)
Biperiden (N04AA02)	Sedative, anticholinergic	3 (0.1)
Orphenadrine (N04AB02)	Sedative, anticholinergic	2 (0.1)
Benzatropine (N04AC01)	Sedative, anticholinergic	1 (0.05)
Amantadine (N04BB01)	Sedative, anticholinergic	1 (0.05)
Other nervous system drugs (N07)		
Betahistine (N07CA01)	Sedative	5 (0.2)
Methadone (N07BC02)	Sedative, anticholinergic	2 (0.1)
Antidiarrheals (A07)		
Loperamide (A07DA03)	Anticholinergic	4 (0.2)
Drugs for bipolar disorder		
Lithium (N06AX)	Anticholinergic	4 (0.2)
Antimigraine preparations (N02C)		
Pizotifen (N02C×01)	Sedative	3 (0.1)
Cough suppressants (R05D)		
Pholcodine (R05DA08)	Sedative	3 (0.1)
Antiarrhythmics, class I and III (C01B)		
Disopyramide (C01BA03)	Anticholinergic	2 (0.1)
Muscle relaxants (M03)		
Baclofen (M03B×01)	Sedative, anticholinergic	1 (0.05)

ATC, Anatomical Therapeutic Chemical.

Our findings on the association of anticholinergics or sedatives with physical function are similar to another Australian cross-sectional study.[3] Similar associations have also been observed in studies involving community-dwelling older adults in USA,[24 25] Italy[26] and Finland.[27] A growing body of evidence has shown that limitations in physical function in older people (a component of frailty) predict risk of fracture, complications or length of hospital stay, disability and mortality.[28–31] An adequate degree of mobility is crucial for independent living and maintenance of quality of life in older people.[32] With the number of adults aged over 65 years in Australia projected to rise from 14% in 2012 to 27% in 2101,[33] an important goal of geriatric medicine is to reduce a patient's medication burden to prevent functional impairment associated with medicine use.

The mean difference of 1.9 kg in adjusted grip strength between users versus non-users of medicines with sedative properties in men was statistically significant. Similarly, the mean difference in adjusted grip strength between users versus non-users of medicines with anticholinergic properties (1.4 kg) in women was statistically significant and clinically relevant.[34] Use of anticholinergics or sedatives was associated with a difference in walking speed of 0.05–0.08 m/s between users and non-users, which was considered to be a clinically meaningful change.[35] Grip strength and walking speed are two commonly included components of frailty, and have been shown to relate to clinically significant outcomes such as functional disability[28 29] and mortality[36] in older people.

Our results indicate that use of anticholinergics or sedatives was not significantly associated with poorer cognitive function. While studies in other countries have reported contrasting results,[37] our findings are in keeping with another Australian cross-sectional study involving 1705 community-dwelling men which reported that anticholinergic and sedative medicine use as measured by the drug burden index was not associated with limitations in cognitive function.[38] It may be that use of anticholinergics or

Table 3 Adjusted means (95% CI) of physical function and cognitive function according to use of medicines with anticholinergic or sedative properties

	Non-users (n=1133)	Anticholinergics (n=383)	Mean difference (95% CI)	P value	Sedatives (n=235)	Mean difference (95% CI)	P value	Sedatives and anticholinergics (n=336)	Mean difference (95% CI)	P value
Physical function										
Grip strength, male*	29.4 (27.1, 31.8)	29.2 (26.8, 31.6)	−0.27 (−1.47 to 0.94)	0.67	27.5 (24.8, 30.2)	−1.92 (−3.54 to 0.30)	0.020	28.3 (25.7, 30.8)	−1.18 (−2.68 to 0.32)	0.12
Grip strength, female*	18.6 (17.1, 20.1)	17.2 (15.5, 18.8)	−1.43 (−2.56 to 0.31)	0.013	18.6 (16.9, 20.3)	−0.01 (−1.14 to 1.12)	0.99	17.8 (16.3, 19.3)	−0.80 (−1.76 to 0.15)	0.100
Walking speed†	0.7 (0.7, 0.8)	0.7 (0.6, 0.7)	−0.05 (−0.09 to 0.02)	0.0038	0.7 (0.6, 0.7)	−0.05 (−0.10 to 0.01)	0.0098	0.6 (0.6, 0.7)	−0.08 (−0.11 to 0.04)	<0.001
Chair stands†	14.1 (12.5, 15.6)	15.0 (13.4, 16.5)	0.90 (0.13 to 1.68)	0.022	14.6 (12.9, 16.3)	0.49 (−0.41 to 1.4)	0.29	14.6 (12.9, 16.2)	0.48 (−0.32 to 1.28)	0.24
ADL†	0.6 (0.5, 0.8)	0.7 (0.5, 0.9)	0.07 (−0.05 to 0.18)	0.25	0.7 (0.5, 0.9)	0.05 (−0.08 to 0.19)	0.43	0.7 (0.5, 0.9)	0.04 (−0.08 to 0.16)	0.48
IADL†	1.1 (0.9, 1.4)	1.4 (1.1, 1.7)	0.22 (0.04 to 0.41)	0.020	1.4 (1.0, 1.7)	0.23 (0.01 to 0.45)	0.043	1.6 (1.3, 1.9)	0.42 (0.22 to 0.61)	<0.001
Cognitive function										
MMSE‡	26.4 (25.7, 27.1)	26.5 (25.7, 27.2)	0.05 (−0.40 to 0.49)	0.84	26.7 (26.0, 27.5)	0.34 (−0.18 to 0.86)	0.20	26.6 (25.9, 27.3)	0.24 (−0.22 to 0.70)	0.31

Grip strength (kg)—a higher value indicates stronger muscle strength. Walking speed (m/s)—a higher value indicates faster walking speed. Chair stands (s)—a higher value indicates slower time required to complete chair stands. ADL and IADL—a higher value indicates higher impairment.
*Adjusted for age, body mass index, residential status, smoking status, cognitive impairment, depressive symptoms and functional comorbidity index.
†Adjusted for age, sex, body mass index, residential status, smoking status, cognitive impairment, depressive symptoms and functional comorbidity index.
‡Adjusted for age, sex, body mass index, residential status, smoking status, depressive symptoms and functional comorbidity index.
ADL, activities of daily living; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination.

sedatives is not associated with poorer cognitive function in our study population; however, it may also be that the MMSE is not sensitive enough to detect mild cognitive impairment.[39] Other measures, such as the Montreal Cognitive Assessment tool, have been shown to be better for detecting mild cognitive impairment. The lack of association between medicines with anticholinergic or sedative properties and poorer cognitive function should be interpreted with caution due to the high mean MMSE score (27 points) and the small percentage of participants with cognitive impairment (16%) in our population. In addition, the dose and duration of use of medicines with anticholinergic or sedative properties could have been below the threshold required to decrease cognitive function. Most patients in our study population used only one medicine with anticholinergic or sedative properties.

Our findings on the association between use of anticholinergics and poorer appetite contribute uniquely to the literature. While a cause–effect relationship cannot be established, it is widely known that anticholinergics can cause dry mouth[40] and it is plausible that this contributed to our finding. In older people, loss of appetite due to dry mouth is difficult to detect and loss of appetite may be misattributed to be part of the natural ageing process. It is likely that loss of appetite due to medicine-induced dry mouth is an underdetected problem; however, this topic has not been well researched.

There are several strengths to our study. We proposed an intermediary pathway by which medicine use contributes to frailty in older people. In analysing the intermediary pathways of deterioration associated with medicine use, we assessed grip strength, chair stands and walking speed all of which were not variables included in our calculation of frailty. We analysed the association between medicines with anticholinergic or sedative properties and grip strength based on sex, which previous studies have not done. The outcome measures chosen were both objective and clinically relevant.

The study is limited by its cross-sectional design. It is not possible to identify a cause–effect relationship between use of medicines with anticholinergic or sedative properties and reduced physical function or poorer appetite using this study design. We did not differentiate between potent and probable anticholinergic medicines, or between peripherally and centrally acting medicines. Another limitation is that we did not examine medication adherence or the effects of dose or the duration of treatment. Although we adjusted our analysis for various potential confounding factors, there is a possibility of residual confounding and confounding by indication. Although the CES-D has been validated, the question on appetite has not been validated by itself. The method of assessing appetite may be subject to recall bias.

In conclusion, use of medicines with anticholinergic or sedative properties is significantly associated with poorer physical function, poorer appetite and increased frailty. Early identification of signs and symptoms of deterioration associated with medicine use is particularly important in older people so that worsening frailty and subsequent adverse events are prevented. Grip strength, chair stands and walking speed are simple assessment tools that could be used routinely in general practice or pharmacy practice to monitor for deterioration in persons considered at risk of frailty. Use of these tools would provide an objective measure by which clinicians could assess deterioration associated with medicine use. Clinicians and pharmacists should review use of medicines with anticholinergic or sedative properties in the older population who are at the highest risk of deterioration associated with medicine use.

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