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RESEARCH ARTICLE

PHARMACISTS' ESSENTIAL KNOWLEDGE ON COGNITIVE IMPAIRMENT IN THE ELDERLY POPULATION

*¹Howraa Abed, ²Patrick Ball and ³Hana Morrissey

¹Pharmacist, Sydney, NSW, Australia

²Professor of Pharmacy, School of Pharmacy, Faculty of Science and Engineering,
University of Wolverhampton, United Kingdom

³Senior Lecturer in Clinical Pharmacy, School of Pharmacy, Faculty of Science and Engineering,
University of Wolverhampton, United Kingdom

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ABSTRACT

Background: There are various factors which can lead to irreversible, reversible cognitive impairments. The progression of reversible cognitive disorders can be halted by identifying and treating the underlying cause.

Aim of the Review: To expand pharmacists' knowledge on underlying causes of cognitive impairment and investigate the possibility of pharmacist involvement in the identification of and/or protection against cognitive impairment.

Method: A search of the literature was conducted through databases to identify studies in the English language of 1975-2016. Peer-reviewed articles and informational websites were included.

Results: There are two broad classifications of cognitive impairment, irreversible and reversible cognitive impairment. Pharmacists can play an essential role in early detection of cognitive impairment caused by medications.

Conclusion: Pharmacists have the potential to lead early detection of cognitive impairment caused by medications through appropriate management of the underlying problem. This may contribute to patients' better health outcomes and quality of life.

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INTRODUCTION

The human brain changes physiologically with aging (Sato and Endo, 2010). The aging process results in a profound impact on multiple levels ranging from sub-cellular to macro-structural changes (Sato and Endo, 2010). Also, medical conditions can damage various biological and physiological systems which directly or indirectly maintain optimal brain function and result in physical deterioration of the brain and subsequent cognitive decline. Some of these conditions are irreversible such as traumatic brain injuries, stroke and dementia. However, there are other factors which can lead to reversible or modifiable cognitive impairment. The progression of reversible cognitive disorders can be halted by identifying and treating the underlying cause of the symptoms. With appropriate treatment, a person's previous level of functioning can be restored or improved if the cause is not organ damage. Thus, cognitive impairment is often classified

into two broad categories; irreversible (not curable) and reversible (curable) based on the cause.

Aim of the review

The aim of this review is to expand pharmacists' knowledge on underlying causes of cognitive impairment and investigate the possibility of pharmacist involvement in identification of and/or protection against cognitive impairment.

MATERIALS AND METHODS

A search of the literature was conducted through Medline™, Embase™ and Google™ Scholar databases to identify studies in English language between 1975 and 2016. The following keywords were used: cognitive impairment, cognitive impairment AND causes, cognitive impairment AND modifiable causes, cognitive impairment AND non-modifiable causes, cognitive impairment AND medications and pharmacist role AND cognitive impairment. Letters, commentaries and commercial websites were excluded, only peer reviewed articles and informational websites were included. (Table I)

*Corresponding author: Howraa Abed,
Pharmacist, Sydney, NSW, Australia

RESULTS

Non-modifiable causes (irreversible) of cognitive impairment

While it is not included under the aim of this paper, it is mentioned here to clarify the difference between the two pathways of cognitive compromise causes and to demonstrate that most of the current literature is concentrating on these when compared to modifiable causes.

Aging

Neuronal and mitochondrial membranes deteriorate with aging which results in impaired neuronal function and loss of cellular integrity (Sato and Endo, 2010). Additionally, with aging, neurotransmitter synthesis and signalling declines (Backman, Lindenberger, Li, and Nyberg, 2010) coupled with reductions in synaptic adaptability and density (Sametsky, Disterhoft, Geinisman, and Nicholson, 2010) and a loss in the length of myelinated axons of as much as fifty percent (Backman *et al.*, 2010). Furthermore, with age, the physical structure of the brain deteriorates as a whole (Fjell and Walhovd, 2010). The sub-cortical volume in some regions of the brain and the cortical thickness reduces annually as much as 0.5% to 1.0% due to the reduced functional synapses and synaptic spine numbers, and the death and shrinkage of neurons (Fjell and Walhovd, 2010). Thus, age-related physical degradation of brain structure results in cognitive decline (Fjell and Walhovd, 2010). It has been estimated that the age related neuroanatomical changes account for between 25% and 100% of the variance in cognitive ability between young and aged individuals (Fjell and Walhovd, 2010). Thus, aggressive and early interventions are required to conserve cognitive performance into later life and preserve the brain in a more youthful functional and physical state (Fjell and Walhovd, 2010).

Medical conditions

Traumatic Brain Injuries

It has been reported by the Australian Institute of Health and Welfare (Rutland-Brown *et al.*, 2006) that in 2005 107 Australian in every 100,000 people experienced long-term loss of function including cognitive impairments as a result of brain injuries (Arciniegas *et al.*, 2002; Rutland-Brown *et al.*, 2006). At all levels of severity of TBI, the disturbances of memory, attention and executive functioning are considered to be the most common neurocognitive consequences (Arciniegas *et al.*, 2002). Disturbances in memory and attention, the relatively basic cognitive functions, are specifically problematic, because they may result in, or exacerbate, additional disturbances in communication, executive function, and other complex cognitive functions (Arciniegas *et al.*, 2002). Thus, TBI is considered to be the leading cause of disability and death in industrialized countries in people less than 45 years of age (Arciniegas *et al.*, 2002).

Dementia

Dementias are degenerative, progressive, irreversible disorders that gradually decrease an individual's ability to function in daily occupational and social activities (Dementia, 2011). Individuals may experience impairment in memory, language skills, orientation, judgment and/or executive functioning.

People with dementia are not able to restore their previous level of functioning, although some of their symptoms may be managed through treatment. (Dementia, 2011) There are many types of dementia such as Lewy body dementia or vascular dementia. However, Alzheimer's disease is the most common form of dementia accounting for nearly 60-80% of all dementias. (Wong *et al.*, 2013) Alzheimer's disease cannot yet be prevented or cured, and the evidence it can be slowed in its progression is equivocal (Wong *et al.*, 2013).

Modifiable causes (reversible) of cognitive impairment

Medical condition

There are many medical conditions which have the potential to cause cognitive impairment including delirium, depression, low HDL levels, hypertension, diabetes and insulin resistance (Table II) (Bellew *et al.*, 2004; Biessels *et al.*, 2006; Centeno, *et al.*, 2004; Panza *et al.*, 2010; Ward *et al.*, 2010).

Medications

Psychoactive Drugs

One of the commonest causes of medication-induced cognitive impairment is psychoactive drugs (Francis *et al.*, 1990; Larson *et al.*, 1987; Marcantonio *et al.*, 1994). The toxicity of these medications is dose-related as well as to the vulnerability of each patient. Delirium and dementia severity has been linked to benzodiazepines. One study showed that 14% of 50 delirious patients had benzodiazepine toxicity (Francis *et al.*, 1990). Delirium has been associated with longer-acting benzodiazepines, such as diazepam, and high dose treatment (more than 5 mg/day or equivalent) (Starr and Whalley, 1994). Also, long-acting benzodiazepines are the commonest medications reported to cause dementia (Starr & Whalley, 1994). Moreover, a common cause of delirium in hospital patients is the abrupt withdrawal of short-acting benzodiazepines (Francis *et al.*, 1990). Barbiturates have the potential to cause chronic cognitive impairment mimicking Alzheimer's disease (Moore and O'Keeffe, 1999). Other psychoactive medications which contribute to cognitive impairment include: opioid analgesics, antipsychotics, antiparkinsonian drugs, antidepressants and anticonvulsants (Moore and O'Keeffe, 1999).

Non-psychoactive Drugs

Non-psychoactive medication-induced cognitive impairment is easily missed due to its idiosyncratic nature (Moore & O'Keeffe, 1999). Histamine-2 (H2) receptor antagonists have been linked with acute CNS toxicity including delirium (Cantu and Korek, 1991). A literature overview concluded that there was no difference between different H2 antagonists in relation to their CNS toxicity although cimetidine has been mentioned in many reports (Cantu and Korek, 1991). Although rare in outpatients, it has been shown that 1-2% of all hospital patients (Kowalsky *et al.*, 1989) and 15-80% of intensive care patients (Schentag *et al.*, 1979) suffered H2 antagonists-induced CNS toxicity. Additionally, proton pump inhibitors such as omeprazole have the potential to cause delirium. Idiosyncratic cognitive impairment has been seen among patients using calcium channel blockers (Maxwell *et al.*, 1999).

Table 1. Number of articles per search term

Search term: Cognitive impairment							
Data bases	Articles found with first search	Articles excluded before being reviewed due to publication date (<1975) and language (other than English).	Articles included For the first review	Articles excluded second round due to subjects' age (<65 years) and the unavailability of full text	Final number of articles included and cited in the thesis to develop the research concept	Final number of articles included and cited in this literature review	Final number of articles included and cited in this literature review
Medline	46,675	2,807	43,868	38,856	5	3	
PubMed	117,982	10,096	107,886	77,875	10	9	
Google Scholar Website	2,210,000	770,000	1,440,000	1423000	1	0	
8,340,000	10,000	8,330,000	4,280,000	5	4		
Search term: Cognitive impairment AND causes							
Data bases	Articles found with first search	Articles excluded before being reviewed due to publication date (<1975) and language (other than English).	Articles included For the first review	Articles excluded second round due to subjects' age (<65 years) and the unavailability of full text	Final number of articles included and cited in the thesis to develop the research concept	Final number of articles included and cited in this literature review	Final number of articles included and cited in this literature review
Medline	4,377	332	4,045	3771	7	4	
PubMed	59,367	5,290	54,077	38,737	13	9	
Google Scholar Website	1,440,000	1,422,500	17,500	500	12	4	
11,400,000	4250,000	7,150,000	2,870,000	0	0		
Search term: Cognitive impairment AND modifiable causes							
Data bases	Articles found with first search	Articles excluded before being reviewed due to publication date (<1975) and language (other than English).	Articles included For the first review	Articles excluded second round due to subjects' age (<65 years) and the unavailability of full text	Final number of articles included and cited in the thesis to develop the research concept	Final number of articles included and cited in this literature review	Final number of articles included and cited in this literature review
Medline	1,653	56	1,597	1,443	1	1	
PubMed	267	8	259	134	10	8	
Google Scholar Website	32,600	16,500	16,100	100	2	1	
141,000	79,700	61,300	600	1	1		
Search term: Cognitive impairment AND non-modifiable causes							
Data bases	Articles found with first search	Articles excluded before being reviewed due to publication date (<1975) and language (other than English).	Articles included For the first review	Articles excluded second round due to subjects' age (<65 years) and the unavailability of full text	Final number of articles included and cited in the thesis to develop the research concept	Final number of articles included and cited in this literature review	Final number of articles included and cited in this literature review
Medline	3,673	143	3,530	3,201	2	2	
PubMed	7	0	7	3	1	0	
Google Scholar Website	3,390	80	3,310	1120	1	1	
139,000	94900	44,100	17,900	0	0		
Search term: Cognitive impairment AND medications and pharmacist role AND cognitive impairment							
Data bases	Articles found with first search	Articles excluded before being reviewed due to publication date (<1975) and language (other than English).	Articles included For the first review	Articles excluded second round due to subjects' age (<65 years) and the unavailability of full text	Final number of articles included and cited in the thesis to develop the research concept	Final number of articles included and cited in this literature review	Final number of articles included and cited in this literature review
Medline	4	0	4	3	1	0	
PubMed	9	1	8	6	2	0	
Google Scholar Website	25,600	9,100	16,500	300	4	3	
3,190,000	2,482,000	708,000	693,500	0	0		
Total of all searches					78	50	

Table 2. Summary of modifiable medical conditions which have the potential to cause cognitive impairment

Medical condition	
Delirium	Delirium is a transient confusion state of acute sudden onset & fluctuating course, with altered level of consciousness and abnormal attention, and/or thinking disturbances such as disordered perception, cognition and/or behaviour (Centeno et al., 2004). These symptoms develop over a short time period and tend to change throughout a 24-hour period, it has been demonstrated that reduction of acetylcholine as well as changes in serotonin, γ -aminobutyric acid, histamine, and noradrenaline have the potential to develop delirium. Delirium is a serious problem which is associated with greater mortality (rates from 10% to 65%) (Inouye, 1994), long hospital stays, high healthcare costs, high rates of institutionalization as well as less functional independence (Wei, Fearing, Sternberg, & Inouye, 2008). It has been shown that delirium increases hospital costs by at least \$2,500 per patient (Wei et al., 2008). There are many causes that contribute to delirium including: infections with or without sepsis, fluid or electrolyte abnormalities, hypoglycaemia, hypoxemia, acute drug withdrawal from benzodiazepines, ethanol or barbiturates and drug intoxications. Additionally chronic use of benzodiazepine considered as one of the most common causes of delirium (Johnson, Sims, & Gottlieb, 1994).

continue.....

Depression	Depression has a close relationship with cognitive dysfunction. It has been shown in many studies that depression has the potential to deteriorate cognitive dysfunction, but individuals with poor cognitive health are predisposed to depression too (Panza et al., 2010). Furthermore, a study which assessed the relationship between depression and age-related cognitive function, showed that more than 50% of depressed individuals scored less than 10% of the control subjects (those non-depressed and of same age and sex group), based on various cognitive tests which they completed (Butters et al., 2004). It has been concluded that depression which occurs later in life is associated with impaired information processing that affects cognition as a whole (Butters et al., 2004). "Depression-associated reversible dementia," has been defined as a cognitive impairment which is associated with depression and resolves upon treatment of depression (Alexopoulos, Meyers, Young, Mattis, & Kakuma, 1993). However, it has been shown that over approximately three years individuals with depression-related dementia were roughly five times more likely to establish true dementia (Alexopoulos et al., 1993).
HDL levels	Fluctuated HDL levels have been linked with cognitive function. Individuals with low HDL levels, potentially, at greater risk for future cognitive impairment than those with high HDL levels (Ward et al., 2010). One study of 183 subjects (mean age was 58 years) showed that the volume brain grey matter were positively associated with HDL levels based on MRI images (Ward et al., 2010). Moreover, individuals with higher HDL levels also scored considerably higher than those with lower HDL on a visuo-spatial memory test (Ward et al., 2010).
Hypertension	Chronic high blood pressure has the potential to damage cerebro-capillaries as they are small and delicate. This damage associates with cognitive impairment and neurodegenerative diseases development. A case-control study of more than 700 patients showed the strong association between rate of cognitive impairment and blood pressure over a period of six months for individuals ≤ 65 years (Bellew et al., 2004). Another observational study of ≥ 1800 subjects showed that people taking one antihypertensive medication were at lower risk for dementia development over a period of three years and less likely to have dementia at the time of the study. Moreover, individuals who weren't on any antihypertensive medications and did suffer dementia at baseline exhibited a two-fold faster rate of cognitive impairment than individuals with dementia whose hypertension is controlled by medication. Furthermore, a study which followed 717 subjects for 38 years showed that individuals with normal systolic blood pressure perform better than those with systolic blood pressure of ≥ 140 mmHg based on a composite measure of memory and verbal learning (Swan, Carmelli, & Larue, 1998).
Diabetes and Insulin Resistance	Small changes in the metabolism of glucose can impact cognitive function due to the brain's high metabolic demand for energy. Diabetes (hyperglycaemia) has been associated with increased incidence of all types of dementia (Biessels et al., 2006). A study of 23 patients (diabetic or pre-diabetic) and 6 subjects without diabetes with a mean age of 74 years showed that during the memorization task both groups show different patterns of brain activity and glucose usage (Baker et al., 2011). Upon the recall attempt, subjects with impaired glucose metabolism remembered fewer words compare with control subjects. Moreover, diabetic/pre-diabetic patients' FDG-PET scans resembled Alzheimer's patients' brain scans (Baker et al., 2011). Another study showed that diabetes has harmful effects on the integrity of neurons (van Elderen et al., 2010). The progression of brain atrophy was accelerated with considerable consequences in cognition among type-2 diabetic elderly patients compared to individuals without type-2 diabetes (van Elderen et al., 2010). Moreover, a different study showed that overall cognitive decline was associated with higher insulin secretion and greater fasting insulin in older individuals (Okereke et al., 2010).

Other non-psychoactive medications that result in cognitive impairment include: corticosteroids, non-steroidal anti-inflammatory drugs and some antibiotics (Moore and O'Keeffe, 1999). A concurrent biochemical imbalance may be a factor in the higher incidence in hospitalised patients.

Anticholinergic Drugs

Due to the role of the cortical cholinergic system in memory function and attention processes (Sarter and Bruno, 1997), the central side effects of medications with anticholinergic properties are associated with attention deficit, confusion and impaired concentration and memory. Moreover, medications which block muscarinic cholinergic receptors have been conclusively demonstrated in many pharmacological studies to impair working memory for some stimuli and the encoding of new memories (Hasselmo, 2006). Many studies have demonstrated short term or cross-sectional links between functional or cognitive impairment and the use of medications which exhibit anticholinergic properties (Ball et al., 2013). A study conducted among the elderly found that delirium was linked with higher serum anticholinergic activity (Hasselmo, 2006). According to a study conducted among a eugeria population of 372 sample size, the continued use of anticholinergic medications was associated with greater risk of having mild cognitive impairment and poorer performance on language tasks, attention, visuospatial construction, narrative recall, delayed non-verbal memory and reaction time (Ancelin et al., 2006). Also, the PAQUID population study (n=1780) showed a significant association between the use of anticholinergic medications and the poorer performance on the mini-mental state examination (MMSE), visual memory and verbal fluency (Lechevallier-Michel et al., 2005). In addition, the BRAiNS study with 3075 participants showed that the baseline use of anticholinergics has led to accelerated decline

over six years on psychomotor speed, executive functioning and attention (Bottiggi et al., 2006). The Health Aging and Body Composition study, which was based on a sample of 3075 people, reported that on the digit symbol substitution test, the use of medications with anticholinergic properties was associated with poorer performance (Hilmer et al., 2007). It has been reported in the elderly volunteers amongst psychogeriatric inpatients with moderate to severe dementia (n=26) (Chew et al., 2005) and a community dwelling cohort (n=201) (Mulsant et al., 2003) that the serum anticholinergic levels are associated with slowing in simple response time, and poorer MMSE scores. Several reports showed serum anticholinergic activity interacts with white matter hyper-intensity volume. A study found that on implicit learning and number comparison, participants with both greater anticholinergic levels and higher hyper-intensity volumes were performing most poorly among participants (Nebes et al., 2005). This suggests that medications with anticholinergic properties have the potential to exacerbate the cognitive decline due to the morphological changes in the brain (Nebes et al., 2005). A recent cohort community-dwelling study of 544 older men who suffered hypertension, demonstrated that cumulative anticholinergic exposure can lead to poor performance on verbal memory over 2 years (Carriere et al., 2009). Thus, several cross sectional studies conducted in the elderly have demonstrated a link between anticholinergic medication and psychomotor speed, global cognitive functioning, implicit learning, cognitive functioning and declarative and visual memory (Carriere et al., 2009). Moreover, cognitive impairment has been identified as central to abnormalities in different medical conditions such as schizophrenia and dementia. The use of medications with anticholinergic properties has the potential to exacerbate pre-existing impairment. Dementia is one of the most common medical conditions in the elderly population (Ball et al., 2013)

The number of Australians who suffered dementia in 2011 was 298,000 (Ball *et al.*, 2013). By the year 2050 number of dementia cases will approach 900,000 (Ball *et al.*, 2013; Landi *et al.*, 2007). Most of those diagnosed with dementia are expected to suffer Alzheimer's disease (Fortin *et al.*, 2011). The earliest and most frequent symptom of Alzheimer's disease is memory impairment, which can trigger further investigations by health professionals of the potential causes. (Fortin *et al.*, 2011) During the early stages of Alzheimer's disease the episodic memory is impaired. (Fortin *et al.*, 2011) Thus, the partial restoration of the brain's acetylcholine levels is the main goal of Alzheimer's disease treatment (Fortin *et al.*, 2011). However, the elderly are often prescribed medications with anticholinergic properties although they often complain of memory loss and are at risk of Alzheimer's disease (Fortin *et al.*, 2011). Many medications are not recognised to have anticholinergic properties (Fortin *et al.*, 2011). It has been estimated that about 600 medications have unwanted anticholinergic properties (Tune, 2000). There is potential that those patients receiving medications with anticholinergic side effects may be misdiagnosed with irreversible cognitive impairment or their pre-existing memory impairment become worse (Fortin *et al.*, 2011). Additionally, literature has shown that treatments combining multiple drugs with modest anticholinergic activity have the potential to increase cognitive impairment in an elderly population with dementia (Thienhaus *et al.*, 1990).

DISCUSSION

Chronic use of medications with anticholinergic side effects may promote the development of delirium in people who are diagnosed with one or more chronic diseases who are frail or aged. The severity of delirium may increase with certain medications, which normally may not cause the same intensity of effect when administered to other less vulnerable or younger patients. Comprehensive list was collated by fox *et al.* 2011 (Fox *et al.*, 2011) such as tricyclic antidepressant (TCA), oxybutynin and frusemide (Fox *et al.*, 2011). Hypothetically, to establish a possible relationship between medication and cognitive impairment, the medication administration must precede the onset of cognitive impairment or worsening within a period of time, often hours to days based on the medication half-life (steady state or area under the curve as applicable), and the cessation of the suspected drug resulting in the improvement or restoration of the patient's cognitive function (this is the hypothesis of an ongoing study conducted by corresponding author). The literature also shows that medications are among the most reported causes of delirium in the elderly patients presenting to emergency departments (Moore and O'Keefe, 1999). More than one study showed that medications with anticholinergic properties increase the accumulative risk of cognitive impairment including delirium and counted for 11-30% of elderly hospital patients (Fox *et al.*, 2011; George *et al.*, 1997; O'Keefe and Lavan, 1999). Additionally, it has been shown that the relative odds ratio of medication-induced cognitive impairment was 1.0 when the patient used 0-1 medication and was elevated to 9.3 when the patient used 4-5 medications (Moore and O'Keefe, 1999). However, this is not always the case. Using medications to treat different medical conditions has been shown to potentially reduce cognitive impairment. Individuals, who had untreated hypertension and dementia at baseline, exhibited a two-fold greater rate of cognitive impairment than individuals with dementia whose hypertension is controlled by medication.

It has been shown that overall cognitive decline was associated with higher insulin secretion and greater fasting insulin in older individuals (Okereke *et al.*, 2010) and depression has the potential to worsen cognitive dysfunction (Panza *et al.*, 2010). Thus, although some cognitive impairment caused by medications cannot be reversed due to the absence of alternatives. This inability to removing this anticholinergic burden is considered to be one of the leading cause of disability in industrialized countries This bring the question of the possibility, when alternative can be found, to reverse some or the entire of the diagnosed cognitive impairment through reviewing patients' medication regimen by a pharmacist (Wong *et al.*, 2013).

Conclusion

While pharmacists can contribute to the identification of cognitive impairment caused by medications, more research is required to improve pharmacy services including the management of medications with anticholinergic burden. The review identified the gap that pharmacists may have the capacity to fill through protocols used medication review.

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