

2016-10-31

The effect of comprehensive geriatric assessment on anticholinergic exposure assessed by four ranked anticholinergic lists

Lampela Pasi

Elsevier BV

info:eu-repo/semantics/article

© Elsevier Inc.

CC BY-NC-ND <https://creativecommons.org/licenses/by-nc-nd/4.0/>

<http://dx.doi.org/10.1016/j.archger.2016.10.014>

<https://erepo.uef.fi/handle/123456789/250>

Downloaded from University of Eastern Finland's eRepository

Accepted Manuscript

Title: The effect of comprehensive geriatric assessment on anticholinergic exposure assessed by four ranked anticholinergic lists

Author: Pasi Lampela Heidi Taipale Piia Lavikainen Sirpa Hartikainen



PII: S0167-4943(16)30194-7
DOI: <http://dx.doi.org/doi:10.1016/j.archger.2016.10.014>
Reference: AGG 3403

To appear in: *Archives of Gerontology and Geriatrics*

Received date: 13-5-2016
Revised date: 30-8-2016
Accepted date: 29-10-2016

Please cite this article as: Lampela, Pasi, Taipale, Heidi, Lavikainen, Piia, Hartikainen, Sirpa, The effect of comprehensive geriatric assessment on anticholinergic exposure assessed by four ranked anticholinergic lists. *Archives of Gerontology and Geriatrics* <http://dx.doi.org/10.1016/j.archger.2016.10.014>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The effect of comprehensive geriatric assessment on anticholinergic exposure assessed by four ranked anticholinergic lists

Pasi Lampela¹, M.D., Ph.D., Pharm.D., **Heidi Taipale**^{1,2}, Pharm.D., **Piia Lavikainen**¹, Ph.D.,
Sirpa Hartikainen¹, M.D., Ph.D.

¹ Kuopio Research Centre of Geriatric Care, School of Pharmacy, University of Eastern Finland

² Research Centre for Comparative Effectiveness and Patient Safety (RECEPS), University of Eastern Finland

Corresponding author. Dr. Pasi Lampela

Kuopio Research Centre of Geriatric Care

School of Pharmacy

University of Eastern Finland

PO BOX FIN-1627

70211 KUOPIO, FINLAND

Fax: +358 17 162424

Email: Pasi.Lampela@uef.fi

Running head: CGA and anticholinergic exposure

Highlights: Comprehensive geriatric assessment did not decrease anticholinergic exposure.

However, improvements towards more appropriate use of anticholinergics were observed especially in the intervention group.

Selection of anticholinergic list may affect the results.

ABSTRACT

Background: Older people often use multiple drugs, and some of them have anticholinergic activity. Anticholinergic drugs may cause adverse reactions, and therefore their use should be limited. To identify anticholinergic load, several ranked lists with different drugs and scoring systems have been developed and used widely in research. We investigated, if a comprehensive geriatric assessment (CGA) decreased the anticholinergic drug score in a 4-year period. We used four different anticholinergic ranked lists to determine the anticholinergic score and to describe how the results differ depending on the list used.

Methods: We analyzed data from population-based intervention study, in which a random sample of 1000 persons aged ≥ 75 years were randomized to either an intervention group or a control group. Those in the intervention group underwent CGA including medication assessment annually between 2004-2007. Current medication use was assessed annually. The anticholinergic load was calculated by using four ranked lists of anticholinergic drugs (Boustani's, Carnahan's, Chew's and Rudolph's) for each person and for each year.

Results: CGA had no statistically significant effect on anticholinergic exposure during the 4-year follow-up, but improvements towards more appropriate medication use were observed especially in the intervention group. However, age, gender and functional comorbidity index were associated to higher anticholinergic exposure, depending on the list used.

Conclusions: Repeated CGAs may result as more appropriate anticholinergic medication use. The selection of the list may affect the results and therefore the selection of the list is important.

Keywords: Anticholinergic drugs, Comprehensive geriatric assessment, Older people

1. INTRODUCTION

Older people use multiple drugs, and the proportion of those without any medication is only 2-3 % (Barat et al. 2000, Jyrkkä et al. 2006). In addition, older people also are vulnerable to adverse drug reactions (Stegemann et al. 2010). Therefore, several criteria have been generated in an attempt to decrease the use of inappropriate drugs, such as explicit (criterion-based) Beers' criteria (American Geriatrics Society 2012 Beers Criteria Update Expert Panel 2012), and implicit (judgement-based) Medication Appropriateness Index (Hamilton et al. 2009).

Anticholinergic drugs are commonly used among older people as reported in previous studies, and the prevalence ranges from 27 % in community-dwelling to up to 80 % in nursing-home residents with dementia (Ness et al. 2006, Kolanowski et al. 2009). Anticholinergic adverse effects include constipation, urinary retention, dry mouth, confusion and attention deficit (Lieberman 2004), and anticholinergic drug use has been associated with e.g. falls (Rudolph et al. 2008) and cognitive impairment (Fox et al. 2011). Therefore, unnecessary use of anticholinergics should be avoided. However, defining an anticholinergic drug has been challenging, and therefore several different ranked lists have been compiled (e.g. Boustani et al 2008, Rudolph et al. 2008, Carnahan et al. 2006, Chew et al. 2008). Generally, these lists score different drugs based on their anticholinergic activity, and they are based on *in vitro* results, published literature, and/ or expert opinion. The anticholinergic lists have been found to associate with anticholinergic adverse effects (Rudolph et al. 2008) or serum anticholinergic activity (Carnahan et al. 2006). Previously published studies generally utilized only one anticholinergic list, and the selection of the list used varied depending on the author and study setting. However, as the lists differ from each other in terms of the drugs included, if the dose is taken into account and the scoring of anticholinergic potential, the results may also change depending on the list used (Lampela et al. 2013a, Mangoni et al. 2013). Therefore,

the selection of the anticholinergic list may affect the results on the reported prevalence of use as well as the associated outcomes.

Comprehensive geriatric assessment (CGA) is one of the cornerstones of modern geriatric care (Ellis et al. 2011). In this process, a multidisciplinary team aims to improve the health and quality of life of an older person focusing on physical health, functional status, psychological health and socioenvironmental parameters (Rubenstein 2004). It has been shown to be effective in helping older people to live safely and independently (Beswick et al. 2008).

Previous studies have focused on the effect of the intervention on anticholinergic exposure (i.e. before and shortly after the intervention) (Tay et al. 2014). In the present study, we studied the effect of CGA in real-life situation, where other health care professionals also may affect the result. We investigated if a comprehensive geriatric assessment has an impact on the anticholinergic load during 4-year follow-up. Instead of just selecting one list to be used, we chose to use four different lists of anticholinergic drugs to see, how the results may change depending on the list.

2. METHODS

2.1. Population

We investigated data derived from the Geriatric Multidisciplinary Strategy for the Good Care of the Elderly (GeMS) Study, which took place in Kuopio, Finland, during 2004-2007. This study has been previously described in detail (Lampela et al. 2010). In short, a random sample of 1000 persons aged ≥ 75 years was drawn from the inhabitants of the city of Kuopio, Finland. They were randomized using computer-generated numbers in control and intervention groups (each $n=500$), and persons in both groups were annually interviewed and examined by trained nurses. They paid

special attention to current drug use by not only asking the participants directly, but also by using medical records from the municipal health centre, home nursing service, local hospitals and Kuopio University Hospital. In addition, those in the intervention group underwent a CGA, which consisted of annual health status examinations including medication assessment by a physician (a trainee in geriatrics), as well as examinations by a dentist, physiotherapist and nutritionist, when necessary. Although the study physicians were trainees in geriatrics, they had been working as a general practitioner for at least 10 years with a lot of experience of older population. They had received training in adverse drug reactions, but they did not use any anticholinergic list when assessing medication. They also had weekly meetings with senior geriatrician (SH). Cognitive status was measured using the Mini-mental state examination. Those in the control group had access to regular health services. In this study, we used medication data from all persons that participated each year. Demographics of the study population is shown in Table 1, and flow chart of persons in the GeMS study in Figure 1.

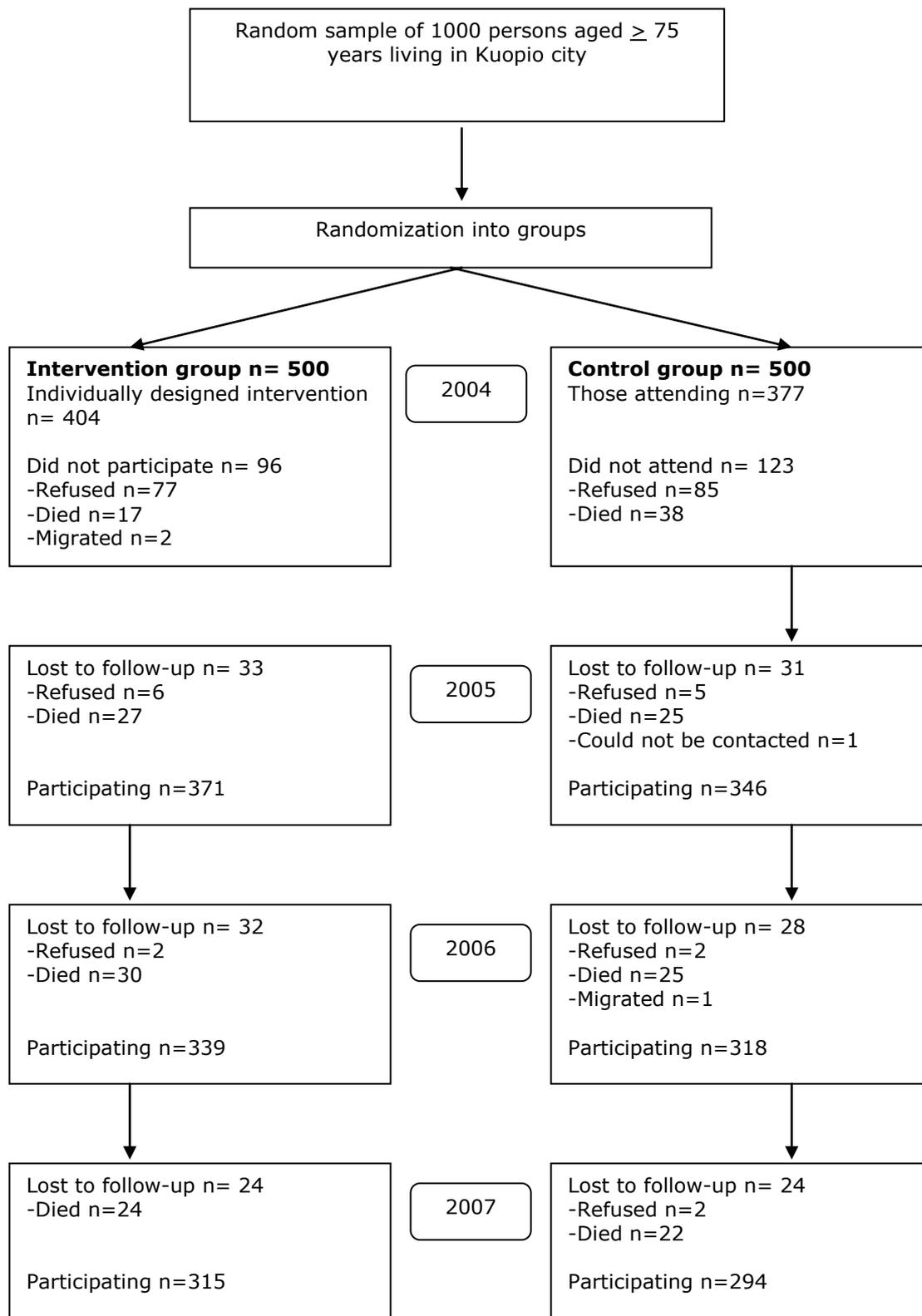
TABLE 1. Demographics of the study population.

Baseline year 2004	Intervention group			Control group			p-value†
	all	men	women	All	men	women	
N	404	116	288	377	117	260	
Age, mean (SD)	81.5 (4.9)	80.7 (4.5)	81.8 (5.0)	82.0 (5.0)	81.1 (4.8)	82.4 (5.1)	0.112
regular medicines, mean (SD)	5.1 (5.0)	4.7 (2.8)	5.3 (3.4)	5.1 (5.0)	4.3 (2.8)	5.5 (3.4)	0.992
As-needed medicines, mean (SD)	1.6 (1.6)	1.1 (1.4)	1.7 (1.6)	1.3 (1.4)	1.0 (1.3)	1.5 (1.5)	0.127
FCI, mean (SD)	2.4 (1.7)	2.5 (1.5)	2.4 (1.7)	2.6 (1.7)	2.4 (1.6)	2.7 (1.7)	0.217
Dementia (DSM-IV), n (%)	90 (22.2)	24 (20.7)	66 (22.9)	77 (20.4)	19 (16.2)	58 (22.3)	0.528
ADS score, mean (SD)	1.3 (1.8)	1.2 (1.4)	1.4 (1.9)	1.3 (1.7)	1.1 (1.3)	1.4 (1.9)	0.760
Chew score, mean (SD)	0.6 (1.0)	0.4 (0.8)	0.7 (1.1)	0.5 (0.9)	0.4 (0.7)	0.6 (1.0)	0.187
ARS score, mean (SD)	0.3 (0.8)	0.2 (0.7)	0.4 (1.0)	0.4 (0.9)	0.2 (0.6)	0.5 (1.1)	0.495
ACB score, mean (SD)	1.3 (1.6)	1.2 (1.4)	1.4 (1.7)	1.3 (1.5)	1.2 (1.4)	1.4 (1.5)	0.748

Year 2007	Intervention group			Control group			p-value†
	all	men	women	all	men	women	
N	315	88	227	294	91	203	
regular medicines, mean (SD)	5.8 (3.1)	5.2 (2.9)	6.0 (3.2)	5.8 (3.3)	5.3 (3.1)	6.1 (3.3)	0.966
As- needed medicines, mean (SD)	1.7 (1.4)	1.2 (1.2)	1.8 (1.5)	1.4 (1.3)	1.0 (1.2)	1.5 (1.4)	0.006
FCI, mean (SD)	3.0 (1.7)	3.1 (1.7)	3.0 (1.6)	2.6 (1.8)	2.4 (1.7)	2.7 (1.8)	0.003
Dementia (DSM-IV), n (%)	76 (24.1)	18 (20.5)	58 (25.6)	66 (22.4)	18 (19.8)	48 (23.6)	0.625
ADS score, mean (SD)	1.2 (1.3)	1.2 (1.2)	1.2 (1.4)	1.3 (1.5)	1.0 (1.1)	1.4 (1.6)	0.692
Chew score, mean (SD)	0.6 (0.9)	0.5 (0.7)	0.6 (0.9)	0.6 (1.0)	0.5 (0.8)	0.7 (1.1)	0.912
ARS score, mean (SD)	0.3 (0.8)	0.3 (0.7)	0.4 (0.9)	0.4 (0.8)	0.2 (0.5)	0.4 (0.9)	0.692
ACB score, mean (SD)	1.4 (1.6)	1.4 (1.5)	1.5 (1.6)	1.6 (1.7)	1.4 (1.5)	1.7 (1.7)	0.300

Abbreviations: ACB, Anticholinergic Cognitive Burden Scale; ADS, Anticholinergic Drug Scale; ARS, Anticholinergic Risk Scale; COPD, Chronic Obstructive Pulmonary Disease; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; FCI, Functional Comorbidity Index; SD, Standard Deviation.

†Between intervention and control groups. p-values were produced using Mann-Whitney U test for continuous variables, and Pearson Chi-Square test for categorical variables.

FIGURE 1. Flow chart of persons throughout the GeMS study.

2.2. Anticholinergic lists

We used four previously published lists about anticholinergic drugs (Boustani et al. 2008, Carnahan et al. 2006, Chew et al. 2008, Rudolph et al. 2008) to determine the anticholinergic load (i.e. the sum of scores of each anticholinergic drug in use for each person) of regularly used drugs. Rudolph's Anticholinergic Risk Scale (ARS) includes 49 anticholinergic drugs and it is based on the 500 most prescribed medications within the veterans (Rudolph et al. 2008). It ranks drugs from 1 to 3 based on their anticholinergic activity. Chew's list was based on anticholinergic activities (score from 0 to +++; score of 0/+ was classified as 0.5) of 107 drugs determined *in vitro* (Chew et al. 2008).

Carnahan's Anticholinergic Drug Scale (ADS) is the broadest (score from 0 to 3), including 536 drugs (117 of them having anticholinergic activity) (Carnahan et al. 2006). Doses of drugs are taken into account in the ADS, and our results were weighed based on the doses. These lists have some similarities, but there are also differences. E.g. only 25 drugs are included on all three lists, and 5 of these drugs have been classified consistently across these lists (Lampela et al. 2013a). In addition, we used Anticholinergic Cognitive Burden scale (ACB) which includes 88 drugs (score from 1 to 3). Majority of drugs listed in ACB are also included in ADS or ARS, but there are also differences between the scales (Boustani et al. 2008). We calculated the anticholinergic score for each person every year of the study based on annual interviews.

2.3. Statistics

We used generalized linear mixed models (GLMMs) to estimate the impact of intervention on the change in anticholinergic sum score over time. Based on graphical exploration of the data and Kolmogorov-Smirnov tests of normality, we assumed Poisson distribution with log link function and a model with random intercept for ACB, ADS and ARS. As the sum of Chew's score could be non-integer, we assumed normal distribution with an identity link and a model with a random intercept for Chew's list. Thus, the model reduced to a linear mixed model. In addition to the

intervention status and time of measurement, all models were adjusted for age, gender, and a modified Functional Comorbidity Index (Tikkanen et al. 2012). For all the outcomes, we explored the effect of interaction between intervention and measurement time. However, the interaction effect was non-significant in all models and, thus, we decided to omit the term from the final models.

During the follow-up, 89 persons (22.0%) of the intervention group and 83 persons (22.0%) of the control group were lost to follow-up. By using GLMMs, analyzes were conducted using all the available data and missing at random mechanism was assumed for missing data. Statistical analyses were performed using SPSS 19.0 (SPSS Inc., USA).

2.4. Ethical approval

Written informed consent was obtained from all the participants or their carers or relatives. The study protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo as required by Finnish legislation (approval number 160/2002).

3. RESULTS

At the baseline, the proportion of persons using at least one anticholinergic drug was 60.1/62.9 % (for intervention and control groups, respectively) (ACB), 57.4/57.6 % (ADS), 15.8/17.5 % (ARS) and 44.1/38.5 % (Chew). The mean anticholinergic score of the whole population at baseline was higher when using ACB or ADS than by using Chew's list or ARS (Table 1).

According to GLMMs, intervention did not affect Chew's score or log of ACB, ADS or ARS after adjusting for age, gender, modified FCI and time of measurement (Table 2). However, increasing

age and modified FCI were associated with higher log ACB and log ADS scores. Mean Chew score was higher for women than for men and the score increased with increasing age and FCI. Lastly, gender and FCI were associated with log ARS score (Table 2).

TABLE 2. Estimated covariate effects on anticholinergic scores from generalized mixed models.

	ADS score [†]		Chew score [‡]		ARS score [†]		ACB score [†]	
	Coefficient (SE)	p-value	Coefficient (SE)	p-value	Coefficient (SE)	p-value	Coefficient (SE)	p-value
Intercept	-3.427 (0.606)	<0.001	-0.689 (0.512)	0.173	-2.948 (1.307)	0.024	-2.226 (0.638)	<0.001
Time of measurement								
2004	-0.050 (0.047)	0.285	-0.118 (0.032)	<0.001	-0.091 (0.099)	0.358	-0.219 (0.047)	<0.001
2005	-0.012 (0.046)	0.800	-0.073 (0.030)	0.015	-0.134 (0.089)	0.133	-0.110 (0.046)	0.017
2006	-0.001 (0.035)	0.970	-0.042 (0.024)	0.080	-0.077 (0.065)	0.236	-0.080 (0.047)	0.085
2007	0		0		0		0	
Group								
Control	0		0		0		0	
Intervention	0.059 (0.078)	0.455	0.043 (0.058)	0.458	-0.080 (0.160)	0.616	-0.029 (0.075)	0.704
Gender								
Male	-0.103 (0.088)	0.239	-0.200 (0.057)	<0.001	-0.522 (0.186)	0.005	-0.086 (0.084)	0.305
Female	0		0		0		0	

Age	0.030 (0.007)	<0.001	0.012 (0.006)	0.045	0.010 (0.016)	0.541	0.021 (0.008)	0.008
FCI score	0.334 (0.023)	<0.001	0.158 (0.020)	<0.001	0.181 (0.047)	<0.001	0.279 (0.022)	<0.001

Abbreviations: ACB, Anticholinergic Cognitive Burden Scale; ADS, Anticholinergic Drug Scale; ARS, Anticholinergic Risk Scale; FCI, Functional comorbidity index; SE, Standard Error.

† Generalized linear mixed model with Poisson distribution, log link function and a random intercept

‡ Generalized linear mixed model with normal distribution, identity link function and a random intercept

In general, the use of stronger anticholinergics (scored with at least 2 in any of the lists) was not common among the study persons. The use of amitriptyline decreased between 2004-07 in the intervention group, but increased in the control group (from 1.5% to 0.3% and from 2.7% to 4.1%, respectively). Change in the use of oxybutynin was from 2% to 1.6% in the intervention group and 1.9% to 0.3% in the control group, while use of tolterodine decreased in the intervention group but not in the control group (1.2% to 0.3% and 0.5% to 0.7%, respectively). On the other hand, use of hydroxyzine increased from 0% to 0.6% in the intervention group while its use decreased in the control group (1.1% to 0.3%). Use of carbamazepine decreased in the intervention group (0.5% to 0%) but increased from 0.3% to 1.0% in the control group. The use of weaker class 1 anticholinergic, mirtazapine, increased in the intervention group from 5.4% to 10.2%, but only from 4.2% to 6.4% in the control group.

At baseline, the percentage of men using a specific drug classified as stronger anticholinergic was less than 1 % in both groups. In women, most frequently used drug classified as stronger anticholinergic in the intervention group was oxybutynin (2.4 %). In addition, thioridazine (1.7 %), combination of amitriptyline and chlordiazepoxide (1.4 %), tolterodine (1.4 %) and ranitidine (1.7 %) were used by more than 1 % of women in the intervention group. In the control group, amitriptyline and oxybutynin (both 2.3 %) as well as cetirizine and hydroxyzine (both 1.5 %) had prevalence higher than 1 %.

The share of stronger anticholinergics in use decreased from 2004 to 2007 when ADS, ARS or Chew's list was used but remained unchanged or increased when anticholinergic use was measured using ACB (Table 3). This resulted from quetiapine use, as its prevalence increased in both groups (from 1.7% to 5.7% and from 0.5% to 6.1% in intervention and control groups, respectively).

Quetiapine is classified as class 3 anticholinergic in ACB but as class 1 in ARS or Chew's list. ADS classified quetiapine as level 0.

TABLE 3. Distribution of anticholinergic drugs in use as measured with different ranked lists.

	Intervention group				Control group			
	2004		2007		2004		2007	
	n	%	n	%	n	%	n	%
ACB								
1	1556	91,7	359	92,1	1489	90,1	341	88,6
2	6	0,4	0	0,0	12	0,7	4	1,0
3	135	8,0	31	7,9	151	9,1	40	10,4
Total	1697		390		1652		385	
ADS								
1	1517	94,6	342	96,6	1388	94,0	323	95,3
2	18	1,1	2	0,6	22	1,5	4	1,2
≥3	69	4,3	10	2,8	66	4,5	12	3,5
Total	1604		354		1476		339	
ARS								
1	268	77,0	76	86,4	205	66,8	54	73,0
2	35	10,1	4	4,5	48	15,6	11	14,9
3	45	12,9	8	9,1	54	17,6	9	12,2
Total	348		88		307		74	
Chew								
0,5	686	64,4	163	64,9	569	62,7	138	61,3
1	303	28,4	77	30,7	243	26,8	67	29,8
2	32	3,0	7	2,8	34	3,7	6	2,7
3	45	4,2	4	1,6	61	6,7	14	6,2
Total	1066		251		907		225	

ACB, Anticholinergic Cognitive Burden Scale; ADS, Anticholinergic Drug Scale; ARS,

Anticholinergic Risk Scale

There was no difference between groups in MMSE score at baseline (mean 24.5 (standard deviation (SD) 7.1) and 24.8 (SD 6.4) for intervention and control groups, respectively) or at 2007 (mean 23.7 (SD 7.9), and 23.7 (SD 7.9) for intervention and control groups, respectively).

4. DISCUSSION

The main finding of this study was that CGA does not decrease the anticholinergic exposure. On the other hand, improvements towards more appropriate medication use were observed especially in the intervention group, as the use of some stronger anticholinergics, e.g. amitriptyline, decreased.

However, these results were not statistically significant as use of stronger anticholinergics was infrequent at the baseline. As anticholinergic drug use is known to be associated with various adverse drug effects, unnecessary use of anticholinergics should be avoided. According to previous studies, anticholinergic drugs may increase the risk of delirium and mortality (Han et al., 2001, Panula et al. 2009, Fox et al. 2011), although there are also studies which found no effect (Kumpula et al. 2011).

Compared to previous studies, the proportion of persons using at least one drug with anticholinergic properties (using ADS) was similar in our study than previously reported (Narayan et al. 2013). In addition, ADS and ARS scores reported by Mangoni et al. (2013) were at the same scale than ours.

CGA has previously been shown to improve drug therapy, mainly due to new diagnoses and reduction of under-treatment (Tulner et al. 2010). In addition, a consultant-led medication review has shown to reduce anticholinergic drug exposure as measured with ARS in acute geriatric assessment ward (Tay et al. 2014). In our study, the CGA did not lead to decrease in anticholinergic burden although there was a trend of decreased use of stronger anticholinergics, with an increase of milder anticholinergics such as mirtazapine. This difference is likely to be caused by the difference of the settings of these two studies; Tay et al. (2014) analysed the change in anticholinergic score before and shortly after the intervention, while we focused on the long-term changes in community-dwelling population. In the GeMS Study, the study physician had had training in adverse drug reactions, but anticholinergic drugs were only one of the drug groups to focus on. No ranked

anticholinergic lists were used during the CGA. The aim of the present study was to analyse, if the anticholinergic burden would be decreased during the CGA that is more comprehensive than just a drug assessment. However, the use of strong anticholinergics was rather low in our study population, and this may be one explanation for the result. We have previously reported, that the CGA has improved drug therapy and health experience in a one-year follow-up (Lampela et al. 2010), mobility (Lihavainen et al. 2012) and it has decreased the prevalence of orthostatic hypotension (Lampela et al. 2013b). Despite the fact that the CGA did not decrease anticholinergic burden in our population, the CGA still resulted in an improvement in the well-being of the patients (Lampela et al. 2010, Lampela et al. 2012, Lampela et al. 2013b). This is most likely due to the multi-disciplinary nature of the CGA that focuses on several aspects on the patients' condition. MMSE results did not differ between intervention and control groups either at baseline or at the end of the study. On the other hand, MMSE is a crude screening tool to measure global cognitive function, and thus its usefulness to detect mild impairment (such as potential anticholinergic effect) is limited (Lampela et al. 2015).

Among all of the drugs that are in clinical use, several drugs possess pronounced anticholinergic effects (e.g. oxybutynin, benztropine, tiotropium). However, apart from these "strong" anticholinergics, anticholinergic properties of many other drugs are not known. Therefore, several different lists exist, which rank drugs based on their anticholinergic properties. There is heterogeneity in the methods by which the lists have been built. They may be based on *in vitro* results (Chew et al. 2008), expert opinion (Carnahan et al. 2006), literature review (Han et al. 2008) or their combinations (Ancelin et al. 2006, Boustani et al. 2008, Minzenberg et al. 2004, Rudolph et al. 2008). In addition, the lists have been developed in different countries and populations with different prescribing practices and different drugs on the market. Therefore, it is no surprise that some drugs are listed in some lists but not in others. However, the fact that the same drug may be

classified differently by its level of anticholinergicity (e.g. perphenazine; class 0 by *in vitro* analyses (Chew et al. 2008), class 3 by combination of literature review and expert opinion (Rudolph et al. 2008) or quetiapine; class 0 by ADS, class 1 by ARS and Chew and class 3 by ACB), is more confusing. Obviously, this is a result from different methods when building the lists, but it limits the usefulness of the lists when calculating the anticholinergic load. In addition, similar effects can arise also via non-cholinergic routes (e.g. benzodiazepines may cause confusion and attention deficits). It raises the question if the adverse effects considered as anticholinergic actually are the result of antimuscarinic effect.

We performed the analyses using four lists to see, how the selection of the list affects the results. Three (ADS, ARS, Chew's) of the lists in use were based on our previous study (Lampela et al. 2013a), in which we found an association between the ranked lists and clinically significant anticholinergic adverse effects. In that study we found some differences in the results based on these lists and reported, that ADS and Chew's list were better associated with anticholinergic adverse effects than ARS. Lately, many studies have compared different anticholinergic lists to each other (e.g. Mangoni et al. 2013, Narayan et al. 2013, Pont et al. 2015). In general, the agreement between the lists is poor. In our study, anticholinergic exposure was highest when using ACB and ADS, which is in agreement with previous results (Pont et al 2015). In contrast to other lists, the share of class 3 anticholinergics remained the same or increased when ACB was used. This was mainly due to different classification of quetiapine between the lists. Use of quetiapine increased in both intervention and control groups. However, whether quetiapine is anticholinergic or not does not remove the fact that severe adverse events are associated with antipsychotic use (including quetiapine) and its use should be limited to patients with psychosis or behavioural symptoms in patients with dementia. All of the four lists gave similar results in statistical analysis, although there were some differences between the lists when anticholinergic burden was measured

against age, gender or FCI. However, these changes did not affect the overall result. It is difficult to definitely rank any list as superior to others, as different lists may result in statistically significant results depending on the study design. This should be considered when designing a study about anticholinergic load.

Is it necessary to have several different lists about anticholinergics globally? Instead of several lists in use and various results published based on those, would it be possible to create one list, that would be universally standardized? As aging is a heterogenous and individual process (Cho et al. 2011), there is plenty of variation between older individuals. It is likely, that inter-individual heterogeneity overpowers the possible effect of nationality in older persons' responses to anticholinergic drugs. Therefore, it is unlikely that a national anticholinergic list would be a more valid tool, than a comprehensive and internationally representative scoring system for anticholinergic drugs. In principle, the list should be based on basic pharmacology (ie. the drug should antagonize the action of a muscarinic receptor in order to be classified as anticholinergic drug). However, there are several challenges. Characteristics of a drug (e.g. lipid solubility, possible effects to other receptors than muscarinic as well), dose and administration route of a drug should be taken into account, as well as clinical conditions and other medications in use. E.g. penetration through blood-brain-barrier is required for central adverse effects to occur, and the permeability of blood-brain-barrier is affected by several medical conditions and aging. In addition, the use of several anticholinergic drugs may have synergistic impact on an individual's risk of anticholinergic adverse effects. These matters should be taken into account when considering validation of the list. Validation of the universal list should be conducted in representative and large sample of older persons and with valid measures of physical and cognitive functioning. In clinical practice, the scoring system for anticholinergic effects, describing the anticholinergic load of a patient may be

useful, although the scores should always be adapted according to the clinical condition of the patient.

The strength of our study is a relatively large number of randomly selected community-dwelling participants, as well as detailed data of clinical parameters and medication use with annual follow-ups. Medication use was thoroughly examined in the interviews and verified from the medical records and prescriptions. Our study has also limitations. Participants were residents of only one Finnish municipality but it is likely that they represent well older persons aged 75 years and older in Finland. Although medication use was assessed annually there may have been changes in drugs used or their doses between these interviews. In addition, although special attention was paid to determine actual drug use it is possible, that study participants may have under- or over-reported their medication use.

In conclusion, CGA did not affect the anticholinergic burden. The result was similar with four different anticholinergic lists. However, as several lists have been created, the selection of the list to use may affect the results. Therefore, one definitive and valid ranked list of anticholinergic drugs that could be generally used in all populations, would be useful.

ACKNOWLEDGEMENTS

The GeMS Study was supported by the Social Insurance Institution of Finland (data collection and analysis) and City of Kuopio (data collection). This study was supported by a grant from the Päivikki and Sakari Sohlberg Foundation (PLam). They have not affected the work in any way.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

REFERENCES

- American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American geriatrics society updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2012; 60: 616-631.
- Ancelin ML, Artero S, Portet F, et al. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *BMJ* 2006; 332: 455-459.
- Barat I, Andreasen F, Damsgaard EM. The consumption of drugs by 75-year-old individuals living in their own homes. *Eur J Clin Pharmacol* 2000; 56: 501-509.
- Beswick AD, Rees K, Dieppe P, et al. Complex interventions to improve physical function and maintain independent living in elderly people: A systematic review and meta-analysis. *Lancet* 2008; 371: 725-735.
- Boustani M, Campbell N, Munger S, et al. Impact of anticholinergics on the aging brain: a review and practical application. *Aging Health* 2008, 4: 311-320.
- Carnahan RM, Lund BC, Perry PJ, et al. The anticholinergic drug scale as a measure of drug-related anticholinergic burden: Associations with serum anticholinergic activity. *J Clin Pharmacol* 2006; 46: 1481-1486.
- Chew ML, Mulsant BH, Pollock BG, et al. Anticholinergic activity of 107 medications commonly used by older adults. *J Am Geriatr Soc* 2008; 56: 1333-1341.
- Cho S, Lau SW, Tandon V, et al. Geriatric drug evaluation: Where are we now and where should we be in the future? *Arch Intern Med* 2011; 171: 937-940. Ellis G, Whitehead MA, Robinson D,

O'Neill D, Langhorne P. Comprehensive geriatric assessment for older adults admitted to hospital: Meta-analysis of randomised controlled trials. *BMJ* 2011; 343: d6553.

Fox C, Richardson K, Maidment ID, et al. Anticholinergic medication use and cognitive impairment in the older population: The medical research council cognitive function and ageing study. *J Am Geriatr Soc* 2011; 59: 1477-1483.

Hamilton HJ, Gallagher PF, O'Mahony D. Inappropriate prescribing and adverse drug events in older people. *BMC Geriatr* 2009; 9: 5-2318-9-5.

Han L, McCusker J, Cole M, et al. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. *Arch Intern Med* 2001; 161: 1099-1105.

Han L, Agostini JV, Allore HG. Cumulative anticholinergic exposure is associated with poor memory and executive function in older men. *J Am Geriatr Soc* 2008; 56: 2203-2210.

Jyrkkä J, Vartiainen L, Hartikainen S, et al. Increasing use of medicines in elderly persons: A five-year follow-up of the kuopio 75+Study. *Eur J Clin Pharmacol* 2006; 62: 151-158.

Kolanowski A, Fick DM, Campbell J, et al. A preliminary study of anticholinergic burden and relationship to a quality of life indicator, engagement in activities, in nursing home residents with dementia. *J Am Med Dir Assoc* 2009; 10: 252-257.

Kumpula EK, Bell JS, Soini H, et al. Anticholinergic drug use and mortality among residents of long-term care facilities: A prospective cohort study. *J Clin Pharmacol* 2011; 51: 256-263.

Lampela P, Hartikainen S, Lavikainen P, et al. Effects of medication assessment as part of a comprehensive geriatric assessment on drug use over a 1-year period: A population-based intervention study. *Drugs Aging* 2010; 27: 507-521.

- Lampela P, Lavikainen P, Garcia-Horsman JA, et al. Anticholinergic drug use, serum anticholinergic activity, and adverse drug events among older people: A population-based study. *Drugs Aging* 2013a; 30: 321-330.
- Lampela P, Lavikainen P, Huupponen R, et al. Comprehensive geriatric assessment decreases prevalence of orthostatic hypotension in older persons. *Scand J Public Health* 2013b; 41: 351-358.
- Lampela P, Paajanen T, Hartikainen S, Huupponen R. Central anticholinergic adverse effects and their measurement. *Drugs Aging* 2015; 32: 963-974.
- Lieberman JA, 3rd. Managing anticholinergic side effects. *Prim Care Companion J Clin Psychiatry* 2004; 6(Suppl 2): 20-23.
- Lihavainen K, Sipilä S, Rantanen T, et al. Effects of comprehensive geriatric assessment and targeted intervention on mobility in persons aged 75 years and over: A randomized controlled trial. *Clin Rehabil* 2012; 26: 314-26.
- Mangoni AA, van Munster BC, Woodman RJ, et al. Measures of anticholinergic drug exposure, serum anticholinergic activity, and all-cause postdischarge mortality in older hospitalized patients with hip fractures. *Am J Geriatr Psychiatry* 2013; 21: 785-793.
- Minzenberg MJ, Poole JH, Benton C, et al. Association of anticholinergic load with impairment of complex attention and memory in schizophrenia. *Am J Psychiatry* 2004; 161: 116-124.
- Narayan SW, Hilmer SN, Horsburgh S, et al. Anticholinergic component of the drug burden index and the anticholinergic drug scale as measures of anticholinergic exposure in older people in New Zealand: A population-level study. *Drugs Aging* 2013; 30: 927-934.

Ness J, Hoth A, Barnett MJ, et al. Anticholinergic medications in community-dwelling older veterans: Prevalence of anticholinergic symptoms, symptom burden, and adverse drug events. *Am J Geriatr Pharmacother* 2006; 4: 42-51.

Panula J, Puustinen J, Jaatinen P, et al. Effects of potent anticholinergics, sedatives and antipsychotics on postoperative mortality in elderly patients with hip fracture: A retrospective, population-based study. *Drugs Aging* 2009; 26: 963-971.

Pont LG, Nielen JT, McLachlan AJ, et al. Measuring anticholinergic drug exposure in older community-dwelling Australian men: A comparison of four different measures. *Br J Clin Pharmacol* 2015; 80: 1169-75.

Rubenstein LZ. Joseph T. Freeman award lecture: Comprehensive geriatric assessment: From miracle to reality. *J Gerontol A Biol Sci Med Sci* 2004; 59: 473-477.

Rudolph JL, Salow MJ, Angelini MC, et al. The anticholinergic risk scale and anticholinergic adverse effects in older persons. *Arch Intern Med* 2008; 168: 508-513.

Stegemann S, Ecker F, Maio M, et al: Geriatric drug therapy: Neglecting the inevitable majority. *Ageing Res Rev* 2010; 9: 384-398.

Tay HS, Soiza RL, Mangoni AA. Minimizing anticholinergic drug prescribing in older hospitalized patients: a full audit cycle. *Ther Adv Drug Saf* 2014; 5: 121-128.

Tikkanen P, Nykänen I, Lönnroos E, et al. Physical activity at age of 20-64 years and mobility and muscle strength in old age: A community-based study. *J Gerontol A Biol Sci Med Sci* 2012; 67: 905-910.

Tulner LR, van Campen JP, Frankfort SV, et al. Changes in under-treatment after comprehensive geriatric assessment: An observational study. *Drugs Aging* 2010; 27: 831-843.