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The association between anticholinergic load and cognitive performance, elevated blood pressure and the presence of peripheral anticholinergic side effects.

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Abstract

BACKGROUND:

To quantify the association between anticholinergic drug use (burden or load) and cognitive function (MMSE), blood pressure and the presence of anticholinergic side effects.

METHODS:

The medical records of 182 aged care home residents in the Perth metropolitan area, Western Australia were reviewed retrospectively to obtain demographic data, past and current medical problems, history of use of agents with anticholinergic effects and the following medication-related problems: cognitive impairment (as determined by Mini Mental State Examination {MMSE} score), blood pressure elevation and the presence of anticholinergic side effects. Anticholinergic load was calculated, and the relationship between the anticholinergic load and the presence of anticholinergic side effects was assessed using stepwise multiple regression and multiple logistic regression analysis.

RESULTS:

Increasing anticholinergic load was associated with the presence of peripheral anticholinergic side effects including hypertension (AOR=1.53), dry mouth (AOR=1.38), dry eyes (AOR=1.30), constipation (AOR=1.24) and urinary hesitancy (AOR=1.21) (all p values ≤0.05). The anticholinergic load was not associated with blurred vision (p=0.084) and Mini Mental State Examination score decline (p=0.142).

CONCLUSIONS:

The anticholinergic load was associated with statistically significantly increased risk of peripheral anticholinergic adverse effects in older aged care residents, however not with cognitive decline.

Keywords: Anticholinergic load, cognition, hypertension, adverse effects

Introduction

Older people have an increased likelihood of illness and as a result receive a disproportionate amount of over-the–counter and prescribed medications.[1] In the USA people over 65 used 30% of prescription and 40% of over-the–counter medicines, despite making up only 13% of population.[1] In the UK, the old aged comprised only 18% of population but consumed 45% of all prescription drugs. Some of these medications are prescribed inappropriately and without attention to side effects. Elderly people living in aged care facilities are even more likely to receive medications and to be exposed to side effects.[1] Blazer et al reported in one year, 97% of elderly patients in aged care facilities obtained a prescribed drug, compared with 71% of patients living in the community.[2] Longitudinal data from Australia (1981 through 2002) has shown the rate of adverse drug events to be on the rise.[3] The largest increase manifested in those persons aged over 80 years; a tenfold increase in men and a sevenfold increase in women.[3]

Moreover, older people frequently have low health expectations and are less likely to recognize medication adverse effects. In addition, patients with cognitive decline have difficulties in communication of their discomfort. Consequently, those living in aged care homes may rely on carers to prompt the physician to realize possible adverse drug events. This is particularly the case for anticholinergic side effects, which are among the most common drug-related problems experienced by elderly people living in nursing homes.[4, 5] According to the Beer et al criteria[6] aimed at identifying drugs deemed inappropriate for use in the elderly (aged ≥65 years), drugs with anticholinergic properties are frequently regarded as examples of inappropriate medications to prescribe because they constitute an increased risk for many

adverse drug effects, such as dry mouth, constipation, urinary retention, visual impairment, falls, confusion, drowsiness, delirium and cognitive decline.[7] There are many common anticholinergic side effects which may contribute to significant clinical problems. For instance, dry mouth can lead to speech difficulties, dental decay or trouble with dentures.[2, 8] Chewing and swallowing may become painful and can result in refusing of solid food. Pupillary dilation and the inability to accommodate will affect near vision, thereby increasing the risk of accidents, including falls and may worsen narrow angle glaucoma in predisposed patients. In the case of constipation, anticholinergic effect may lead to stomatitis, paralytic ileus or faecal impaction.[2, 8] Drug-induced increases in heart rate may precipitate angina symptoms and inhibition of sweating may cause life-threatening hyperthermia. Urinary retention can cause urinary tract infection, a common cause of delirium. Men with benign prostatic hypertrophy are at high increased risk of acute urinary retention from an anticholinergic side effect.[2, 8]

Anticholinergic medications are the most common cause of drug-induced delirium. In patients with dementia, anticholinergic drugs can inhibit cognitive performance and compromise the beneficial effect of cholinergic enhancers used to treat cognitive impairment.[9, 10] Additionally, polypharmacy and the concurrent chronic use of multiple drugs are a reality for older patients.[11] Thus, anticholinergic adverse effects may result from the cumulative anticholinergic burden of multiple drugs. Consequently, the combination of drugs can contribute clinically important adverse drug reactions, even if the individual drugs do not cause obvious side effects.[12]

A number of studies have reported on the common use of anticholinergic medications in elderly people. Blazer et al[2] reported that during one year, nearly 60% of aged care facility residents had received drugs with anticholinergic activity, compared with 23% of elderly people living in the community. The Established Population of Epidemiologic Studies of the elderly study, a US prospective cohort study,

showed that chlorpheniramine and diphenhydramine were among the 10 most commonly identified inappropriate drugs used in elderly patients.[13] A prospective cohort study in 532 patients with intact cognitive function conducted in the primary care clinics at the Veterans Affairs Medical Center (VAMC), Iowa City, demonstrated that 27.1% of patients used at least one medication with anticholinergic action.[14] In a longitudinal study in 9294 community-based elderly patients in France[15], 6.4% of patients used drugs with anticholinergic properties. In a retrospective cohort study involving 765,423 elderly patients covered by a pharmaceutical benefit manager and who filed ≥ 1 prescription drug claim in 1999 in US[16], amitriptyline and doxepin were reported to account for almost one quarter of all inappropriate drugs prescribed.

In addition, there are several studies that demonstrated the association between the use of anticholinergic drugs (anticholinergic load) and anticholinergic side effects. A prospective cohort study in 364 elderly patients in Italy[17] found that anticholinergic drug use was associated with impaired physical performance and muscle strength, irrespective of potential confounders and that this association correlated with the increasing number of anticholinergic drugs used. Additionally, a number of other studies have reported the association of anticholinergic drug use with cognitive impairment.[12, 18-23] A retrospective, medical record review at two urban tertiary care teaching hospitals, found that the most common side-effects from anticholinergic medications were decreased secretions, tachycardia, confusion and drowsiness. [24]

To our knowledge, few studies have investigated the association between anticholinergic load and overall anticholinergic side-effects. Therefore, identifying the association of anticholinergic load and anticholinergic drug-related problems could contribute to the better understanding, assessment, prevention and management of anticholinergic side effects in elderly people. This study was therefore

undertaken to quantify the association between the anticholinergic load and medication-related problems amongst residents of aged care homes.

Methods

SETTING

A retrospective cohort study was conducted at three aged care homes in the Perth metropolitan area, Western Australia. It was undertaken as a quality use of medicines (QUM) activity as part of the residents' annual medication management reviews (MMR), which are undertaken by an accredited pharmacist and funded by the Australian Government.

PARTICIPANTS

Participants in the study were aged care home residents aged over 65 years old. The participants were recruited through the medication management review program conducted in their aged care homes as part of standard care. All residents in aged care homes in Australia are entitled to an annual medication management review. As part of the medication management review process, the review pharmacists are required to undertake a range of quality use of medicines (QUM) activities and this study was undertaken as one of these activities. Aged care home residents at the time of their admission are required to provide written consent for medication management reviews to be undertaken. Therefore, individual patient consent for the study was not required. This study was approved by the Curtin University of Technology Human Research Ethics Committee and Ethics Committees of the aged care homes.

DATA COLLECTION

All study data were collected by the primary researcher via patient interviews and review of patients' medical records. The data was collected using a standardized data collection form and included patient demographics, current and past medical conditions (co-morbidities), medication history, in particular the use of drugs with anticholinergic activity, and the presence of specific medication-related problems, namely cognitive impairment (as determined by the Mini Mental State Examination score), high blood pressure and the presence of other potential anticholinergic side effects. Patient interviews were carried out to determine the presence of symptoms consistent with anticholinergic adverse effects.

Anticholinergic drugs were categorized into two groups; anticholinergic drugs and drugs with anticholinergic effects. The lists of anticholinergic medications used in this study are adapted from several studies.[5, 12, 18, 19, 22, 24-28] Cognitive performance was assessed using the Mini Mental State Examination.[29] The Mini Mental State Examination score is used to ascertain the severity of the patient's cognitive impairment by assessing orientation, registration, attention, calculation, recall, and praxis. Possible scores range from 0 to 30, with lower scores representing greater cognitive impairment.

The following five anticholinergic symptoms modified from Jose Ness et al[14] were used as the anticholinergic side effects; dry mouth, dry eyes, blurred vision, constipation and urinary hesitancy. The presence of these side effects was evaluated based on the patient's past medical history, use of medications potentially used to treat anticholinergic symptoms including artificial tears, stool softeners, laxatives, alpha-blockers, finasteride and saw palmetto; and findings from the patient interviews.

The anticholinergic load was derived from the total number of anticholinergic medications taken by the patient. The prevalence of cognitive impairment, hypertension and anticholinergic adverse events was evaluated based on the patient's anticholinergic load taking into consideration any co-morbidities.

STATISTICAL ANALYSIS

Descriptive statistics were complied in the sample according to age, gender, co-morbidities, the use and the number of medications with anticholinergic properties (anticholinergic load), anticholinergic side effects, and the Mini Mental State Examination scores. The association between anticholinergic load and cognitive impairment (the Mini Mental State Examination scores) was assessed using stepwise multiple regression analysis adjusted for all related co-morbidities. To assess the extent to which the presence of peripheral anticholinergic side effects was related to the anticholinergic load, a multiple logistic regression model was created to predict such a relationship taking into account the anticholinergic load and all identified co-morbidities related to each anticholinergic side effect. A p value ≤ 0.05 was considered statistically significant. All analyses were conducted using SPSS program version 15.0.

Results

A total of 182 patients' medical records were reviewed for the study. Of these, seven patients were excluded as they were found to be less than 65 years old. Therefore, 175 patients' data were included in the data analysis. For the cognitive function, data on the Mini Mental State Examination scores was obtained from 161 patients; in 12 of the remaining 14 patients Mini Mental State Examination was not able to be performed due to severe cognitive impairment and, whilst the other two patients declined to

be tested. These 14 patients consisted of three males and 11 females who had a mean (SD) anticholinergic load 3.2 (1.8).

The distribution of age, sex, marital status, the use and number of anticholinergic medications, the Mini Mental State Examination scores, anticholinergic side effects, and co-morbidities are summarized in Table 1. The mean age was 87.0 (8.0) years and 71.4% of the subjects were women. Of the 175 patients, 89.6% were receiving at least one anticholinergic medication; with the mean number of medications being of 2.9 (1.9). The mean Mini Mental State Examination score of the 161 evaluable patients was 20.2 (7.0). The three most common potential anticholinergic side effects identified were hypertension (66.3%), constipation (63.4%) and blurred vision (40.0%). The most frequently prescribed medications with anticholinergic activity were temazepam (35.4%), frusemide (31.4%) and loperamide (14.3%). The most common co-morbidities were hypertension (66.3%), dementia (64.6%) and psychological/behavioral disorders (58.3%).

The association between the anticholinergic load (the number of anticholinergic medication used) and cognitive impairment was assessed using the stepwise multiple logistic regression (Table 2) after adjusting for age and the following co-morbidities: urinary tract infection, hypothyroidism, renal failure, thiamine deficiency, vitamin B12 deficiency, diabetes mellitus, dementia, psychotic disorders and Korsakoff's syndrome. Among all co-morbidities, only dementia (p=0.000) and psychotic disorders (p=0.021) were included in the regression model as they had a significant negative impact on the Mini Mental State Examination scores. There was an inverse correlation between anticholinergic load and Mini Mental State Examination scores but this was not statistically significant (beta = -0.114, p=0.142) after adjusting for these co-morbidities.

Table 3 presents the factors significantly associated with each of the targeted anticholinergic side effects. The effect of age and the various co-morbidities (diabetes mellitus, chronic renal failure, ischaemic heart

disease, hypercholesterolemia and hypothyroidism) and anticholinergic load on hypertension was assessed using the multiple logistic regression. From this analysis, hypercholesterolemia (p=0.005) and the anticholinergic load (p=0.000) were the only variables that had a significant impact on increasing the likelihood of patients experiencing hypertension. Each increase in the number of anticholinergic medications prescribed was associated with a 1.53-fold increase in the likelihood of hypertension (Adjusted Odds Ratio [AOR] = 1.53, 95% CI: 1.24-1.88, p= 0.000).

For dry mouth, the related factors included in the analysis were diabetes mellitus, anaemia, dementia, stroke, psychological disorders, postmenopausal status and age. After adjusting for all these factors, only the anticholinergic load demonstrated a significant impact on the likelihood on dry mouth. The increase in the number of anticholinergic medications accounted for an increased risk in the presence of dry mouth. (AOR = 1.38, 95%CI: 1.16-1.65, p= 0.000).

Similar to dry mouth, after adjusting other contributing factors (postmenopausal status, diabetes mellitus, stroke, asthma, glaucoma and age), only the anticholinergic load had a positive association with dry eyes. For each increase in the number of anticholinergic medications received there was an associated 1.30-fold increase in the likelihood of dry eyes (AOR = 1.30, 95%CI: 1.08-1.56, p= 0.007).

A multiple logistic regression analysis failed to show the anticholinergic load to be a predictive factor for blurred vision (p=0.084). After adjusting all related co-morbidities (macular degeneration, diabetes mellitus, cataract, stroke and glaucoma) and age, the number of anticholinergic medications did not have a significant impact on blurred vision, whereas, the presence of glaucoma (p= 0.000) and macular degeneration (p=0.005) increased the likelihood of blurred vision significantly. The anticholinergic load did

not have an impact on likelihood of patients suffering from glaucoma after adjusting for age, hypertension, diabetes mellitus and the use of corticosteroids (p = 0.702).

In terms of constipation, after adjustment for other possible causes of constipation including hypothyroidism, diabetes mellitus, psychological disorders, stroke and age, the only significant predictors of constipation were the anticholinergic load (p=0.031) and psychological disorders (p=0.025). For each increase in the number of anticholinergic medications received there was an associated 1.24-fold increase in the likelihood of constipation (AOR 1.2495%CI: 1.02-1.50, p= 0.031).

Lastly, urinary hesitancy was affected by the presence of benign prostatic hyperplasia (p=0.020) prostate cancer (p=0.045) anticholinergic load (p=0.050) after adjustment of all possible risk factors (benign prostatic hyperplasia, prostate cancer, diabetes mellitus, chronic renal failure, urinary incontinence, recurrent urinary tract infection and age). For each increase in the number of anticholinergic medications received there was an associated 1.21-fold increase in the likelihood of urinary hesitancy (AOR = 1.21. 95% CI: 1.00-1.45, p= 0.050).

Discussion

The results of this study demonstrated that the anticholinergic load measured by the number of anticholinergic drugs received was significantly associated with the presence of all peripheral anticholinergic side effects with the exception of blurred vision, suggesting that these side effects are clinically significant. This association was not attributable to co-morbidities or age. In the case of blurred

vision, its occurrence was correlated with glaucoma and macular degeneration, but not anticholinergic load. Given that anticholinergic agents should be used with caution in patients with glaucoma a sub-analysis was undertaken to determine if there was a relationship between anticholinergic load and glaucoma, and hence anticholinergic load may be secondary contributor to blurred vision. This was not found to be the case, which validated the initial finding that anticholinergic load was not associated with blurred vision.

Whilst anticholinergic load was found to be inversely correlated with decline in the Mini Mental State Examination scores, the association was not statistically significant (p=0.142). The lack of a significant association between the anticholinerigic load and the Mini Mental State Examination score decline is of particular interest because several previous experimental and epidemiological studies indicated that the use of medications with anticholinergic activity were associated with changes on several measures of cognitive function (including the Mini Mental State Examination).[12, 19-23, 30-34] Several studies have also shown that the use of anticholinergic drugs was a common risk factor for delirium.[9, 18, 28, 35-38] One study showed that even a low anticholinergic serum level can cause mild but measurable cognitive impairment in the presurgical elderly[39] and memory deficit in geriatric depressed subjects. Mulsant et al[20] measured serum anticholinergic activity in a sample of 201 elderly subjects living in the community and examined the relationship between serum anticholinergic activity and cognitive performance. They found that subjects with serum anticholinergic activity at or above the sample's 90th percentile point were significantly more likely than subjects with undetectable serum anticholinergic activity to show a low Mini Mental State Examination score. However, all the studies mentioned above used serum anticholinergic activity as the anticholinergic load. Serum anticholinergic activity, despite a number of limitations, is still considered the current gold standard in quantifying the anticholinergic burden.[40]

The result of this study, that is the lack of a negative effect of anticholinergic load on Mini Mental State Examination scores, is however supported by several other studies. Remillard et al[41] reported that there was no association between serum anticholinergic activity and the Mini Mental State Examination score decline and Audrey-verbal learning test in a small group of subjects. Tracy et al[42] examined the anticholinergic burden imposed by clozapine and risperidone, and found that the Mini Mental State Examination scores were not related to the anticholinergic level, although the anticholinergic levels were significantly higher for clozapine group than risperidone group ($p<0.001$). Seifert et al[43] also reported that no statistically significant correlation could be found between the presence of confusion and the amount of anticholinergic administered. Again, these two studies used a small sample size and focused on antidepressants and antipsychotics only. Another study revealed a weak association between anticholinergic burden with physical function and cognition when the anticholinergic burden was calculated using the number of anticholinergic drugs rather than the standardized dose of the drug and principle of maximum effect (dose and frequency of use).[34]

The finding of an association between the use of anticholinergic drugs and peripheral anticholinergic side effects but not central anticholinergic side effects could represent a real difference in the sensitivity of central and peripheral nervous system or could result from the heterogenicity of subject population.[44] Furthermore, the more pronounced association between the anticholinergic load and peripheral anticholinergic side effects than central anticholinergic side effects may be due to the fact that peripheral side effects are more physical than central side effects, and therefore might be easier to diagnose and more sensitive to manifest according to the anticholinergic load.[45]

In terms of peripheral side effects, the results were consistent to several studies. Monane et al[46] measured the relationship between the use of anticholinergic drugs and bowel dysfunction in nursing

home patients and found a strong association in institutionalized elderly between the use of specific anticholinergic medications and constipation as reflected in the increased use of laxatives. The result of dry mouth and the anticholinergic load was congruent with Thomson et al's[47] study showing the higher prevalence of xerostomia in patients taking anticholinergic medications.

In a recent study by Rudolph et al[48], the Anticholinergic Risk Scale, a ranked categorical list of commonly prescribed medications with anticholinergic potential was developed. The study then evaluated Anticholinergic Risk Scale scores as the risk factor of anticholinergic adverse effects in two cohorts of patients (a geriatric evaluation and management (GEM) cohort and in primary care cohort). Higher Anticholinergic Risk Scale scores were linked to an increased risk for central anticholinergic adverse effects in GEM group and peripheral anticholinergic side effects in both groups.

Another interesting finding of this study was the common use drugs with anticholinergic activity amongst residents of aged-care homes (89.6%) which is consistent with the findings of previously published studies.[13-16] This finding supports the growing concern about the prescribing of drugs with anticholinergic activity deemed as an inappropriate in this age group according to the Beer et al criteria.[6] Concerning was the fact that the majority of medications with anticholinergic activity being consumed by the patients in this study were available only on prescription. Therefore, it was assumed a physician prescribed the medications thereby suggesting the need of education program for prescribers aimed at producing a substantial reduction in the use of these medications.[49] The high frequency of benzodiazepine use, in this case, temazepam, can increase the risk of delirium and falls.[36] Therefore, healthcare providers should offer other options to such patients (i.e. nonphamacological) rather than prescribing the medication as the first choice.[50] Kay et al[12] suggested that prescribers should review patient's medical history, total anticholinergic burden and level of cognitive impairment prior to prescribing anticholinergic medications.

The study has a number of limitations. Firstly, the generalizability beyond the elderly living in aged-care facilities is limited. Secondly, the use of number of anticholinergic drugs as the anticholinergic load is an estimate. It is possible that the accuracy of the anticholinergic load could be further improved by using the more intensive methods like serum anticholinergic activity[40] or drug burden index[34] which accounted for the dose and frequency of use or the anticholinergic drug scale[40] which has been shown to relate to serum anticholinergic activity. In addition, it would have been useful if the duration of therapy could have been incorporated into the anticholinergic load, which would have allowed evaluation of the duration-response relationship between the use of anticholinergic drugs and overall side effects. However, accurate data on the duration of therapy was not available in this study. Nevertheless, the anticholinergic load calculated by the relatively straightforward method used in this study still demonstrated an effect on peripheral anticholinergic side effects that was independent of the patients' co-morbidities. Thirdly, despite the use of information from several published literature sources, the identification of all possible medications with anticholinergic activity was not possible. This deficiency may have lead to the underestimation of the anticholinergic load. Fourthly, the use of the Mini Mental State Examination as the measurement of cognitive performance may not able to detect mild or transient impairment. This test was designed primarily to establish the sort of marked cognitive decline that accounts for frank delirium or dementia.[29] However, the use of logistic regression analysis in which adjustment for all related co-morbidities was undertaken enhances the confidence with which the relationship between the anticholinergic load and anticholinergic side effects can be reported.

Conclusions

We have established an association between the anticholinergic load, as defined by the number of anticholinergic drugs a patient is taking, and occurrence of peripheral anticholinergic side effects with the exception of blurred vision amongst residents of age-care home. These results highlight the need for prescribers and other health care providers to aware of wide range of medications with anticholinergic activity, and the need to assess anticholinergic load when elderly patients develop common problems such as hypertension, constipation and dry eyes. However, further studies involving larger numbers of elderly subjects are required to verify whether the number of medications with anticholinergic activity which a person is receiving is a sufficiently sensitive indicator of anticholinergic load.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

Associate Professor Jeff Hughes developed the research question and research methodology. Ms Jiraporn Puangsombat undertook the research as part of the requirements for her Master of Clinical Pharmacy Degree. Associate Professor Jeff Hughes and Adjunct Associate Professor Malcolm Roberts co-supervised her research, and assisted in the production and review of the research manuscript.

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Tables

Table 1. Baseline demographic and clinical characteristic of study participants (N = 175)

Characteristic	Number of Patients	Value
Age (years)		
Mean (SD)	175	87.0 (8.0)
Median (range)	176	89.0 (65-103)
Gender		
Male	50	28.6%
Female	125	71.4%
Anticholinergic medication use		
No	20	11.4
Yes	155	89.6
No. of anticholinergic medications		
Mean (SD)	175	2.9 (1.9)
Median (range)	175	3.0 (0-8)
Level of anticholinergic medication use (no. of medications prescribed)		
0-3	115	65.8%
4-6	54	30.8%
>6	6	3.4%
MMSE scores		
Mean (SD)	161	20.2 (7.0)
Median (range)	161	21.0 (1-30)

No. of anticholinergic side effects		
Mean (SD)	175	2.5 (1.4)
Median (range)	175	2.0 (0-6)
Hypertension	116	66.3%
Dry mouth	55	31.4%
Dry eye	40	22.9%
Blurred vision	70	40.0%
Constipation	111	63.4%
Urinary hesitancy	45	25.7%
Most common anticholinergic medications prescribed		
Temazepam	62	35.4%
Frusemide	55	31.4%
Loperamide	25	14.3%
Metoprolol	24	13.7%
Paracetamol/codeine	21	12%
Digoxin	17	9.7%
Oxazepam	17	9.7%
Most common co-morbidities		
Hypertension	116	66.3%
Dementia	113	64.6%
Psychological/behavioral disorder	102	58.3%
Urinary Incontinence	78	44.6%
Osteoarthritis	76	43.4%

Abbreviation: MMSE, Mini-Mental State Examination

Table 2. Stepwise multiple logistic regression analysis of variables associated with cognitive impairment (MMSE scores)

	Standardized coefficients (β)	p value
Dementia	-.440	0.000
Psychotic disorder/behavioral disorder	-.178	0.021
Anticholinergic load	-.114	0.142

Table 3. Multiple logistic regression analysis of variables associated with anticholinergic side effects

	AOR*	95.0% CI	p value
Hypertension			
Hypercholesterolemia	4.05	1.54-10.65	0.005
Anticholinergic load	1.53	1.24-1.88	0.000
Dry mouth			
Anticholinergic load	1.38	1.16-1.65	0.000
Dry eye			
Anticholinergic load	1.30	1.08-1.56	0.007
Blurred vision			
Macular degeneration	9.56	1.96-46.77	0.005
Glaucoma	40.86	5.28-316.16	0.000
Glaucoma			
Hypertension	5.24	1.17-23.39	0.030
Constipation			
Psychological disorder	2.18	1.10-4.30	0.025
Anticholinergic load	1.24	1.02-1.50	0.031
Urinary hesitancy			
Benign prostatic hyperplasia	14.76	1.53-142.52	0.020
Prostate cancer	10.40	1.06-102.12	0.045
Anticholinergic load	1.21	1.00-1.45	0.050

* AOR = Adjusted Odds Ratio