Drugs - Real World Outcomes (2015) 2:53–60
DOI 10.1007/s40801-015-0012-y

ORIGINAL RESEARCH ARTICLE

Use of Medicines with Anticholinergic and Sedative Effect Before and After Initiation of Anti-Dementia Medications

Svetla Gadzhanova · Elizabeth Roughead · Maxine Robinson

Published online: 12 February 2015

Abstract
Background People with dementia may be particularly sensitive to cognitive impairment induced by anticholinergic and sedative medicines.
Objective This study aimed to examine if utilisation of medicines with anticholinergic and sedative effects changed before and after initiation of anti-dementia therapy.
Methods A retrospective cohort study was conducted using Australian pharmacy claim data (Pharmaceutical Benefit Scheme). People with first (index) dispensing for a cholinesterase inhibitor or memantine between 1 January 2009 and 31 December 2010 who were aged 65 years or over at the time of initiation were included. The proportion who received sedatives or anticholinergics in the 6 months prior to and post initiation of anti-dementia therapy was determined.
Results The cohort included 24,110 patients, with over half aged 75−84 years. Overall, 30 % received any class of anticholinergic or sedative medicine for at least 1 month in the 6 months prior to initiation of anti-dementia agents, and 36 % post initiation. Some patients (6 %) ceased anticholinergics or sedatives post initiation even though they had them in the months prior. However, 12 % commenced therapy with anticholinergics or sedatives post anti-dementia therapy initiation even though they were naïve to them in the 6 months prior to therapy.
Conclusion Medicines with anticholinergic or sedative effects were commonly dispensed in one-third of people with dementia. Prescribers need to consider a review of patients on anticholinergic therapy with cholinesterase inhibitors as the effectiveness of the cholinesterase therapy may be compromised.

S. Gadzhanova (✉) · E. Roughead
Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia
e-mail: svetla.gadzhanova@unisa.edu.au

M. Robinson
Post Market Review Section, Pharmaceutical Evaluation Branch, Pharmaceutical Benefits Division, Department of Health, Canberra, Australia

Introduction

In 2011, there were 300,000 people with dementia in Australia, with the number expected to increase to approximately 900,000 by 2050 [1]. Dementia is a leading cause of death, and accounted for 6 % of all deaths in 2010 [1]. Alzheimer's disease (AD) is the most common form of dementia, accounting for between 50 and 75 % of all cases [1]. It is a progressive, degenerative illness affecting brain functions. Three cholinesterase inhibitors (CEIs) are subsidised under the Australian Pharmaceutical Benefits Scheme (PBS) for the treatment of cognitive impairment in persons with mild to moderately severe Alzheimer's disease: donepezil, galantamine and rivastigmine. Memantine, a *N*-methyl-D-aspartate receptor (NMDA) inhibitor, is subsidised for people with moderately severe to severe AD.

Many medicines have the potential to impair cognitive function. A recent literature review found a consistent correlation between anticholinergic use and cognitive decline (including delirium) in older adults based on findings from 27 studies [2]. Most studies included in the review reported that the use of anticholinergics and their burden was associated with worsening in cognitive performance as determined by the mini-mental state scores [2]. People with

dementia undergo progressive cognitive decline due to damage to the cholinergic neurons system and may be particularly susceptible to worsening of cognitive function because of adverse effects caused by anticholinergic and sedative medicines [3–6]. A study in subjects with Alzheimer's disease reported an average 4-point drop in total Mini-Mental State Scores in those with positive anticholinergic activity compared to those with negative anticholinergic activity in their serum [7] and worsened symptoms of dementia, including delusions and hallucinations [8]. Moreover, some reports show that anticholinergic activity accelerates Alzheimer's pathology [9, 10]. Use of multiple anticholinergic medications was found to be associated with greater risk of hospitalisation for confusion [11].

Medicines with significant anticholinergic effects include antipsychotics, antidepressants, medicines for urinary incontinence and antihistamines [6, 12, 13]. When taken concurrently with CEIs, anticholinergics decrease the effectiveness of CEIs as they have the opposite pharmacological action (anticholinergics block the action of acetylcholine in the brain, the amount of which is increased by CEIs to improve the symptoms of dementia) [14].

Medicines with sedative effects also worsen cognitive impairment and increase the risk of falls and should be avoided in people with dementia as the presence of dementia itself increases the risk of falls due to impaired judgement, gait and balance [15, 16]. Benzodiazepines and other hypnosedatives, antipsychotics, antidepressants, antihistamines, opioids and anticonvulsants are examples of medicines with sedative effects [5, 12]. Many of these medicines also have anticholinergic properties. Even though medicines with anticholinergic and sedative effects should be avoided where possible in people with dementia [5], past literature suggested their use is common. A study from the US found that 30 and 34 % of patients who initiated CEIs received anticholinergics in the 90 days before and after initiation, respectively [17]. Another US study reported that people with dementia were more likely to take anticholinergics than matched controls (33 vs. 23 %, $p = 0.001$) [18], and a Canadian study reported 36 % prevalence of anticholinergic prescribing in dementia patients [19]. One Australian study analysing PBS data from 2006 found that 23 % of CEI initiators received selected anticholinergic medicines in the 14 weeks prior to the date of initiation, and 28 % received them within 14 weeks post initiation [20]. The studies assessing co-prescription of anticholinergics and anti-dementia medicines are all more than 5 years old and the extent to which current practice has changed is not known.

Aim of the Study

This study aimed to determine current utilisation of medicines with anticholinergic and sedative effects amongst people who initiated anti-dementia therapy.

Methods

Study Population

De-identified pharmacy claim data for medicines subsidised and dispensed under the PBS were examined for the period 2008–2011. Under the PBS, the Australian Government subsidised the medicine cost above the co-payment threshold. The co-payment is the amount paid by the patients towards the cost of their PBS medicines. From 1 January 2012, general patients pay up to $35.40 for most PBS medicines or $5.80 if they have a concession card. PBS data is collected from pharmacies and public and private hospitals. It provides patient information (age, gender, general/concessional status), as well as prescribing information (date of supply, drug name, prescribed from, quantity dispensed, number of repeats). A retrospective cohort study was undertaken on both concessional and general patients to determine the extent of dispensing of sedatives and anticholinergic medicines prior to and post initiation of CEIs or memantine in this cohort. Patients who had their first ever (index) CEI or memantine dispensed between 1 January 2009 and 31 December 2010 and who were aged 65 years or over at the time of initiation were included in the cohort. Those who initiated memantine after initiation of CEIs were excluded. Proportions of the cohort who were dispensed medicines with sedative or anticholinergic properties in any one month in the 6 months prior to and including the month of anti-dementia therapy initiation, as well as in the 6 months post initiation, were determined. Use or concurrent use with anti-dementia agents in a month was defined when the use of the medicine(s) of interest continued for the length of the whole month (e.g., to have co-dispensing of sedatives and CEIs, at least one medicine from each group had to be in use for the whole of the month). Changes in use of anticholinergics and sedatives in the 6 months pre and post anti-dementia therapy initiation at the level of individual patients were also assessed.

Medicines Included in the Analyses

Medicines were coded in accordance with the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system [21].

Anti-dementia medicines included in the analysis were: cholinesterase inhibitors—donepezil (N06DA02), rivastigmine (N06DA03) and galantamine (N06DA04); NDMA inhibitors: memantine (N06DX01).

Medicines that are considered clinically important and are commonly prescribed in the elderly have been identified by a clinical pharmacist using the Anticholinergic Risk Scale [6] and the Anticholinergic Drug Scale [13]. The Anticholinergic Risk Scale defines medicines as having limited or no anticholinergic potential (rating 0), moderate anticholinergic potential (rating 1), strong anticholinergic potential (rating 2) or very strong anticholinergic potential (rating 3) [6]. The Anticholinergic Drug Scale rates medicines as level 1 (potentially anticholinergic based on the findings of receptor binding studies), level 2 (anticholinergic effects sometimes occur, generally at high doses) and level 3 (markedly anticholinergic) [13]. Medicines rated 0 on the Anticholinergic Risk Scale and level 1 on the Anticholinergic Drug Scale were excluded due to the low likelihood of these medicines causing anticholinergic side effects in practice. When a medication was rated differently on the two scales, the higher rate was used. Central nervous system-acting medicines with sedative effects (e.g., opioid analgesics, antiepileptics, etc.) were identified by a clinical pharmacist using the Australian Medicines Handbook and Australian product information for each medication. Table 1 provides a list of medicines with sedative and anticholinergic effects included in the study. For the analysis, these medicines were grouped into six classes according to their sedative and anticholinergic effect (Table 2).

Statistical Analysis

McNemar's test was used to test for differences between proportions at two time points (e.g., pre-and post comparisons) of non-independent samples (subjects from the same cohort) and p values were reported. Logistic regression was undertaken to assess the effect of age (gender was not available in the data for this study) as predictor of the use of anticholinergics/sedatives concurrently with anti-dementia agents and the odds ratio was reported. Analyses were performed using the SAS 9.4 statistical package (SAS Institute, Cary, NC, USA).

Results

The cohort included 24,110 unique patients who initiated anti-dementia therapy with a CEI or memantine between 1 January 2009 and 31 December 2010. The majority initiated CEIs (97 %). The age distribution was as follows: 20 % were aged 65–74 years, 55 % were aged 75–84 years, and the remaining 25 % were 85 years or over.

Of the 24,110 patients, 7,294 distinct patients (30 %) had used medicines with anticholinergic or sedative effects for at least one whole month in the prior 6 months. The proportion who had received anticholinergics or sedatives for at least one whole month in the 6-month period post initiation increased to 36 % ($N = 8{,}610$) ($p < 0.0001$). A subgroup of 4,305 unique patients (18 % of all anti-dementia agent initiators) received medicines with anticholinergic properties concurrently with CEI or memantine for at least one whole month post initiation and another 1,995 unique patients (8 % of all initiators) received medicines with sedative only (no anticholinergic) properties concurrently with CEI or memantine. Those who were aged 85 years or over were more likely to have anticholinergics/sedatives co-dispensed with anti-dementia agents compared to those under 85 years of age (Odds Ratio = 1.09, 95 % CI 1.02, 1.16, $p = 0.016$).

Medicines with anticholinergic or sedative properties were dispensed to between 17 and 20 % of the cohort in each month of the 6 months prior to and at the time of anti-dementia therapy initiation, with the overall use stabilising at around 22 % in each month post initiation (Fig. 1). In the first month immediately after anti-dementia medicine initiation, 15 % of patients were dispensed anticholinergic or sedative medicines concurrently with anti-dementia medicines, decreasing to 8 % at month six ($p < 0.0001$), (Fig. 1). At 1 month post initiation of the dementia medicine, 7 % of patients received anticholinergics or sedatives but were no longer on the anti-dementia medicine, increasing to 14 % by month six ($p < 0.0001$) (Fig. 1). The remaining patients either had no therapy at all (neither anti-dementia therapy nor anticholinergics nor sedatives—26 % at month one increasing to 51 % by month six, $p < 0.0001$), or continued to receive anti-dementia therapy but no anticholinergics or sedatives (52 % at month one decreasing to 27 % by month six, $p < 0.0001$).

Figure 2 presents the subsidised anticholinergics and sedatives dispensed to the cohort of initiators stratified by the class of those medicines. The figure shows that 70 % of the patients who initiated anti-dementia therapy did not receive subsidised medicines with anticholinergic or sedatives effect prior to initiation—the majority (58 % of the full cohort) continued not to have those medicines after initiation of a CEI or memantine;, however, 12 % commenced them post initiation even though they were naïve in the months prior. Only 6 % stopped anticholinergic and sedative therapy post initiation even though they had had it prior to initiation.

Comparison of prior with post anticholinergic/sedative therapy by class shows that most of the patients continued to receive the same class or classes of medicines. For

Table 1 Rating of medicines with sedative or anticholinergic effects

ATC code, medicine	Rating	ATC code, Medicine	Rating
Antispasmodics and antidiarrhoeals		*Antypsychotics*	
A03AB05 Propantheline	A3	N05AA01 Chlorpromazine	S, A3
A03BA01 Atropine	A3	N05AB04 Prochlorperazine	S, A2
A03FA01 Metoclopramide	A1	N05AB06 Trifluoperazine	S, A3
A07DA03 Loperamide	A2	N05AC01 Pericyazine	S, A3
Antiarrhythmics and antihypertensives		N05AD01 Haloperidol	S, A2
C01BA03 Disopyramide	A2	N05AE04 Ziprasidone	S, A2
C02AB01 Methyldopa	S	*Atypical antipsychotics*	
C02AC01 Clonidine	S	N05AH03 Olanzapine	S, A3
Drug for urinary incontinence		N05AH04 Quetiapine	S, A2
G04BD04 Oxybutynin	A3	N05AL05 Amisulpride	S
Muscle relaxants		N05AX08 Risperidone	S, A2
M03BX01 Baclofen	S, A2	N05AX12 Aripiprazole	S
		N05AX13 Paliperidone	S, A2
Opioids		*Benzodiazepines*	
N02AA01 Morphine	S	N05BA01 Diazepam	S
N02AA03 Hydromorphone	S	N05BA04 Oxazepam	S
N02AA05 Oxycodone	S	N05BA08 Bromazepam	S
N02AA59 Codeine/paracetamol	S	N05BA12 Alprazolam	S
N02AB03 Fentanyl	S	N05CD02 Nitrazepam	S
N02AC04 Dextropropoxyphene	S	N05CD03 Flunitrazepam	S
N02AE01 Buprenorphine	S	N05CD07 Temazepam	S
N02AX02 Tramadol	S	*Non-benzodiazipine hypnotics*	
Antiepileptics		N05CF01 Zopiclone	S
N03AA02 Phenobarbital	S	N05CF02 Zolpidem	S
N03AA03 Primidone	S	*Antidepressants*	
N03AB02 Phenytoin	S	N06AA02 Imipramine	S, A3
N03AE01 Clonazepam	S	N06AA04 Clomipramine	S, A3
N03AF01 Carbamazepine	S, A2	N06AA09 Amitriptyline	S, A3
N03AG01 Valproate	S	N06AA10 Nortriptyline	S, A3
N03AG04 Vigabatrin	S	N06AA12 Doxepin	S, A3
N03AX09 Lamotrigine	S	N06AA16 Dothiepin	S, A3
N03AX11 Topiramate	S	N06AB05 Paroxetine	A2
N03AX12 Gabapentin	S	N06AX03 Mianserin	S
N03AX16 Pregabalin	S	N06AX11 Mirtazapine	S
Anti-parkinsonian drugs		*Broncholidators*	
N04AA01 Benzhexol	S, A3	R03BB01 Ipratropium	A2
N04AA02 Biperiden	A3	R03BB04 Tiotropium	A2
N04AC01 Benzatropine	A3	*Antihistamines*	
N04BB01 Amantadine	A2	R06AD02 Promethazine	S, A3
		R06AX02 Cyproheptadine	S, A3

S sedative effect, *A1* limited anticholinergic activity, *A2* moderately anticholinergic, *A3* highly anticholinergic

example, medicines with a sedative effect were dispensed to 10 % of the patients prior to therapy, and to 10.8 % post therapy ($p < 0.0001$). A combination of two or more classes was dispensed to 7 % prior to therapy, and to 6.8 % post therapy ($p = 0.167$). Highly anticholinergic and sedative medicines were received for at least 1 month by 4.6 % prior to therapy, and by 4.0 % post therapy ($p < 0.0001$). Moderately anticholinergic and sedative medicines were dispensed to 3.5 % prior to therapy, increasing to 6.7 % post therapy ($p < 0.0001$). Moderately anticholinergic

Table 2 Classes of sedative and anticholinergic medicines

Class	Abbreviation in the results presentation	Inclusion criteria
Medicines with sedative effect	Sed	Any medicine from Table 1 with S rating
Highly anticholinergic and sedative medicines	HighAS	Any medicine from Table 1 with S, A3 rating
Moderately anticholinergic and sedative medicines	ModAS	Any medicine from Table 1 with S, A2 rating
Highly anticholinergic medicines	HighA	Any medicine from Table 1 with A3 rating
Moderately anticholinergic medicines	ModA	Any medicine from Table 1 with A2 rating
Mildly anticholinergic medicines	MildA	Any medicine from Table 1 with A1 rating

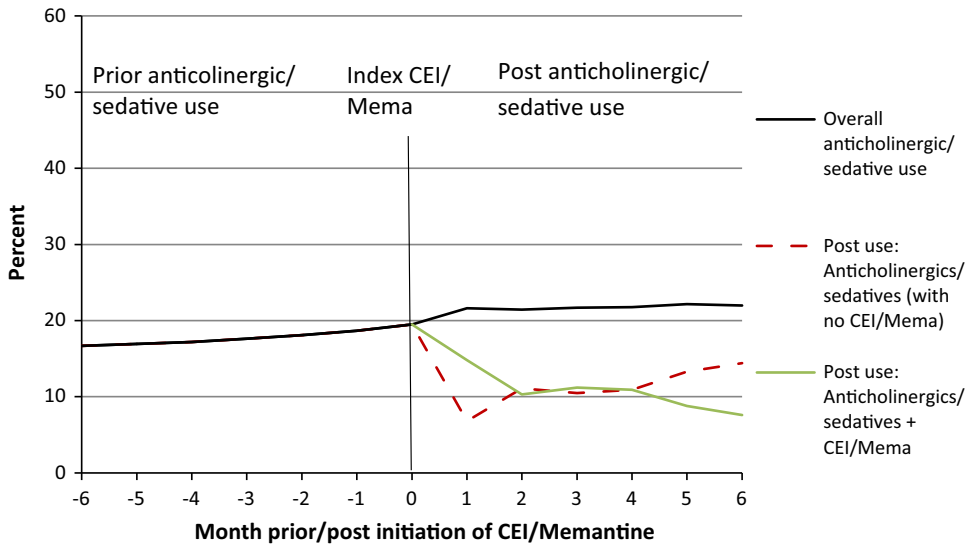

Fig. 1 Month-by-month anticholinergic/sedative use prior to and post index cholinesterase inhibitor (CEI)/ memantine (Mema) use (whole month use or co-use)

drugs were dispensed to 3.5 % prior to therapy, and to 3.3 % post therapy ($p = 0.050$)—the inhaled medications ipratropium and tiotropium accounted for most of the use; however, their overall prevalence was low. Highly anticholinergic medicines were dispensed to 1.4 % prior to therapy and to 1.3 % post therapy ($p = 0.105$), with oxybutinin being the most commonly used.

Antidepressants were dispensed to 12 % of the cohort prior to anti-dementia therapy initiation and the proportion stayed the same (12 %) post initiation ($p = 0.057$). Mirtazapine, amitriptyline and paroxetine were the most commonly dispensed antidepressants. Antipsychotics were received by 10 % of the cohort prior to and by 16 % post initiation ($p < 0.0001$), with risperidone, olanzapine and quetiapine most commonly used (all atypical antipsychotics). Benzodiazepines were dispensed to 17 % of the cohort prior to and 18 % post initiations ($p < 0.0001$), with temazepam, oxazepam and diazepam most commonly used.

Discussion

In this study 30 % of the cohort received any class of anticholinergic or sedative medicine for at least 1 month in the 6 months prior to initiation of anti-dementia agents, increasing significantly to 36 % post initiation. Our results are very similar to a US study reporting that 30 and 34 % of patients who initiated CEIs received anticholinergics in the 90 days before and after initiation, respectively [17]. An earlier Australian study analysing PBS data from 2006 and using a limited number of medicines with anticholinergic properties found that 23 % of CEI initiators received selected anticholinergic medicines in the 14 weeks prior to the date of initiation, and 28 % received them within 14 weeks post initiation [20]. Our results are slightly higher; however, we included additional medicines with anticholinergic and sedative properties.

Overall, 26 % received anticholinergics/sedatives concurrently with CEI or memantine for at least 1 month in the

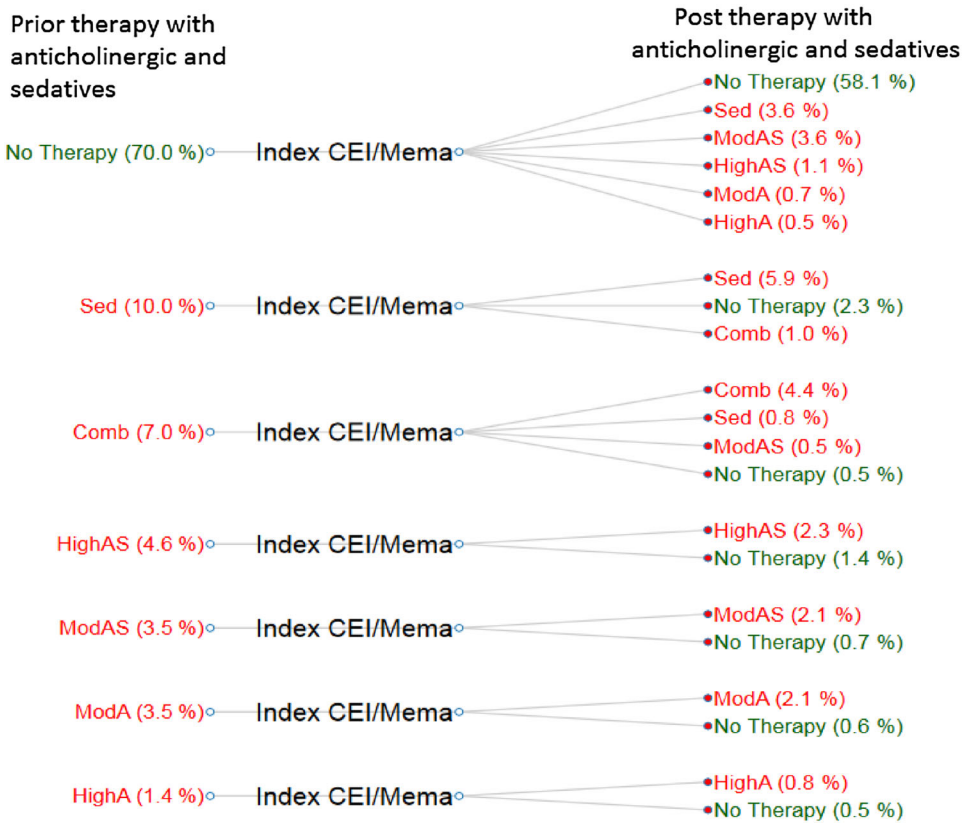

Fig. 2 Anticholinergic/sedative use prior and post initiation of anti-dementia therapy—by class (as defined in Table 2). *No therapy* denotes no use of medicines with anticholinergic and/or sedative effect in any month prior to or post initiation; *Comb* denotes use of more than one class of sedatives and/or anticholinergics over the 6 months prior to or post initiation; *Sed*, *HighAS*, etc. denote use of the specific class only, for at least 1 month prior to/post initiation. The post therapy percentages do not add up to 100 as therapies with use in below 0.5 % of the patients are omitted in the figure

6 months post the date of initiation, with those aged 85 years and over more likely to receive co-medications. The consequences to a patient of having medicines with an anticholinergic effect that oppose the action of CEIs have been stated elsewhere [14]. At any 1-month time point, our analysis showed that around one in five patients who initiated anti-dementia therapy received medicines with anticholinergic or sedative effect prior to initiation. In the month immediately after initiation, 15 % received anticholinergic or sedative medicines concurrently with the anti-dementia agents, with this proportion decreasing to 8 % at 6 months post initiation. However, the proportion of subjects who discontinued their anti-dementia medicines but received anticholinergics or sedatives increased by an equivalent 7 % from month one to month six, implying a stable monthly use of anticholinergics or sedatives over the 6-month period. Medicines with anticholinergic properties have been associated with a decline in cognitive functions in elderly people, including a decline in visual impairment, confusion, poor verbal and semantic memory, and decreased executive functions [3, 4, 22]. Older people with dementia may be particularly susceptible to cognitive decline (especially of memory) induced by medicines with an anticholinergic and sedative effect [5–8]. Reducing the number of those medicines may improve cognitive function and reduce the likelihood of adverse events [5]. Further, reduction of use prior to initiation of therapy may be necessary to determine patient response to therapy. One French study found an increase in the risk of incident dementia over a 4-year follow-up period in continuous users of anticholinergic medicines (hazard ratio 1.65, 95 % CI 1.00–2.73) [23]. A second French study found that even though consistent users of anticholinergics had poorer cognitive performance at 8 years' follow-up, this did not increase the risk of developing dementia; however, the study may have been under-powered for the dementia endpoint [24].

Use of medicines with highly anticholinergic and sedative effects decreased slightly after initiation (4.6 % prior to vs. 4.0 % post), while use of medicines with moderate anticholinergic and sedative effects increased significantly after initiation (3.5 % prior to vs. 6.7 % post). Antidepressants were used by 12 % of the cohort prior to and post initiation. This is lower than the 22 % prevalence of depression and mood affective disorders in people with dementia in Australia in 2009 [25]; however, we only analysed antidepressants with anticholinergic effects. The use of antipsychotics increased significantly post initiation of anti-dementia therapy (from 10 % prior to therapy to 16 % post therapy). Risperidone, quetiapine and olanzapine were found to be commonly prescribed both in the earlier Australian study [20] and in our study. The higher use of atypical antipsychotics might relate to their use for treatment of behavioural and psychological symptoms

associated with dementia; however, these medicines have shown only a small beneficial effect and should be used for a limited time [26, 27]. Oxybutynin is likely to be prescribed to control urinary incontinence, which can also be an adverse effect of CEIs. The overall prevalence of the inhaled medications ipratropium and tiotropium was low; besides, they are expected to have a low likelihood of systemic absorption. Results from the current study reconfirm that even though medicines with anticholinergic and sedative effects should be avoided in people with dementia, they are continuing to be commonly dispensed.

We analyzed data from a national dataset capturing prescription data of all Australians. A limitation is that some medicines with anticholinergic or sedative effects were under co-payment for general patients and were not available in the PBS dataset [28]. However, the majority of patients of age 65 years or over have concession status and thus the number of missed prescriptions is assumed to be low. Some over-the-counter products also have anticholinergic properties which may have an additive effect to those in the prescribed medicines. No data on these medicines is available for this study. We used a conservative approach for dispensing and co-dispensing where people had to be co-prescribed medicines for each day in the month to be considered co-administered therapies. This may underestimate the actual proportion of concurrent use where shorter durations of co-administration occurred.

Conclusion

Medicines with anticholinergic or sedative effects were commonly dispensed amongst people with dementia, with one-third receiving them at some time in the 6 months prior to and post initiation of anti-dementia agents. While concurrent use with anti-dementia medicines did decrease over time, one in six patients was prescribed CEIs and anticholinergics or sedatives in the month after CEI initiation. Some patients (6 %) ceased anticholinergic or sedative medicines post initiation even though they had them in the months prior to initiation. However, 12 % commenced anticholinergics or sedatives post anti-dementia therapy initiation, even though they were naïve to them in the months prior to the therapy. Prescribers need to consider reviewing patients on anticholinergic therapy with CEIs as the effectiveness of the cholinesterase therapy may be compromised.

Acknowledgment This study was funded under the initiative of the Australian Government Department of Health for post market reviews of Pharmaceutical Benefits Scheme subsidised medicines.

References

1. Australian Institute of Health and Welfare (AIHW). Dementia in Australia. Cat. no. AGE 70. Canberra: AIHW; 2012.
2. Campbell N, Boustani M, Limbil T, Ott C, Fox C, Maidment I, et al. The cognitive impact of anticholinergics: a clinical review. Clin Interv Ageing. 2009;4:225–33.
3. Han L, Agostini J, Allore H. Cumulative anticholinergic exposure is associated with poor memory and executive function in older men. J Am Geriatr Soc. 2008;56:2203–10.
4. Tune L. Anticholinergic effects of medications in elderly patients. J Clin Psychiatry. 2001;62:11–4.
5. Bell S, Mezrani C, Blacker N, et al. Anticholinergic and sedative medicines—prescribing consideration for people with dementia. Aust Fam Phys. 2012;41(1):45–9.
6. Rudolph J, Salow M, Angelini M, McGlinchey R. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med. 2008;168(5):508–13.
7. Konishi K, Hori K, Uchida H, Watanabe K, Tominaga I, Kimura M, et al. Adverse effects of anticholinergic activity on cognitive functions in Alzheimer's disease. Psychogeriatrics. 2010;10(1):34–8.
8. Hori K, Konishi K, Watanabe K, Uchida H, Tsuboi T, Moriyasu M, et al. Influence of anticholinergic activity in serum on clinical symptoms of Alzheimer's disease. Neuropsychobiology. 2011;63(3):147–53.
9. Hori K, Konish K, Tani M, Tomioka H, Akita R, Kitajima Y, et al. Serum anticholinergic activity: a possible peripheral marker of the anticholinergic burden in the central nervous system in Alzheimer's disease. Dis Markers. 2014; doi:10.1155/2014/459013.
10. Hori K, Konishi K, Tani M, Tomioka H, Akita R, Kitajima Y, et al. Why does the progression of Alzheimer's disease accelerate? Ann Psychiatry Ment Health. 2014;2(1):1006.
11. Kalisch E, Pratt N, Ramsay E, Barratt J, Roughead E. Multiple anticholinergic medication use and risk of hospital admission for confusion or dementia. J Am Geriatr Soc. 2014; doi:10.1111/jgs.13054 [Epub ahead of print].
12. Australian Medicines Handbook. Adelaide. Australian Medicines Handbook Pty Ltd; 2010.
13. Carnahan R, Lund B, Perry P, Pollock B, Culp K. The anticholinergic drug scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. J Clin Pharmacol. 2006;46(12):1481–6.
14. Johnell K, Fastbom J. Concurrent use of anti-cholinergic drugs and cholinesterase inhibitors: register-based study of over 700,000 elderly patients. Drugs Aging. 2008;25:871–7.
15. Buchner D, Larson E. Falls and fractures in patients with Alzheimer-type dementia. JAMA. 1987;257:1492–5.
16. Visser H. Gait and balance in senile dementia of Alzheimer's type. Age Ageing. 1983;12:296–301.
17. Carnahan R, Lund B, Perry P, Chrischilles E. The concurrent use of anticholinergics and cholinesterase inhibitors: rare event or common practice? J Am Geriatr Soc. 2004;52(12):2082–7.
18. Roe C, Anderson M, Spivack B. Use of anticholinergic medications by older adults with dementia. J Am Geriatr Soc. 2002;50(5):836–42.
19. Remillard A. A pharmacoepidemiological evaluation of anticholinergic prescribing patterns in elderly. Pharmacoepidemiol Drug Saf. 1996;5:155–64.

20. Robinson M, Rowett D, Leverton A, Mabbott V. Changes in utilisation of anticholinergic drugs after initiation of cholinesterase inhibitors. Pharmacoepidemiol Drug Saf. 2009;18:659–64.
21. World Health Organization Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical Code Classification index with Defined Daily Doses. http://www.whocc.no/atcddd/. Accessed 5 Aug 2014.
22. Uusvaara J, Pitkala K, Kautiainen H, Tilvis R, Strandberg T. Detailed cognitive function and use of drugs with anticholinergic properties in older people: a community-based cross sectional study. Drugs Aging. 2013;30(3):177–82.
23. Carriere I, Fourrier-Reglat A, Dartigues J, Rouaud O, Pasquier F, Ritchie K, et al. Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. Arch Intern Med. 2009;169(14):1317–24.
24. Ancelin M, Artero S, Porter F, Dupuy A, Touchon J, Ritchie K. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. BMJ. 2006;332(7539):455–9.
25. Australian Institute of Health and Welfare. Dementia in Australia; Cat no AGE 70, Canberra: AIHW; 2012.
26. National Prescribing Service Limited. Drugs used in dementia in the elderly. NPS News 59; Aug 2008.
27. National Prescribing Service Limited. Tole of antipsychotics in managing behavioural and psychological symptoms of dementia. Prescribing Practice Review 37; Apr 2007.
28. Department of Health. Pharmaceutical Benefits Scheme. http://www.pbs.gov.au. Accessed 5 Aug 2014.