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Impact of Multiple Low Level Anticholinergic Medications on Anticholinergic Load of Community Dwelling Elderly With and Without Dementia

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Running Title: Medications contributing to anticholinergic load in the elderly, with and without dementia

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Abstract

Background Elderly people, particularly those with dementia, are sensitive to adverse anticholinergic drug effects. This study examines the prevalence of anticholinergic medication, and anticholinergic load and its predictors, in community-dwelling elderly patients (aged 75 and older) in Australia.

Methods A research nurse visited the home of each participant, compiled a list of current medications, and assessed participants' cognitive status using a subsection of the revised Cambridge Examination for Mental Disorders of the Elderly (CAMCOG-R). Anticholinergic load was determined for each patient using the Anticholinergic Drug Scale (ADS).

Results Multivariate analysis identified several patient factors that were associated with higher anticholinergic burden including polypharmacy (i.e. taking five or more medications) ($p < 0.001$), increasing age ($p = 0.018$), CAMCOG-R dementia ($p = 0.003$), depression ($p = 0.003$) and lower physical quality of life ($p < 0.001$). The dementia group took a significantly higher number of medications (4.6 vs. 3.9; $p = 0.04$), and had a significantly higher anticholinergic load (1.5 vs. 0.8; $p=0.002$). Approximately 60% of the dementia group (n=86) and 40% of the non-dementia group (n = 958) were on at least one anticholinergic drug. This difference was due to the higher proportion dementia patients taking Level 1 (potentially-anticholinergic) ($p = 0.002$) and Level 3 (markedly-anticholinergic) ($p = 0.005$) drugs.

Conclusions There is considerable scope for the improvement of prescribing practices in the elderly, and particularly those with dementia. Importantly, it is level 1 anticholinergics that are responsible for much of the anticholinergic load in people with dementia. Longitudinal studies are required to determine the effects of increased and decreased anticholinergic load on cognitive function and other clinical outcomes for people with dementia.

Key Points

• patient factors associated with higher anticholinergic burden were polypharmacy (i.e. taking five or more medications), increasing age, CAMCOG-R dementia, depression and lower physical quality of life

• anticholinergic medication(s) were used more frequently in people with dementia

• level 1 anticholinergic drugs contributed, on average, 70% to the total burden

Introduction

Drugs should be prescribed with caution in elderly patients, as they are more sensitive to adverse effects and drug clearance is reduced [1, 2]. The elderly are more likely to be taking multiple medications for the treatment of multimorbidity, which also puts them at greater risk of a severe adverse drug reaction [3].

The *Beers Criteria for Potentially Inappropriate Medication Use in Older Adults* specify medications that are inappropriate for use in older (age ≥ 65 years) adults generally, and in the elderly with particular diseases or syndromes including dementia [4]. The Beers list includes drugs with strong anticholinergic properties that should be avoided in older adults due to their well-known adverse effects. Given that anticholinergic (or more correctly, antimuscarinic) drugs are widely used, as are diverse classes of other drugs with anticholinergic side effects (e.g. antihistamines, antidepressants, anti-Parkinson agents, antipsychotics, antispasmodics and skeletal muscle relaxants), it is common that many patients are subjected to a high anticholinergic load or burden. This is particularly undesirable in the elderly since cholinergic neurons, important in memory function, degenerate with age [5] and conditions such as dementia may be exacerbated by anticholinergic medications [1, 6, 7]. It is therefore specifically recommended that anticholinergic drugs be avoided in older adults with delirium, dementia and cognitive/mental impairment. Another reason for avoiding such drugs in this population is that drug-induced physical and cognitive impairment in the elderly with dementia may be incorrectly ascribed to the progression of the underlying disease [8]. Patients with dementia have lower levels of acetylcholine [9], and anticholinergic drugs aggravate this situation by blocking the action of acetylcholine on its (muscarinic) receptors. Even weak anticholinergic drugs may cause adverse effects by contributing to an older person's anticholinergic load [8]. Numerous studies have reported an association of anticholinergic medication use with cognitive impairment in the elderly [10,

11, 6, 7, 12, 13]. A clinical review found in 25 of 27 studies that the anticholinergic activity of medications was correlated significantly with the presence of either cognitive impairment, delirium or dementia in older adults [14]. There is some limited evidence that cessation of anticholinergic use reduces the risk of cognitive impairment and dementia in the elderly [6].

Although general practitioners (GPs) are well aware of the potential adverse effects of many of the potentially inappropriate medications specified by the Beers criteria, their knowledge around cognitive effects of anticholinergic medication is incomplete [15]. GPs were very aware of the common anticholinergic adverse effects (dry mouth, blurred vision, cardiac effects etc), but most did not consider the additive anticholinergic effects of different medications ("anticholinergic load") when prescribing for the elderly. Anticholinergic toxicity usually occurs because of the summed effects of multiple drugs rather than an overdose of a single drug [16]. It is, therefore, prudent to consider not only individual drugs with marked anticholinergic activity, but also the cumulative effect of multiple medications with modest anti-muscarinic activity when prescribing for the elderly [17, 18].

Despite the recommendations, medications with anticholinergic properties are used frequently in the elderly, including patients with dementia. Older adults with probable dementia were found to be more likely to be on anticholinergics than matched controls [13]. It has been reported that 40-60% of dementia patients use at least one anticholinergic medication [19-21], and 10-20% used drugs with clinically significant anticholinergic effects [20, 21]. The prevalence of anticholinergic drug use is higher in elderly nursing home residents with dementia; 74% used at least one anticholinergic medication, and more than 20% used medications with marked anticholinergic activities [22]. Approximately a third of dementia patients receiving cholinesterase inhibitors were concurrently using at least one anticholinergic medication [13, 23]. Such irrational prescribing is likely to negate the modest

benefit of the treatment. Of further concern, there was no reduction in exposure to anticholinergic drugs after commencement of cholinesterase inhibitor treatment [23].

This study examines the prevalence of anticholinergic medications and its predictors in a representative sample of community-dwelling elderly patients in Australia, with and without dementia. The identification of patient and GP predictors of anticholinergic drug use will help to identify elderly patients most at risk, and GPs that can be most effectively targeted for education.

Methods

Study population

This study utilized data collected from the "Ageing in General Practice" (AGP) study [24]. The AGP study was a randomized controlled trial that examined the effectiveness of peer education on GP diagnostic assessment and management of dementia. Briefly, consenting GPs from four sites, Newcastle, Sydney, Melbourne and Adelaide, recruited their patients by mail to be a part of the AGP study [24]. Patients who could speak English, were aged 75 years or over and had visited the GP within the last 12 months were eligible for inclusion into the study. Patients were excluded if they suffered from multiple sclerosis, Parkinson's disease, motor neuron disease, central nervous system inflammation, psychotic symptoms, progressive malignancy, had a developmental disability or resided in an aged care facility.

The Human Ethics Committees of the University of Newcastle, University of New South Wales, Melbourne University, and the University of Adelaide approved the protocol of the study. All participants, including GPs and patients, provided written informed consent.

Data collection

Research nurses compiled a list of all prescription medications that were currently being used by the patient by interviewing participants in their own home. Medications and doses for each participant were entered into a database, using the Anatomical Therapeutic Chemical (ATC) classification system (http://www.whocc.no/). Demographic details of each participant were also collected during the visit and a number of instruments were administered by the nurse including

- geriatric depression scale (GDS), a 15 item scale [25] widely used in primary health care settings

- revised Cambridge Cognitive Examination (CAMCOG-R), a subsection of the Cambridge examination for mental disorders of the elderly, that has been validated for measurement of cognitive status [26]
- Australian version of the WHOQOL-BREF, a widely used and validated quality of life instrument that measures four separate domains [27].

Further details of the participant interview and collection of GP demographics are available in the published study protocol [24].

Anticholinergic Load

Anticholinergic load was determined for each patient using the Anticholinergic Drug Scale (ADS) [28]. The 117 drugs listed (as level 1, 2 or 3) on the ADS have been assigned scores that correlate with serum anticholinergic activity (SAA) [28] and have been validated recently as predictors of anticholinergic adverse drug events [29]. All drugs were rated based on their anticholinergic properties (Level 0: no known anticholinergic property; Level 1: potential anticholinergic effects seen in receptor binding studies; Level 2: anticholinergic adverse events noted; Level 3: markedly anticholinergic). Anticholinergic load was calculated simply by summing the ratings (0-3) for each medication taken by each patient. Preliminary calculations using dose-adjusted scores [28] showed no significant difference in outcome when compared to this method.

Statistical analysis

Univariate analysis was performed using Student's t-tests for continuous data and chi-squared analysis for categorical data using Microsoft Office Excel 2011 and SPSS v18. Multivariate analysis was used to determine the predictors of anticholinergic scores in all patients of the study cohort (Table 2). This was done using a linear regression model fitted within a

generalized estimating equation (GEE) framework, which adjusts for clustering of patients within practices. The dependent variable was ADS anticholinergic score. GP demographic factors were included in the model, based on previous studies demonstrating marked GP and practice level variability in prescribing patterns [30-32]. Participant variables with $p<0.2$ in univariate analysis were included as independent variables in the model. The multivariate analyses were programmed in Stata v11.2 or later.

Results

A total of 1044 patients aged 75 years and over participated in the study. Of these, 86 (8.2%) were classified as having probable dementia based on a CAMCOG-R score of 79 or less (Table 1), and 438 (42.0%) were taking at least one anticholinergic medication. The mean ADS score was 0.82 ± 1.33 (range 0-11). There were 360 patients taking anticholinergic drugs that were level 1 only; the mean ADS score was 1.48±0.77 (range 1-5).

Multivariate analysis identified several patient factors that were associated with higher anticholinergic burden (ADS score) including polypharmacy (i.e. taking five or more medications) ($p < 0.001$), increasing age ($p = 0.018$), CAMCOG-R dementia ($p = 0.003$), depression ($p = 0.003$) and lower physical quality of life ($p < 0.001$) (Table 2). Environmental, psychological and social quality of life domains were not associated with anticholinergic burden. Widows/widowers were found to have a significantly higher anticholinergic load ($p = 0.043$) compared to married patients. GP factors including age, time in practice and practice size were not significantly associated with anticholinergic burden.

In order to further examine the use of anticholinergics in people with CAMCOG-R dementia, the dementia and non-dementia groups were examined separately. The dementia group was significantly older (83.3 vs 81.1 years) than the non-dementia group ($p < 0.001$), but they did not differ in other demographic factors, including gender, marital status and Index of Relative Social Advantage and Disadvantage (IRSAD) (Table 3). As well as lower CAMCOG scores, the dementia group also scored lower than the non-dementia group on the physical, psychological, social and environmental quality of life domains ($p = 0.004$, $p <0.001$, $p = 0.016$ and $p < 0.001$, respectively). Geriatric depression scale scores were significantly higher in the dementia group ($p < 0.001$), indicative of higher likelihood of depression (Table 3).

Patients in the dementia group took a significantly higher number of medications (4.6 *vs.* 3.9; $p = 0.04$), and had a significantly higher anticholinergic load (1.5 *vs.* 0.8; $p=0.002$) than the non-dementia group. The proportion of anticholinergic drug users was significantly higher ($p <0.001$) in the dementia group (59.3%) compared to the non-dementia group (40.8%). This difference was due to the higher proportion of dementia patients taking Level 1 ($p = 0.002$) and Level 3 ($p = 0.005$) drugs. The relative contributions of levels 1-3 drugs to total anticholinergic load in the dementia and non-dementia groups are shown in Table 4. In both groups, level 1 drugs were the major contributor to anticholinergic load (64-70%), followed by the level 3 drugs (20-29%). Level 2 drugs contributed less than 10% of the total anticholinergic load in the sample population.

The anticholinergic drugs that were taken by 2 or more patients in the dementia group are shown in Table 5. Doxepin and oxybutynin were the most common level 3 anticholinergic drugs taken by the dementia group, while ranitidine was the only level 2 anticholinergic drugs taken by this group. The most common level 1 anticholinergics taken by the dementia group, which were also the most common drugs taken overall by this group, were the cardiovascular drugs, furosemide, warfarin, isosorbide mononitrate, digoxin and diltiazem. The percentages of dementia patients on both level 1 and level 3 anticholinergic antidepressant drugs were greater than those of the non-dementia patients (9.4 vs 4% and 4.7 vs 3.1%, respectively). Amytriptyline (a level 3 drug) was used by 18 (1.9%) patients without dementia, but no patients with dementia (data not shown).

Discussion

Dementia, depression, polypharmacy and lower physical quality of life were identified as associations of higher anticholinergic load in this study of elderly (≥ 75 years) community dwelling Australians. The anticholinergic load of medications taken by people with CAMCOG-R dementia was significantly higher (1.5 *vs* 0.8; $p < 0.001$) than participants without dementia. Our study results confirm the higher incidence of anticholinergic use reported previously in dementia patients [13]. It is possible that in some cases, cognitive impairment may due to the use of anticholinergic medication(s) rather than the presence of dementia.

Almost 60% of people with dementia in our study were taking at least one anticholinergic medication and 17% were taking one or more, higher potency (level 2 or 3) anticholinergic medications. The rate was lower in participants without dementia; 40% used at least one anticholinergic drug, and 9% used drugs with higher potency anticholinergic properties. This is consistent with the reported prevalence of anticholinergic medication use in the United States and United Kingdom. Depending upon the sample population and the methodology used, the reported prevalence of anticholinergic use in the elderly varies from 9% to 47% [12, 33, 34, 7]. A recent large study of approximately 1.5 million elderly dementia patients reported that 23% used drugs with clinically significant anticholinergic activities [21]. Earlier studies reported that 40-60% of dementia patients use at least one anticholinergic medication [19-21, 35], and 10-20% used higher potency (level 2 or 3) anticholinergic drugs [20, 21]. These high rates of use are of particular concern for elderly dementia patients that already suffer from cognitive problems, as central nervous adverse effects of anticholinergic medication (lethargy, confusion, delirium and cognitive impairment) are more likely to occur [36] but may not be recognized as such.

The largest contribution (> 60%) to the total anticholinergic load of participants (both with and without dementia) was made by level 1 drugs. For several participants, their entire anticholinergic load (up to a value of 6) was due to the summative effect of multiple level 1 drugs. It has been reported previously that adverse drug events are often the result of the cumulative anticholinergic burden of multiple prescription medications and metabolites rather than of a single compound [16], and cumulative anticholinergic use has been shown to increase hospitalisations and mortality in the elderly in general [37]. Given these findings and that polypharmacy was an important predictor of anticholinergic load in this study and others [22, 20], prescribers should be cognizant of the summative effects of the numerous level 1 anticholinergic drugs. Clinicians may be less aware of the relatively large number of medications classified as level 1 anticholinergic drugs [28] than the level 2 and 3 medicines, with generally well recognized anticholinergic properties. Many scientific studies have also focussed primarily on level 2 and 3 drugs [20, 13, 21] or not taken the summative effect of multiple anticholinergic medications into account [38]. It should be considered that even medicines with minor anticholinergic properties may contribute to unwanted central and peripheral adverse events if used in combination with other agents with anticholinergic effects.

Several drugs were prescribed more frequently to people with dementia, compared with the non-dementia group. A greater percentage of dementia patients were using doxepin and oxybutynin (both level 3 drugs) and several level 1 drugs used for treatment of cardiovascular conditions including furosemide, warfarin, isosorbide mononitrate and digoxin. Dementia patients have on average 2-8 additional chronic diseases or co-morbidities [35, 39], significantly more than other elderly people [39]. There are several chronic diseases specifically associated with dementia including congestive heart failure and cardiac arrhythmia [40] which may explain the increased use of cardiovascular related medications

by people with dementia in our study. In addition to their anticholinergic properties, several cardiovascular drugs may have unintended effects (potentially positive or negative) on the pathogenesis of Alzheimer's disease via their β-amyloid modifying activity [41]. The groupings and associations of particular chronic diseases around dementia present a complex challenge for primary care providers, and often result in complex medication regimens and increased anticholinergic load for the patient.

Almost 12 % of dementia patients and 6% of non-dementia patients were on a strong (level 3) anticholinergic medication. While members of certain drug classes needed to treat a particular condition all have anticholinergic properties, there are sometimes options available to mitigate adverse effects. For example, the severity of anticholinergic adverse effects may be limited by the route of administration or the formulation of a drug. Oxybutynin, a level 3 anticholinergic drug that can worsen disease-related deficits in Azheimers dementia[42], was being used by 3.5% of people with dementia in our study. While most drugs for urinary incontinence are anticholinergics, the degree of adverse effect varies depending on the route of administration or the choice of drug. Transdermal delivery of oxybutynin results in decreased adverse effects [43] and controlled–release oxybutynin tablets exhibited only 57% of the adverse effects of conventional oxybutynin tablets [44]. Unlike oxybutynin, darifenacin has shown no impairment of memory or other cognitive functions in three randomised, controlled trials [45]. Mirabegron, a β3-adrenergic receptor agonist, was not available when this study data was collected, but was recently approved in Australia for treatment of urinary incontinence.

A score of five or greater on the geriatric depression scale (GDS), indicative of depression, was also a predictor of increased anticholinergic load. It is likely that the depression was undiagnosed and untreated in many patients, as GPs correctly identify depression in only 50% of cases [46]. The use of antidepressants did however contribute to the anticholinergic

burden in this study. Doxepin, was prescribed to dementia patients with greater frequency than to non-dementia patients (3.5 vs 0.9%). Mood disorders are common among elderly dementia patients, and were associated with an increased likelihood of receiving a higher-level anticholinergic drug in one study [21] but with decreased use of a higher-level anticholinergic drug in another [20]. While the anticholinergic effects of tricyclic antidepressants (e.g. amitriptyline) are well known, the status of other classes of antidepressants is less clear. The selective serotonin reuptake inhibitors (SSRIs) are generally considered free of anticholinergic effects. However, paroxetine is rated as a level 1 anticholinergic by both the ADS [28] and the Anticholinergic Risk Scale [47] and a level 3 by the Anticholinergic Cognitive Burden scale (ACB) [48].

One of the strengths of our data is that they were gathered by research nurses during a home visit to each patient, and reflect the medications and doses actually being taken by the patients at that time. Secondly, although not as accurate as a geriatrician assessment of dementia, the use of the CAMCOG-R enabled identification of all patients with a level of cognitive impairment consistent with dementia, regardless of whether they had received a formal diagnosis or whether they were being treated with anti-dementia medication. This provides a realistic view of the medications used by community dwelling elderly with and without dementia. Although more than 50% of the patients with dementia in our study population had not been diagnosed by their GP [49], the prevalence of anticholinergic use was similar to that reported in other studies for participants with a formal diagnosis of dementia [21, 20]. This is consistent with findings that there was no reduction in exposure to anticholinergic drug exposure after commencement of cholinesterase inhibitor treatment [23]. The lack of a definitve list of anticholinergic medications, and a standardized calculation tool for anticholinergic load that incorporates level of activity, dose and summative effects is a general limitation of research in this field. There are at least eight different scales for

evaluating exposure to anticholinergic medications [50], which makes comparisons and generalization of findings difficult. Furthermore, the possible contribution of drug interactions to drug levels and, thence, to anticholinergic load is not addressed by current scales. A limitation specific to this study is the exclusion of patients with several conditions, including those with psychotic symptoms and Parkinson's disease. Since some anti-Parkinson agents and many antipsychotics have strong anticholinergic properties [4], it is likely that our study underestimates the extent of the problem of anticholinergic burden in elderly Australians. Another limitation is that the study did not evaluate the clinical outcomes of anticholinergic use. A longitudinal study to determine the effects of initiation and de-prescribing of level 1, 2 and 3 anticholinergic drugs on cognitive function and other clinical outcomes for dementia patients would be useful for development of models of care that balance the competing needs and adverse effects of treatments for comorbid conditions.

There is considerable scope for the improvement of prescribing practices in the elderly, and particularly those with dementia. In many cases, it is the low level anticholinergics that are the major contributors to anticholinergic load. The anticholinergic burden in a patient may develop insidiously over time, as they are subject to increasingly complex medication regimens to manage co-morbidities. Several promising strategies for optimizing prescribing in the elderly have been suggested including academic detailing, which has been shown to reduce the prescribing of highly anticholinergic antidepressants in the elderly [51]. Our study did not identify any particular GP demographic to target for education but did find that older and widowed patients were at greater risk for high anticholinergic load. Theoretical modelling predicts that medication management review could potentially reduce anticholinergic burden in the elderly [52], with the most successful approaches in this area involving the use of pharmacists or multidisciplinary teams including geriatric medicine services [53].

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Table 1 Demographic characteristics of the study population

Characteristic	n = 1044
Age (years), mean ±SD	81.3±4.2
Gender (% male)	43.8
Married/defacto, %	51.0
IRSAD, mean ±SD	7.0±2.4
CAMCOG-R[c]	90.5 ± 7.9
Dementia (% CAMCOG-R < 80)	8.2

SD, standard deviation; IRSAD, Index of Relative Social Advantage and Disadvantage (scale 1-10, higher score indicative of higher socioeconomic status); CAMCOG-R, revised Cambridge cognitive assessment

Table 2 Factors associated with anticholinergic load in the community dwelling elderly (≥ 75 years of age)

Characteristic	Effect size (95% CI)	Adjusted P-value GEE model‡
Polypharmacy[a]	0.81 (0.63 to 0.98)	<0.001
Age	0.02 (0.01 to 0.04)	0.018
Marital Status		
Married	Referent	
Divorced/Sep	0.14 (-0.2 to 0.48)	0.412
Single	-0.04 (-0.43 to 0.35)	0.852
Widow	0.2 (0.01 to 0.4)	0.043
Depression (GDS)	0.52 (0.18 to 0.86)	0.003
Dementia (CAMCOG-R)	0.48 (0.16 to 0.79)	0.003
Physical QoL Score	-0.01 (-0.02 to -0.01)	<0.001

‡ P-values are adjusted for all other variables included in the model

[a] greater than 4 medications

GDS, geriatric depression scale; CAMCOG-R, revised Cambridge cognitive assessment; QoL, quality of life

The following factors were included in the model but were not significant: gender (p=0.904), Index of Relative Social Advantage and Disadvantage (p=0.123), home ownership (p=0.851), environmental QoL (p=0.9180, social QoL (p=0.146), psychological QoL (p=0.687), GP gender (p=0.437), GP age (p=0.9840, GP experience (p=0.883), practice size (solo, referent; 2-4 GPs, p=0.436; ≥5 GPs, p=0.091).

Table 3 Comparison of several factors for patients with and without probable dementia (CAMCOG-R<80).

	Dementia	Non-Dementia	*P*-value
Patient Factors	*n=86*	*n=958*	
Age, mean ±SD	83.3 ± 5.2	81.1 ± 4.1	< 0.001
Male, %	43.0	44.3	0.856
Married/defacto, %	50.6	50.9	0.910
IRSAD	6.8 ± 2.7	7.0 ± 2.3	0.561
CAMCOG-R	71.2 ± 8.9	92.3 ± 4.9	< 0.001
GDS	3.4 ± 2.7	2.1 ± 2.0	< 0.001
Quality of Life[a]			
Physical	64.0 ± 15.5	69.2 ± 14.8	0.004
Psychological	64.8 ± 12.1	70.8 ± 12.5	< 0.001
Social	75.5 ± 10.0	78.6 ± 13.4	0.016
Environmental	73.7 ± 12.8	80.1 ± 11.2	< 0.001
No. Of medications	4.6 ± 3.0	3.9 ± 2.5	0.04
Anticholinergic Load	1.5 ± 2.0	0.8 ± 1.4	0.002
Patients Taking ≥1:			
Anticholinergic (any level), %	59.3	40.8	<0.001
Level 1 Anticholinergic, %	53.5	38.5	0.002
Level 2 Anticholinergic, %	4.7	3.6	0.418
Level 3 Anticholinergic, %	12.8	5.6	0.005

SD, standard deviation; IRSAD, Index of Relative Social Advantage and Disadvantage (scale 1-10, higher score indicative of higher socioeconomic status); CAMCOG-R, revised Cambridge Cognitive Examination (score < 80 indicative of dementia); GDS, Geriatric Depression Scale (score > 5 indicative of depression)

[a] Higher scores indicate higher quality of life for all domains

Table 4 Contribution of level 1, 2 and 3 drugs to total anticholinergic load in patients with or without dementia.

Anticholinergic Drug Rating	% of Total Anticholinergic Load		
	Dementia (n = 86)	Non-Dementia (n = 958)	Total
Level 1	64.5	70.5	69.4
Level 2	6.5	9.5	8.8
Level 3	29.0	20.0	21.9

Table 5 Anticholinergic drugs used most frequently by participants with dementia

Anticholinergic Drug	Organ System/ Therapeutic Category	% (n) Taking Drug	
		Dementia	Non-Dementia
Level 3			
Doxepin	CNS	3.5 (3)	0.2 (2)
Oxybutynin	Genitourinary	3.5 (3)	0.9 (9)
Level 2			
Ranitidine	Gastrointestinal	2.3 (2)	2.5 (24)
Level 1			
Furosemide	Cardiovascular	23.3 (20)	9.9 (96)
Warfarin	Cardiovascular	14.0 (12)	8.1 (79)
Isosorbide mononitrate	Cardiovascular	7.0 (6)	3.2 (31)
Sertraline	CNS	7.0 (6)	2.8 (27)
Digoxin	Cardiovascular	5.8 (5)	3.3 (32)
Diltiazem	Cardiovascular	4.7 (4)	4.2 (41)
Alprazolam	CNS	3.5 (3)	0.4 (4)
Loperamide	Gastrointestinal	3.5 (3)	0.7 (7)
Oxazepam	CNS	3.5 (3)	2.0 (19)
Codeine	CNS	2.3 (2)	0 (0)
Nifedipine	Cardiovascular	2.3 (2)	1.6 (16)
Prednisone	Corticosteroid	2.3 (2)	1.4 (14)
Prochlorperazine	Gastrointestinal	2.3 (2)	2.1 (20)
Temazepam	CNS	2.3 (2)	4.2 (41)
Valproic acid	CNS	2.3 (2)	0.2 (2)