Use of potentially inappropriate medications in people with dementia in Vietnam and its associated factors

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Abstract

This study examined the use of potentially inappropriate medicines that may affect cognition (PIMcog) in people with dementia and its associated factors. Medical records of all out-patients with dementia attending a tertiary hospital in Vietnam between 1st, Jan 2015 and 31st, Dec 2016 were examined. Medicine use was assessed against a list of PIMcog. Variables associated with having a PIMcog were assessed using a multiple logistic regression. Of the 128 patients, 41% used a PIMcog, 39.1% used CEIs concomitantly with anticholinergics, and 18% used antipsychotics. Number of hospital visits (adjusted OR 1.08; 95% CI 1.02 – 1.16) and number of treating specialists (adjusted OR 0.61; 95% CI 0.45 – 0.83) were associated with PIMcog use. This study highlights a high level use of medicines that can further impair cognition or reduce the effectiveness of CEIs in people with dementia. Efforts to improve quality use of medicines for this population are warranted.

Keywords

Dementia, quality use of medicines, potentially inappropriate medicines, anticholinergics, antipsychotics, sedatives

Introduction

Dementia is a costly health condition that has a significant impact on individuals, their family caregivers, communities and society.[1] By 2018, dementia will become a trillion US dollar disease and the cost continues to rise to USD 2 trillion by 2030.[1] Already being the home of nearly 60% of people with dementia worldwide, compared to high income countries, low and middle income countries (LMICs) are facing a much more rapid growth in numbers of people with dementia[1] often without a well-developed or well-funded healthcare system, resulting in lack of diagnosis and poor quality treatment for people with dementia.[2] Not an exception, Vietnam with a projected increase from 10% in 2015 to 28% in 2050 in the proportion of its population aged 60 years and above[3] and an estimated dementia prevalence ranging from 4.2% to 7.9% in these elderly[4,5] may have as many as 2.4 million people living with dementia by the mid-21st century.

Most people living with dementia are older,[6] thus likely to have multiple chronic conditions and taking multiple medicines[7] with the associated increased risk of adverse drug reactions due to drug interactions and due to altered pharmacokinetic and pharmacodynamic profiles in older persons.[8] These issues can confound dementia management where multiple medicine use and aging make individuals more sensitive to the effects of medicines on cognition.[9,10] Lack of evidence from randomised controlled trials for the use of medicines in people with dementia because of their exclusion in most clinical trials further compounds the problems of medicine use in this population.[11,12]

In the absence of preventive or curative treatments of dementia, current pharmacological therapies focus on modifying symptoms of cognitive impairment (e.g. using anti-dementia medicines such as cholinesterase inhibitors - CEIs or memantine), managing behavioural and psychological symptoms of dementia (BPSD) and managing cardiovascular and cardio-metabolic symptoms, which if not managed would make dementia worse. Other management strategies focus on maintaining cognition. For this reasons, medicines with anticholinergic or sedative effects should be avoided where possible in persons with dementia due to the association between these medicines and cognitive decline.[9,13,14]

Further, anticholinergic medicines have the potential to antagonise the effect of CEIs, the medicines to treat symptoms of dementia.[15] Among anticholinergic and sedative medicines, antipsychotics are often used to manage BPSD. However, they have limited efficacy[16] and can be successfully de-prescribed.[17]

Different factors have been reported to be associated with inappropriate medication use.[18-21] They can be categorised into system and environmental factors (e.g. residential aged care structure),[22] physician and health professional related factors (e.g. diagnostic and therapeutic knowledge and skills, prescribing culture)[23] or patient related factors (e.g. age, gender, education or socioeconomic status, comorbidity or number of medicines prescribed).[24,25] Little is known about the quality use of medicines in people with dementia in Vietnam and its associated factors. This study was conducted to examine the prevalence of potentially inappropriate medication use for people with dementia, with a focus on those that affect cognition (PIMcog) and to analyse potential variables associated with having a PIMcog to provide evidence-based information for subsequent programs supporting quality use of medicines in dementia care in Vietnam. We also examined the prevalence of concomitant use of CEIs and anticholinergics, as well as the appropriateness of selection, initiation dosing and the length of use of antipsychotics in people with dementia in Vietnam.

Methods

Data source and study design

The National Geriatric Hospital (NGH) is the leading tertiary hospital in Vietnam taking care of geriatric patients. In 2008 the hospital started its national program on "Management, care and treatment of people with dementia". Patients referred to NGH for cognitive impairment have a thorough medical review, including medical history, assessment of mental status and mood testing, physical and neurological examination and tests to rule out other causes of dementia-like symptoms. Patients diagnosed with dementia are included in the hospital's dementia program and are requested to visit every month for check-up and medicine dispensing, which is subsidised under a special

insurance program. A database of these patients has been established and data since January 2015 have been computerised.

Analyses of medicine use in all out-patients with dementia attending NGH were conducted for the period 1st, Jan 2015 to 31st, Dec 2016. Medical records and prescriptions of all patients diagnosed with dementia during the study period were examined. The medical record contains information on patients' demographics, diagnosis of dementia, cognitive function test (e.g. MMSE score), other comorbidities and prescribing information (medicine name, strength, dosage, quantity and route of administration). Health service characteristics were recorded, including the specialty of prescribers.

Medicines included in analyses

Data were collected using a data collection form developed in a macro enabled excel spreadsheet. Medicines were coded according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system.[26] Anti-dementia medicines included in the analysis were donepezil (N06DA02), rivastigmine (N06DA03) and galantamine (N06DA04). Memantine (N06DX01) was not available in the Vietnam market. A master list of all medicines used in people with dementia at the hospital during the study period was established. The medicines on this list were first assessed against a PIMcog list[24] - Vietnamese modification, which contained individual medicines available in Vietnam considered potentially inappropriate for use in older people with cognitive impairment (Appendix 1) and developed based on Beers 2012 criteria[27] and STOPP 2014 criteria[28] but limited to those medicines that are related to cognitive impairment.[24] Second, concomitant use of CEIs with anticholinergic medicines was assessed using a list of medicines available in Vietnam with clinically relevant anticholinergic and sedative properties (Appendix 2) following a previously published approach[29,30] and based on a consensus combination of different anticholinergic scales.[31] Concomitant use was defined where co-prescribing of ECIs with anticholinergic agents was recorded at the same hospital visit. Medicines accounting for the difference between the PIMcog list and the list of medicines with anticholinergic or sedative effects are presented in Appendix 3.

A list of antipsychotics used by study participants was also compiled. Incident use of antipsychotics was defined as prescribing antipsychotics after no prescription of antipsychotics was recorded at any of the previous three monthly hospital visits. Continuous use of antipsychotics was defined as prescribing antipsychotics at consecutive monthly hospital visits. Information on type, initial and maximum doses, as well as duration of antipsychotics continuously prescribed were collected and assessed against the Australia's dementia care guidelines[16] and Australian Medicines Handbook.[32] These references were used in the absence of Vietnam's dementia care guidelines. In Australia, risperidone is the only antipsychotic medicine subsidised for treatment of BPSD resistant to non-pharmacological measures in Alzheimer-type moderate-to-severe-dementia (for up to 12 weeks), with an initial dose of 0.25mg twice daily, increasing by 0.25mg daily every two or more days if necessary to a maximum dose of 2mg per day.[32]

Statistical analyses

Descriptive statistics were used to describe the demographics and medicine use in the dementia population, including the proportion of patients who used at least one medicine on the PIMcog list, who used CEIs with anticholinergic medicines concomitantly or who used at least one antipsychotic medicine during the study period. The median number of unique medicines used by individual patients across hospital visits was calculated and the median of median value across patients was reported. Multiple logistic regressions were conducted to assess the association of different variables and having a PIMcog, including age, gender, type of dementia, severity of dementia, number of co-morbidities, number of medicines used other than PIMcog, number of hospital visits and number of treating specialists. Missing data were imputed using the fully conditional method in a multiple imputation approach.[33] All analyses were performed using the SAS 9.4 statistical package (SAS Institute, Cary, NC, USA).

Results

Participant characteristics

Data were retrieved from 128 patients who participated in the national program on "Management, care and treatment of people with dementia" at some time during the study period (Table 1). The mean age (Standard deviation - SD) of the participants at the first hospital visit for dementia treatment during the study period was 71.9 years (11.0). Sixty four (50%) patients had at least one comorbidity and 32 (25%) had two or more comorbidities. The most common comorbidities include hypertension (n = 30, 23.4%), hyperlipidemia (n = 24, 18.8%) and diabetes (n = 12, 9.4%).

Table 1 is about here

General use of medicines and anti-dementia medications

Half of the participants were prescribed between two and four medicines per hospital visit (Table 2) and 18 (14.1%) patients had a median of five or more medicines prescribed per visit.

Throughout the study period, the most commonly used medicines included CEIs and ginkgobiloba. In total, 122 (95.3%) patients used medicines considered to improve cognitive function at some time during the study period, of whom 115 (89.8%) patients used CEIs and 77 (60.2%) used ginkgobiloba products. Among 115 patients who were prescribed CEIs, 94 patients (81.7%) had these medicines prescribed continuously for more than six months and 31 patients (27.0%) were at a severe stage of dementia. CEIs being prescribed to patients were galantamine (n = 109, 85.2%), rivastigmin (n = 23, 18.0%) and donepezil (n = 11, 8.6%).

Other medicines commonly prescribed were vitamins, e.g. vitamin E (n = 86, 67.2%), vitamin B1 (n = 63, 49.2%), vitamin B6 (n = 47, 36.7%), and vitamin B12 (n = 45, 35.2%). The use of diazepam (n = 42, 32.8%) and piracetam (n = 31, 24.2%) was also frequently observed.

Table 2 is about here

Use of PIMcogs

Fifty three patients (41.4%) were prescribed at least one PIMcog at some time during the study period. Three patients were prescribed two or more PIMcog concomitantly at the same visit on at least one occasion in the two year period (Table 2). Similar figures were observed when assessing the PIMcog use in study participants aged 65 years or above only (data not shown).

The most commonly used classes of PIMcog were sedatives (e.g. benzodiazepines – n = 42; non-benzodiazepine hypnotic – n = 1) and anticholinergics (e.g. tricyclic antidepressants – n = 10; antiparkinson agents – n = 5; antipsychotics – n = 2). The most commonly used individual PIMcogs were diazepam (n = 42), amitriptyline (n = 10) and trihexyphenidyl (n = 5).

Our initial multiple logistic regression model consisted of the following variables: age, gender, type of dementia, severity of dementia recorded by treating doctors, number of co-morbidities, median number of medicines other than PIMcog used per hospital visit, number of hospital visits and number of treating specialists. The backward elimination using a significance level of 0.2 to retain variables in the model resulted in a final model, which contained the following variables: gender, age, number of hospital visits and number of treating specialists. The final logistic regression model indicated that a higher number of hospital visits during the study period (adjusted OR 1.08; 95% CI 1.02 – 1.16) was positively associated with PIMcog use. By contrast, higher number of treating specialists (adjusted OR 0.61; 95% CI 0.45 – 0.83) was negatively associated with PIMcog use. No statistically significant associations between older age (adjusted OR 1.02; 95% CI 0.99 – 1.06) or female gender (adjusted OR 1.55; 95% CI 0.72 – 3.30) and PIMcog use were found.

Concomitant use of CEIs with anticholinergics

Seventy eight patients (60.9%) were prescribed at least one medicine with sedative or anticholinergic effects at some time during the study period. Excluding those using medicines with sedative effect only, 66 (51.6%) patients were prescribed at least one anticholinergic medicine at some time during the study period. Fifty patients concurrently used an anticholinergic agent with CEIs, accounting for 39.1% of all 128 patients or 43.5% of 115 patients who were using CEIs.

Antipsychotics use

Twenty three (18.0%) patients were prescribed at least one antipsychotic medicine at some time during the study period. Sixteen patients (12.5%) were concomitantly prescribed antipsychotic medicines with CEIs. Antipsychotic medicines most commonly used were sulpiride (n = 9), followed by risperidone (n = 8), quetiapine (n = 8), clozapine (n = 1) and olanzapine (n = 1). Ten patients initiated antipsychotics during the study period and 13 patients were prescribed antipsychotics within their first three hospital visits. Six patients used antipsychotics continuously for more than three months.

Among eight patients who used risperidone, three patients initiated risperidone during the study period, all of whom had their initial dose of more than 0.5mg/day; one with an initial dose of 2.0mg/day and two with 1.0mg/day.

Discussion

Our results show that potentially inappropriate medicine use is common in patients with dementia attending a tertiary hospital in Vietnam. Forty one percent of patients used at least one medicine considered potentially inappropriate for use in older people with cognitive impairment, while 39.1% used CEIs together with an anticholinergic agent. Eighteen percent of patients were prescribed antipsychotics, of whom a quarter used the medicines continuously for more than three months. Of those who initiated risperidone, the initial dose of risperidone was not optimal in treatment of BPSD.

These findings are not unique to Vietnam. Studies in developed countries have shown that anticholinergic and sedative medicines have been frequently prescribed in people with dementia or concurrently used with CEIs although the extent might vary.[24,29,34-36] PIMcog use was reported among 21.4% of patients with dementia attending memory clinics in Australia, with anticholinergics and sedatives being the most common classes of PIMcog.[24] In our study, these two classes were also the most frequent among PIMcog with benzodiazepines (e.g. diazepam), which have both sedative and anticholinergic properties, topping the list. The prevalence of PIMcog in our study (41%), however,

almost doubles the number in the Australian study. [24] One possible explanation for this difference is the different designs of the studies. In our study, we looked at all prescriptions at repeated hospital visits of individual patients during the study period of two years whereas the Australian study only looked at medication exposure of individual patients at one time point of recruitment.[24] Another possibility is the difference in the quality of health service delivery between a high income country and a LMIC with LMICs having been reported to have a more severe problem of inappropriate medication use.[37]

In the US, 37% of CEI users received anticholinergics,[34] which is similar to the finding in our study (39.1%). A study on the use of antipsychotics among people with dementia in Australian residential aged care facilities showed that 44% of patients with dementia received antipsychotics concomitantly with anti-dementia medicines at some time during the study period, of the subset who initiated antipsychotics 53% used antipsychotics continuously for more than six months and 43% had suboptimal initial doses of risperidone.[38] The institutional setting of residential aged care facilities might explain the higher prevalence of antipsychotic use in the Australian study compared to that in our study of community-dwelling outpatients (18.0%).[39,40] A prevalence of antipsychotic use of 12.8% and 25.3% (18.1% overall) was reported for people with dementia in non-institutional and institutional settings, respectively in Sweden,[40] and up to 25% of people with dementia in the UK were estimated to be on antipsychotics at any time.[41]

Our results show anti-dementia medicines used to boost cognitive function in people with dementia in Vietnam included CEIs and ginkgobiloba. More than 95% of patients were prescribed at least one anti-dementia medicine, of which 89.8% were prescribed a CEI and 60.2% were prescribed ginkgobiloba products. CEIs and ginkgobiloba have a modest efficacy if any in dementia and cognitive impairment,[42,43] and conflicting evidence or no long-term efficacy (more than 6 months).[44,45] CEIs have been associated with a number of adverse reactions (e.g. bradycardia and syncope).[44] Ginkgobiloba has a better safety profile[43,46] but cerebral bleeding and prolonged bleeding have been reported to be associated with ginkgobiloba use, and this may be intensified with use of

antidepressants,[47] a common medicine class used by people with dementia.[40] The anti-dementia medicines therefore should be considered for de-prescribing when patient's dementia has progressed to a severe stage.[44] Among patients who were prescribed CEIs in this study, 81.7% had these medicines prescribed continuously for more than six months and 27.0% were at a severe stage of dementia. Periodical review taking into account both perceived benefits and adverse effects to consider stopping anti-dementia medicines is recommended.[16]

More than two in five patients with dementia in our study used a PIMcog. We found that PIMcog use was positively associated with a higher number of hospital visits. Interestingly, a higher number of treating specialists, who were all neurologists, were found negatively associated with PIMcog use. A possible explanation is that seeing different providers creates a check and balance system that helps to reduce the discretion of individual physicians in prescribing. However, further exploration is warranted to understand the rationale behind the prescribing practices of medical specialists for people with dementia in Vietnam.

In this study we also looked at the use of all PIMs with sedative and anticholinergic properties. Anticholinergics have been known to be associated with cognitive decline[9,13,14] and might reduce the efficacy of CEIs due to an antagonistic mechanism.[9,15] Apart from worsening cognitive impairment [48], sedatives also increase the risk of falls.[49] People with dementia have impaired cognition and are vulnerable to falling,[50] thus should not be prescribed sedatives and anticholinergics where possible. Nearly 61% of our participants were prescribed sedatives and anticholinergics during the study period and almost 40% used CEIs and anticholinergics concomitantly.

Eighteen percent of our patients used antipsychotics for the management of BPSD. Sulpiride was the most commonly used antipsychotic, which may not be ideal because sulpiride has been found to be associated with an increased risk of extrapyramidal symptoms at a similar level to haloperidol.[51] Risperidone might be a better option as it is considered the best evidenced treatment of BPSD.[52-54] Nevertheless, due to modest efficacy and poor tolerability[53,55] as well as association with stroke,[56] hip fracture and pneumonia,[57] a poorer quality of life[58] and increased mortality[59] of antipsychotics , these

medicines should only be used as a last resort to manage severe BPSD with low initial dose and regular review every one to three months for de-prescribing.[16]

Our study had some limitations. Firstly, we only examined the use of medicines in patients with dementia attending one tertiary teaching hospital in Vietnam and these patients were in a national program on "Management, care and treatment of people with dementia". The pattern of medicine use in people with dementia in our study therefore only reflects the prescribing practice within the teaching hospital. There is a special insurance cap that limits the total cost of medicines per prescription for patients in this program and this is likely to affect the prescribing practice. In addition, our sample is quite small and of one ethnicity only. While these shortcomings limit the generalisation of our findings to dementia treatment in Vietnam and to other samples, particularly those in high-income countries, our study has identified the scope for improvement in prescribing practice for people with dementia at a tertiary teaching hospital level.

Secondly, PIMcog list was developed based on Beers and STOPP criteria which are for patients aged 65 years or over and 24.2% of our patients aged less than 65 years. However, while reporting the prevalence of PIMcog use for all study participants, this prevalence was similar to the PIMcog use prevalence assessed in the subgroup of patients aged 65 years or over only. We also examined the use of medicines against a list of medicines with anticholinergic and sedative effects, which should be avoided in people with dementia because of their potential adverse effects including but not limited to cognitive impairment. Several scales have been developed for screening anticholinergic medications but considerable variation exists across those scales.[31] Using a uniform list of anticholinergic medicines developed based on consensus on the clinical relevance of alleged anticholinergic properties among different scales in addition to sedative medicines for screening PIMs with anticholinergic and sedative effect can be considered as strength of our study.

In conclusion, PIMcog use, anticholinergics and sedatives use, and concurrent use of CEIs with anticholinergics were prevalent in patients in the Vietnam national dementia care program. The use of antipsychotic medicines seemed suboptimal from the selection of antipsychotic products to the

initiation dosing to the treatment duration. Further research exploring the rationale behind the current prescribing practice and interventions such as pharmacist medicine review, clinical audits and targeted de-prescribing is needed to improve quality use of medicines and health outcomes of people with dementia in Vietnam.

Conflicts of interest: none

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Table 1: Participants' demographic characteristics

Characteristic	**Participants [n = 128]**
Age at the first hospital visit for dementia treatment during the study period [years; mean (SD)][*]	71.9 (11.0)
Less than 65 years [n (%)]	31 (24.2%)
Between 65 and 79 years [n (%)]	75 (58.6%)
80 years or above [n (%)]	22 (17.2%)
Female gender [n (%)]	66 (51.6%)
Diagnoses	
Alzheimer's dementia [n (%)]	103 (80.5%)
Vascular dementia [n (%)]	19 (14.8%)
Mixed dementia [n (%)]	6 (4.7%)
MMSE score [median ((IQR)][†] at the last hospital visit	18 (11-23) (n = 93, missing data from 35 patients).
Severity of dementia recorded by treating specialists	
Mild	39 (30.5%)
Moderate	33 (25.8%)
Advanced	32 (25.0%)
Missing	24 (18.7%)
Number of co-morbidities [median (IQR)] [‡]	0.5(0-1.5)
Number of dementia treating specialists [median (IQR)] [‡]	4 (3-5)

[*] SD standard deviation

[†] IQR interquartile range,

[‡] Values for the study period of two years

Table 2: Medicine use

Features	Participants [n = 128]
General use	
Number of unique medicines prescribed per hospital visit [median (IQR)*]†	2.25 (2-4)
Number of unique medicines prescribed per patient in the two year period [median (IQR)]	8 (6-11)
Prescribing of ginkgobiloba products at any time in the two year period [n (%)]	77 (60.2%)
Prescribing of CEIs‡ at any time in the two year period [n (%)]	115 (89.8%)
PIMcog use	
Prescribing of at least one PIMcog§ at any time in the two year period [n (%)]	53 (41.4%)
Prescribing of two or more PIMcogs concomitantly at the same visit on at least one hospital visit in the two year period [n (%)]	3 (2.3%)
Co-prescribing of CEIs with anticholinergics at the same visit on at least one occasion in the two year period [n (%)]	50 (39.1%)
Antipsychotics use	
Prescribing of at least one antipsychotic medicine at any time in the two year period [n (%)]	23 (18.0%)
Continuous prescribing of antipsychotics for more than three months [n (%)]	6 (4.7%)
Co-prescribing of antipsychotics with CEIs at the same visit on at least one occasion in the two year period [n (%)]	16 (12.5%)

* IQR interquartile range

† The median number of unique medicines prescribed for individual patients across hospital visits was first calculated and the median of median values across patients was reported.

‡ CEIs cholinesterase inhibitors.

§ PIMcog potentially inappropriate medicine for people with cognitive impairment.

Appendix 1: Potentially inappropriate medicines related to cognitive impairment (PIMcog) [24] in Vietnam

Group	Name	ATC
Antipsychotics	Chlorpromazine	N05AA01
	Clozapine	N05AH02
	Loxapine	N05AH01
	Olanzapine	N05AH03
Tricyclic antidepressants	Amitriptyline	N06AA09
Antimuscarinics (urinary)	Flavoxate	G04BD02
	Oxybutynin	G04BD04
Antispasmodics	Atropine products	A03BA01
	Hyoscyamine products	A03BA03
	Loperamide	A07DA03
First generation antihistamines	Brompheniramine	R06AB01
	Chlorpheniramine	R06AB04
	Dexbrompheniramine	R06AB06
	Dexchlorpheniramine	R06AB02
	Diphenhydramine	R06AA02
	Hydroxyzine	N05BB01
	Promethazine	R06AD02
	Triprolidine	R06AX07
Other antihistamines (with anticholinergic properties)	Dimenhydrinate	R06AA52
	Loratadine	R06AX13
Antiparkinson agents	Trihexyphenidyl (benzhexol)	N04AA01
Benzodiazepines (BZD)	Diazepam	N05BA01
	Midazolam	N05CD08
Non-BZD hypnotics	Zolpidem	N05CF02
	Zopiclone	N05CF01
Barbiturates	Phenobarbital (Phenobarbitone)	N03AA02
Systemic corticosteroids	Betamethasone	H02AB01
	Betamethasone	R03BA04
	Dexamethasone	H02AB02
	Hydrocortisone	H02AB09
	Methylprednisolone	H02AB04
	Prednisolone/prednisone	H02AB06
	Triamcinolone	H02AB08
Histamine-2 receptor antagonists	Cimetidine	A02BA01
	Famotidine	A02BA03
	Ranitidine	A02BA02

Appendix 2: Medicines with anticholinergic and sedative properties [29,31] in Vietnam

Group	Name	ATC	Effect
H2 antagonists	Cimetidine	A02BA01	A1
H2 antagonists	Ranitidine	A02BA02	A1
GI disorder	Dicyclomine	A03AA07	A2
GI disorder	Atropine	A03BA01	A2
GI disorder	Domperidone	A03FA03	A1
Intestinal antiinfectives	Loperamide	A07DA03	A1
Antihypertensives	Methyldopa	C02AB01	S
Urinary incontinence	Flavoxate	G04BD02	A2
Urinary incontinence	Oxybutynin	G04BD04	A2
NSAID	Ketorolac	M01AB15	A1
Muscle relaxants	Methocarbamol	M03BA03	A1
Muscle relaxants	Baclofen	M03BX01	A1,S
Opioids	Morphine	N02AA01	A1,S
Opioids	Codeine/paracetamol	N02AA59	S
Opioids	Fentanyl	N02AB03	A1,S
Opioids	Dextropropoxyphene	N02AC04	S
Opioids	Tramadol	N02AX02	A1,S
Antiepileptics	Phenobarbital	N03AA02	S
Antiepileptics	Phenytoin	N03AB02	S
Antiepileptics	Clonazepam	N03AE01	A1,S
Antiepileptics	Carbamazepine	N03AF01	A1,S
Antiepileptics	Oxcarbazepine	N03AF02	A1
Antiepileptics	Valproate	N03AG01	S
Antiepileptics	Vigabatrin	N03AG04	S
Antiepileptics	Lamotrigine	N03AX09	S
Antiepileptics	Topiramate	N03AX11	S
Antiepileptics	Gabapentin	N03AX12	S
Antiepileptics	Pregabalin	N03AX16	S
Anticholinergic antiparkingson	Trihexyphenidyl	N04AA01	A2
Dopaminergic antiparkingson	Entacapone	N04BX02	A1
Antipsychotics	Chlorpromazine	N05AA01	A2,S
Antipsychotics	Levomepromazine	N05AA02	A2
Antipsychotics	Haloperidol	N05AD01	A1,S
Antipsychotics	Clozapine	N05AH02	A2
Antipsychotics	Olanzapine	N05AH03	A1,S
Antipsychotics	Quetiapine (fumarate)	N05AH04	A1,S
Antipsychotics	Amisulpride	N05AL05	S
Antipsychotics	Lithium	N05AN01	A1
Antipsychotics	Risperidone	N05AX08	A1,S
Anxiolytics Benzodiazepine	Diazepam	N05BA01	A1,S
Anxiolytics Benzodiazepine	Chlordiazepoxide	N05BA02	A1
Anxiolytics Benzodiazepine	Bromazepam	N05BA08	S

Anxiolytics other	Hydroxyzine	N05BB01	A2
Hypnotics Benzodiazepine related	Zopiclone	N05CF01	S
Hypnotics Benzodiazepine related	Zolpidem	N05CF02	S
Antidepressants	Amitriptyline	N06AA09	A2,S
Antidepressants	Fluoxetine	N06AB03	A1
Antidepressants	Citalopram	N06AB04	A1
Antidepressants	Fluvoxamine	N06AB08	A1
Antidepressants	Trazodone	N06AX05	A1
Antidepressants	Mirtazapine	N06AX11	A1,S
Opioid dependence	Methadone	N07BC02	A1
Obstructive airway diseases	Ipratropium	R03BB01	A2
Obstructive airway diseases	Theophylline	R03DA04	A1
Cough suppressants opium	Codeine	R05DA04	A1
Antihistamines	Dimenhydrinate	R06AA52	A2
Antihistamines	Diphenhydramine	R06AA02	A2
Antihistamines	Brompheniramine	R06AB01	A2
Antihistamines	Dexchlorpheniramine	R06AB02	A2
Antihistamines	Chlorphenamine	R06AB04	A2
Antihistamines	Pyrilamine	R06AC01	A2
Antihistamines	Alimemazine	R06AD01	A1
Antihistamines	Promethazine	R06AD02	A2,S
Antihistamines	Cetirizine	R06AE07	A1
Antihistamines	Loratadine	R06AX13	A1
Antihistamines	Fexofenadine	R06AX26	A1

Appendix 3: Medicines accounting for the difference between PIMcog list and the list of anticholinergic and sedative agents

Medicines on the list of anticholinergics and sedatives only			Medicines on the PIMcog list only	
Name	**ATC**	**Effect**	**Name**	**ATC**
Dicyclomine	A03AA07	A2	Famotidine	A02BA03
Domperidone	A03FA03	A1	Hyoscyamine products	A03BA03
Methyldopa	C02AB01	S	Betamethasone	H02AB01
Ketorolac	M01AB15	A1	Dexamethasone	H02AB02
Methocarbamol	M03BA03	A1	Methylprednisolone	H02AB04
Baclofen	M03BX01	A1,S	Prednisolone/prednisone	H02AB06
Morphine	N02AA01	A1,S	Triamcinolone	H02AB08
Codeine/paracetamol	N02AA59	S	Hydrocortisone	H02AB09
Fentanyl	N02AB03	A1,S	Loxapine	N05AH01
Dextropropoxyphene	N02AC04	S	Midazolam	N05CD08
Tramadol	N02AX02	A1,S	Betamethasone	R03BA04
Phenytoin	N03AB02	S	Dexbrompheniramine	R06AB06
Clonazepam	N03AE01	A1,S	Triprolidine	R06AX07
Carbamazepine	N03AF01	A1,S		
Oxcarbazepine	N03AF02	A1		
Valproate	N03AG01	S		
Vigabatrin	N03AG04	S		
Lamotrigine	N03AX09	S		
Topiramate	N03AX11	S		
Gabapentin	N03AX12	S		
Pregabalin	N03AX16	S		
Entacapone	N04BX02	A1		
Levomepromazine	N05AA02	A2		
Haloperidol	N05AD01	A1,S		
Quetiapine (fumarate)	N05AH04	A1,S		
Amisulpride	N05AL05	S		
Lithium	N05AN01	A1		
Risperidone	N05AX08	A1,S		
Chlordiazepoxide	N05BA02	A1		
Bromazepam	N05BA08	S		
Fluoxetine	N06AB03	A1		
Citalopram	N06AB04	A1		
Fluvoxamine	N06AB08	A1		
Trazodone	N06AX05	A1		
Mirtazapine	N06AX11	A1,S		
Methadone	N07BC02	A1		
Ipratropium	R03BB01	A2		
Theophylline	R03DA04	A1		

Codeine	R05DA04	A1
Pyrilamine	R06AC01	A2
Alimemazine	R06AD01	A1
Cetirizine	R06AE07	A1
Fexofenadine	R06AX26	A1