Effect of Antimuscarinic Drugs on Cognitive Functions in the Management of Overactive Bladder in Elderly

Ervandy Rangganata, Fina Widia, Harrina E. Rahardjo

Department of Urology, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Harrina Erlianti Rahardjo, MD., PhD. Department of Urology, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. email: harrinaerlianti@gmail.com.

ABSTRAK

Latar belakang: *overactive bladder (OAB) terjadi pada sekitar 17-41% pada lansia di lingkungan tempat tinggal komunitas. Selama beberapa tahun, antimuskarinik telah divalidasi sebagai pilihan pertama untuk tata laksana OAB. Meskipun banyak data yang diperoleh dari uji klinis terkait penggunaan antimuskarinik. Penelitian terkait efek samping dari obat antimuskarinik terhadap fungsi kognitif pada lansia masih jarang dilakukan. Tujuan dari penelitian ini adalah untuk mengetahui efek dari terapi antimuskarinik terhadap fungsi kognitif pada pasien lanjut usia dengan OAB.* ***Metode:*** *desain penelitian ini adalah tinjauan sistematis dan meta-analisis. Studi dikumpulkan menggunakan beberapa mesin pencari; diantaranya adalah PubMed, Science Direct, Cochrane, and EBSCOhost menggunakan kata kunci MeSH yang sudah ditentukan sebelumnya dengan operator Boolean. Pemilihan studi dilakukan oleh 3 pengulas. Seluruh studi yang memenuhi kriteria inklusi selanjutnya melalui proses review full-text. Untuk setiap artikel full-text yang terpilih, ekstraksi data dilakukan pada data: demografis pasien, tipe antimuskarinik yang digunakan, placebo, dosis, follow-up, dan skor total Mini Mental State Examination(MMSE).* ***Hasil:*** *total sebanyak 8 studi yang terpilih dari 146 publikasi yang ada sebelumnya. Terdapat 8 jenis antimuskarinik yang dievaluasi dari studi-studi yang ada, yaitu: Oksibutinin, Darifenacin, Tolterodin, Trospium, Imidafenacin, Propiverin hidroklorida, Fesoterodin, dan Solifenacin. Oksibutinin menunjukkan efek yang paling besar pada penurunan skor MMSE [Perbedaan rerata: -2,90; 95% CI: -4,07, -1,73]. Darifenacin dan Tolterodin juga menunjukkan penurunan yang signifikan pada skor total MMSE, namun lebih inferior daripada Oksibutinin.* ***Kesimpulan:*** *penggunaan obat-obatan antimuskarinik hanya memiliki efek yang minimal terhadap fungsi kognitif dalam penanganan OAB pada pasien usia lanjut. Akan tetapi, Oksibutinin, Darifenacin, dan Tolterodin menunjukkan penurunan yang signifikan terhadap fungsi kognitif, ditunjukkan dari penurunan total skor MMSE.*

Keywords: *obat antimuskarinik, fungsi kognitif, overactive bladder, mini-mental state examination (MMSE).*

ABSTRACT

Background: *overactive bladder (OAB) affects 17-41% older adults in community dwelled setting. For several years, antimuscarinics have been validated as the first-line medical treatment for OAB. Despite abundant data obtained from clinical trials provisions the use of antimuscarinics, investigation about the effect of this drug on cognitive function in elderly remains scarce. The objective of this study is to investigate the effect of antimuscarinics therapy on cognitive functions in OAB geriatric patients.* ***Methods:*** *this study design is a systematic review and meta-analysis. Studies were collected using several search engines; those were PubMed, Science Direct, Cochrane, and EBSCOhost using predetermined MeSH keywords with Boolean operators. Selection of studies was done by three reviewers. Studies which fulfilled the inclusion and exclusion criteria underwent full-text review. For every selected full text, we extracted the following data if available: patients demographics, types of antimuscarinics used, placebo, dose, follow-up period, and Mini-Mental State Examination (MMSE) total score.* ***Results:*** *a total of 8*

studies from an initial 146 publications were selected. There were 8 antimuscarinic agents evaluated in the studies, including Oxybutynin, Darifenacin, Tolterodine, Trospium, Imidafenacin, Propiverine hydrochloride, Fesoterodine, and Solifenacin. Oxybutynin was shown to have largest effect towards the decline of MMSE score [Mean difference: -2.90; 95% CI: -4.07, -1.73]. Darifenacin and Tolterodine were also shown to be significant in the decline of total MMSE score, although still inferior to Oxybutynin. ***Conclusion:*** *the use of most antimuscarinics medication has little to no effect towards the cognitive function in the management of overactive bladder in elderly patients. However, Oxybutynin, Darifenacin, and Tolterodine was shown to have significant decrease in cognitive functions, as shown in the decline of total MMSE score.*

Keywords: *antimuscarinic drugs, cognitive functions, overactive bladder, mini-mental state examination (MMSE).*

INTRODUCTION

Overactive bladder (OAB) affects 17-41% of community-dwelling older adults.[1] It is best described as a chronic condition which is usually characterized with frequency and nocturia symptoms and urgency, with or without urge incontinence.[2,3] The prevalence of OAB is positively correlated with aging.[4] Not only does OAB cause urinary complaints, OAB may also cause falls and fractures in older adults.[4] The efficacy and tolerability of antimuscarinic therapy for the management of OAB is well established. For several years, antimuscarinics have been validated as the first-line medical treatment for OAB.[5]

Antimuscarinics therapy have several adverse effects, such as constipation, dry mouth, and blurred vision which happen due to the acetylcholine receptors inhibition. The CNS side effects include memory loss, insomnia, anxiety, headache, pain, and cognitive dysfunction.[5] The cholinergic system has an important role in cognitive functions and memory.

Elderly with Alzheimer's disease is more prone to get CNS side effects after taking antimuscarinics drugs. This tendency may also be caused by the blood-brain barrier (BBB) impairment.[6] In daily clinical setting, the antimuscarinic medication is only administered when the benefits outweigh the risks. The prescription of antimuscarinic drugs for geriatric population is often challenging due to the consideration regarding efficacy and side effects.[7] The available products of antimuscarinics include oxybutynin, solifenacin, tolterodine, darifenacin, propiverine hydrochloride, imidafenacin, fesoterodine, and trospium.[8]

The investigation about the effect of this drug on cognitive function in elderly remains scarce. Studies which investigate the effect of antimuscarinics on cognitive function in OAB patients are lacking. Consequently, the current available scientific evidence is not in accordance with clinical pictures. It is due to several reasons, such as the pre-existing cognitive impairment in elderly, comorbidities, geriatric problems, and various cognitive measurement tools. The objective of this study is to investigate the effect of antimuscarinics therapy on cognitive functions in OAB geriatric patients.

METHODS

Eligibility Criteria

This systematic review and meta-analysis aims to investigate the effect of antimuscarinic drug on cognitive functions in the management of overactive bladder in elderly. Our PICO is mentioned in **Table 1**. Searching strategy was not limited by date of publication and only full-text articles were used. The data searching process was not limited by language.

Information Sources

Studies were collected using several databases; namely PubMed, Science Direct, Cochrane, and EBSCOhost and obtained

Table 1. PICO

Patients	Elderly patients with overactive bladder (OAB)
Interventions	Antimuscarinic drugs
Comparisons	Placebo
Outcome	Cognitive functions

unpublished data through manual searching. The exact keywords used were: (antimuscarinics OR oxybutynin OR solifenacin OR trospium OR darifenacin OR tolterodine OR imidafenacin OR fesoterodine OR propiverine hydrochloride) AND (placebo OR sham) AND (overactive bladder OR detrusor overactivity) AND (cognitive function OR delirium OR dementia OR MMSE OR Mini-Mental State Examination) AND (elderly OR senile OR geriatric OR old*).

All keywords used were searched for their respective MeSH thesaurus. Data searching process was not limited by date of publication and only full-text articles were used. Article selection was not limited by English language. Article selection was done according to the search strategy recommended by Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). Only studies investigating the effect of antimuscarinics on cognitive functions in elderly OAB patients were assessed for further analysis. Studies conducted in other than human and non-placebo controlled were excluded from the review. Data from all selected articles were extracted independently by three reviewers. Any disagreements were solved by consensus. Relevant parameters explored using Review Manager V5.3.

Study Selection and Data Extraction

All studies were screened for duplication. Duplication-free article underwent title and abstract examination based on predetermined inclusion and exclusion criteria. Selection of studies was done by three reviewers (ER, HE, and FW). In case of disagreement, resolution was achieved through discussion or a third party's adjudication. Studies which fulfilled the inclusion and exclusion criteria underwent full-text review. We extracted the following data from selected full text if available: patients demographics, types of antimuscarinics used (oxybutynin, darifenacin, tolterodine, trospium, imidafenacin, propiverine hydrochloride, fesoterodine, and solifenacin), placebo, dose, follow-up period, and Mini-Mental State Examination (MMSE) total score.

Criteria for Studies

Types of studies. This review included all studies that investigate the effect of antimuscarinic drug on cognitive functions in the management of overactive bladder in elderly. Types of literature included in this study were either clinical trial or cohort design. There were no date nor language restrictions of studies.

Types of outcome measures. The outcome measure of this study is the total score of MMSE which comprises of 5 parameters, namely orientation, registration, attention and calculation, recall, and language.

Data Collection and analysis. Data collected were relevant information about intervention,

Table 2. Database, search terms and number of articles retrieved.

Database	Search strategy	Hits
PubMed	((antimuscarinics OR oxybutynin OR solifenacin OR trospium OR darifenacin OR tolterodine OR imidafenacin OR fesoterodine OR propiverine hydrochloride) AND (placebo OR sham) AND (overactive bladder OR detrusor overactivity) AND (cognitive function OR delirium OR dementia OR MMSE OR Mini-Mental State Examination) AND (elderly OR senile OR geriatric OR old*))	20
Cochrane	((antimuscarinics OR oxybutynin OR solifenacin OR trospium OR darifenacin OR tolterodine OR imidafenacin OR fesoterodine OR propiverine hydrochloride) AND (placebo OR sham) AND (overactive bladder OR detrusor overactivity) AND (cognitive function OR delirium OR dementia OR MMSE OR Mini-Mental State Examination) AND (elderly OR senile OR geriatric OR old*))	9
ScienceDirect	((antimuscarinics OR oxybutynin OR solifenacin OR trospium OR darifenacin OR tolterodine OR imidafenacin OR fesoterodine OR propiverine hydrochloride) AND (placebo OR sham) AND (overactive bladder OR detrusor overactivity) AND (cognitive function OR delirium OR dementia OR MMSE OR Mini-Mental State Examination) AND (elderly OR senile OR geriatric OR old*))	113
EBSCOhost	((antimuscarinics OR oxybutynin OR solifenacin OR trospium OR darifenacin OR tolterodine OR imidafenacin OR fesoterodine OR propiverine hydrochloride) AND (placebo OR sham) AND (overactive bladder OR detrusor overactivity) AND (cognitive function OR delirium OR dementia OR MMSE OR Mini-Mental State Examination) AND (elderly OR senile OR geriatric OR old*))	4

characteristics and outcomes suits inclusion criteria formed by reviewers. Data analyses were conducted by two independent reviewers. Studies were appraised based on the Oxford Center of Evidence-Based Medicine Worksheet for therapy and analyzed using Review Manager 5.3 to study meta-analysis. Weighted mean differences (WMD) and odds ratio were used to analyze each study variables. The confidence interval was 95%, and p-value less than 0.05 are considered insignificant.

Cochrane Q test was used to study the heterogeneity of studies. Heterogeneity was assessed using I2 statistic. The I2 value less than 50% indicated that studies were homogeneous, consequently fixed effect model was used. The I2 value more than 50% indicated that studies were heterogeneous, and random effect model were used.

RESULTS

Literature Search

A total of 146 publications were initially retrieved (**Figure 1**). Of these, 106 studies were excluded due to duplication. Moreover, 28 were excluded during title and abstract screening. Eight studies underwent full-text appraisal, both qualitative and quantitative analysis.

Eight studies were assessed to estimate the effect of various antimuscarinic agents on the cognitive functions in the elderly OAB patients. There were 8 antimuscarinic agents evaluated in the studies. Oxybutynin was shown to have largest effect towards the decline of MMSE score [Mean difference: -2.90; 95% CI: -4.07, -1.73]. Darifenacin and Tolterodine were also shown to be significant in the decline of total MMSE score. However, the total MMSE score decline

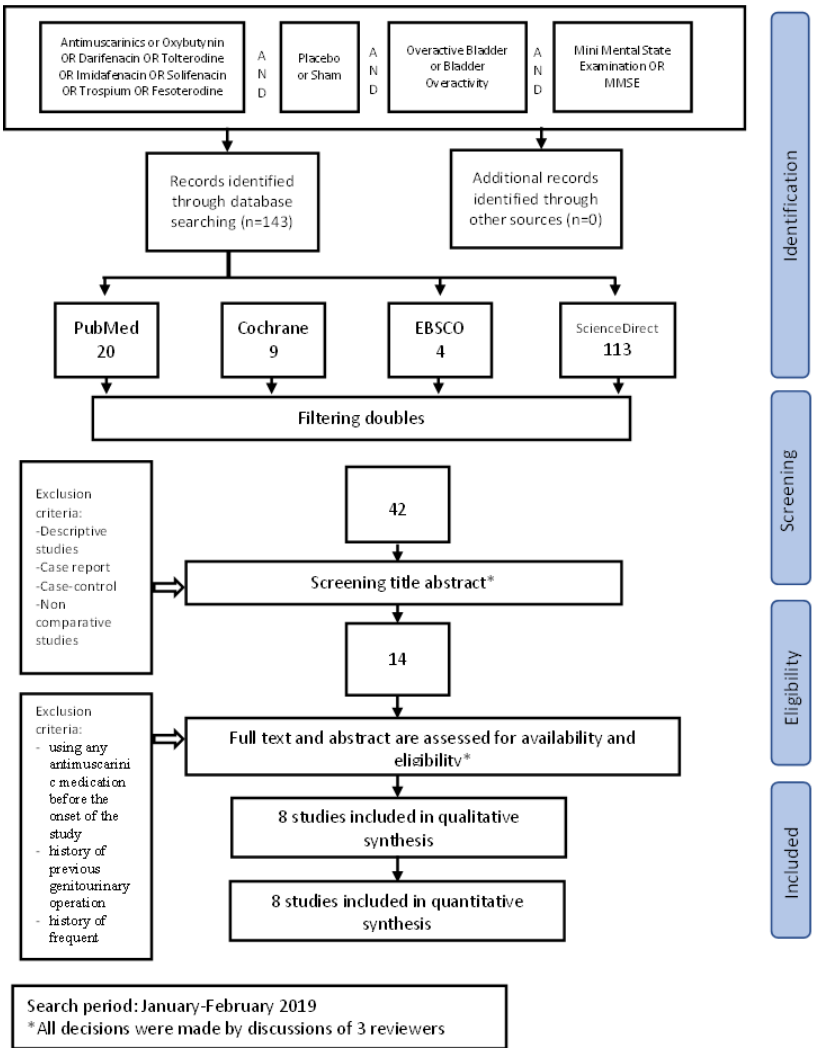

Figure 1. Study flow diagram.

mean difference of Darifenacin and Tolterodine was inferior compared to Oxybutynin. The total MMSE score decline mean difference of MMSE score in Darifenacin group was -2.70 (-4.03, -1.37), while in Tolterodine group was -1.60 (-3.04, -0.16). Other agents such as Trospium, Imidafenacin, Fesoterodine, and Solifenacin were not shown to decrease MMSE total score in elderly OAB patients. There was one study assessing the effect of Propiverine hydrochloride

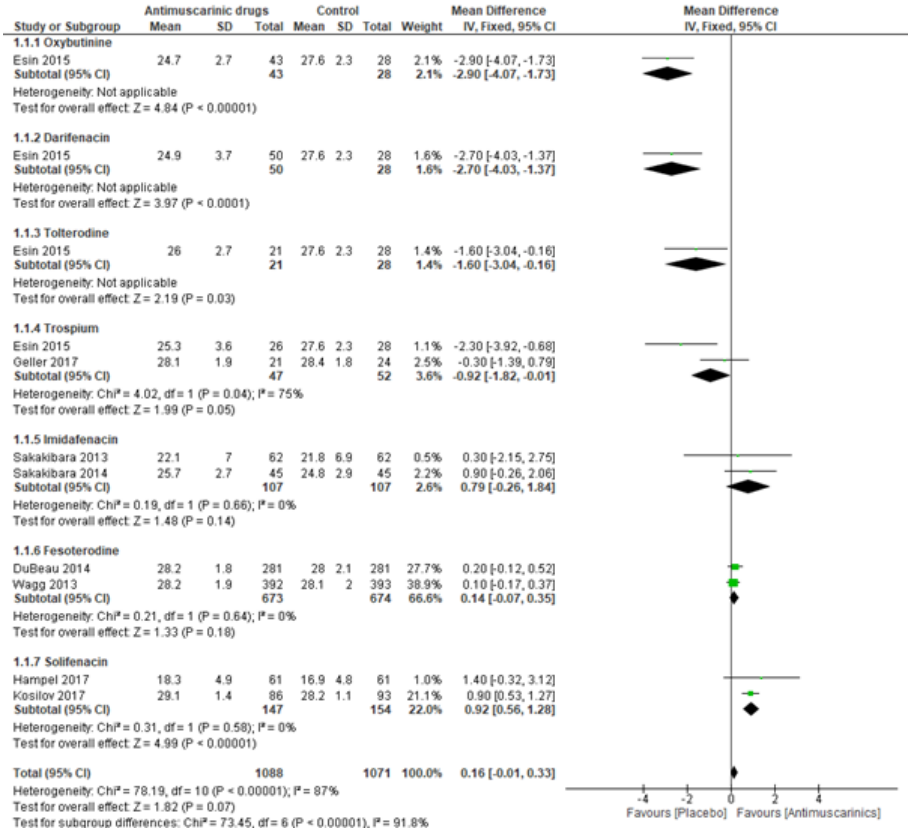

Figure 2.

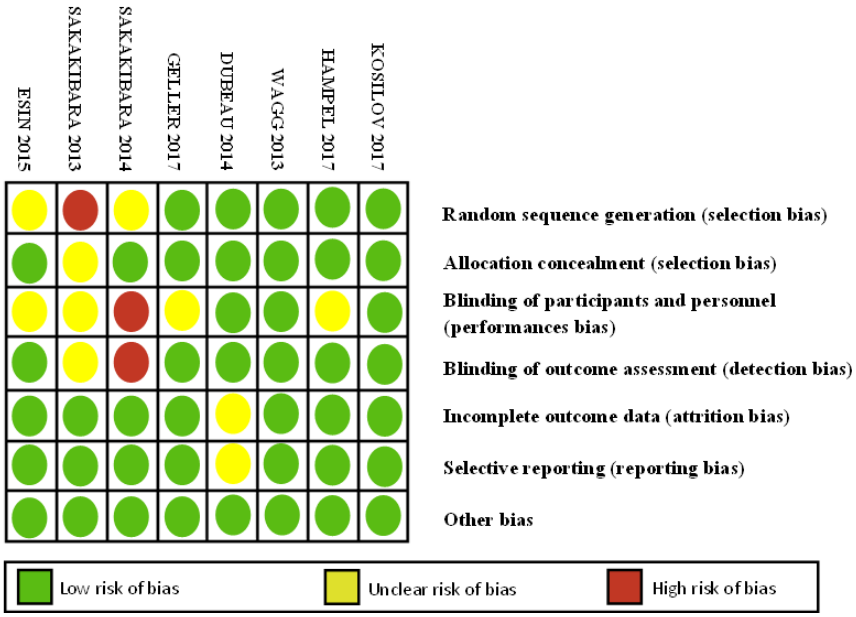

Figure 3. Risk of bias assessment of the included studies.

towards cognitive function, but the subject criteria was not elderly.

The risk of biases, as assessed by using version 2 of Cochrane risk-of-bias tool, can be seen on **Figure 3**. High risk of bias were found in Sakikabara 2013 and 2014. There was selection bias found in study by Sakakibara et al.[9] caused by the temporal availability of NIRS. In, Sakakibara et al.[10], there were no placebo control group nor blinding.

DISCUSSION

In the upcoming decades, the elderly population will increase. There will be a shift in the age composition of the older population.

The prevalence of OAB increases with aging. Studies revealed that OAB and detrusor overactivity may occur due to increased release of acetylcholine from nonneuronal and neuronal sources during bladder filling.[5] Antimuscarinics can inhibit this afferent activity. Moreover, the pathway may be altered in the urothelium of aged bladder because of increased purinergic receptor sensitivity and raised P2X3 receptor expression.[5] The other contributing factors to bladder dysfunction in the elderly include chronic ischemia and inflammation.

In geriatric population, OAB is debilitating, frequent, and troublesome situation. Based on the data delivered by American Diabetes Association and the National Kidney Foundation, it is revealed that one of two women and one of four men who visited outpatient geriatric clinic were present with OAB symptoms. In addition, dementia is also common in geriatric population with OAB. The prevalence of dementia increases as advancing age. Moreover, this condition is commonly associated with other geriatric syndromes.[8]

In addition, advancing age contributes to both OAB and cognitive impairment condition. Therefore, the proportion of elderly who harbors both conditions will consequently increase.

The diagnosis and management of OAB in elderly are affected by neurologic, cardiovascular disorders, musculoskeletal conditions, diabetes, and psychiatric disorders.[9] The patients are commonly prescribed multiple medications which can contribute to OAB symptoms. The medications taken can also interact with OAB drug treatment. Polypharmacy is defined as a condition when the patient is taking five or more drugs regularly. Besides, there are several factors which play an important role in the OAB management, including mobility disorders, cognitive impairment, bowel habits, and fluid intake.[10]

Esin et al[8] investigated the effect of antimuscarinic medications on elderly cognitive functions. It was shown that no cognitive impairment was observed in the patients involved in the study who were using these medications.[8] No cognitive impairment was observed in study population who had dementia at the beginning of the study. From the antimuscarinic medications being used in the study, oxybutinin and darifenacin group was shown to significantly decrease MMSE scores.

CNS adverse effects such as cognitive impairment might occur because many antimuscarinics can cross the blood-brain barrier. This issue is addressed as a serious consideration in antimuscarinic therapy for elderly OAB patients. The guidelines often recommended oxybutynin.[5] However, a high incidence of cognitive impairment is noted with the administration of this drug. Therefore, administration of oxybutynin is not recommended in frail elderly OAB patients.[8]

Oxybutynin is highly lipophilic compound, which allows it to cross the blood-brain barrier and causes effects on central nervous system (CNS). The high lipophilicity, neutrality, and small molecular size of oxybutynin may allow the drug to cross the blood-brain barrier and skin more easily relative to other antimuscarinic agents.[12]

Oxybutynin chloride is the longest commercially available and approved antimuscarinic drug for the treatment of OAB. To date, there is no study consistently demonstrated that oxybutynin chloride has superior efficacy compared to other medications within this drug class.[13] However, it has been shown that Oxybutynin has the worst adverse effect profile. Several studies suggest that Oxybutynin (either immediate [IR] or extended release [ER]) has a significantly negative effect on cognitive

function.[13] Kay et al reported that a 3-week treatment with Oxybutynin ER resulted in significant memory impairment which was shown on delayed recall performance in the Name-Face Association test. Even in young patients, it has been reported that the use of Oxybutynin resulted in hallucinations and episodes of psychosis.[14] This systematic review and meta-analysis shows similar result as the previous studies. Oxybutynin was shown to have the worst adverse effect profile towards the decline in the MMSE score. The mean difference of MMSE score between Oxybutynin group and control group was -2.90 (-4.07, -1.73; 95% CI).

Darifenacin was previously shown to have minimal CNS penetration. In an autoradiographic study in rats by Devineni et al.[15], it is reported that levels of C-darifenacin in the brain following a single intravenous injection remain low. Darifenacin is a substrate for the P-glycoprotein-mediated efflux transporter. This property is not reported for other antimuscarinic agents. Therefore, darifenacin which crossed the blood-brain barrier and entering the CNS can be actively removed. This system may reduce the potential CNS adverse effects. CNS concentrations of darifenacin are considered low, indicated by its lipophilicity, molecular size, and positive molecular charge.[16] On the contrary, this systematic review and meta-analysis showed that Darifenacin had a significant adverse effect towards the decline of MMSE score. In a study conducted by Esin et al, it was shown that Darifenacin may decline the MMSE score by -2.70 (-4,03, -1,37; 95% CI) points. The difference may result from the decreased blood-brain barrier P-glycoprotein in elderly. In a study conducted by Assema et al which acquired sixty minutes dynamic (R)-[11C]verapamil scans with metabolite-corrected arterial plasma input curves, it was shown that The volume of distribution of (R)-[11C]verapamil increases with age in several cortical brain regions, strongly suggesting a progressive decrease in BBB Pgp function with age.[17]

In a study conducted by Nilvebrant et al, it is previously reported that tolterodine has low lipophilicity and low CNS penetration. The brain/blood ratio for tolterodine is 0.1 to 0.3 for radioactivity in mice.[18-19] Despite its low lipophilicity, this current study showed that Tolterodine still had a negative adverse effect towards the decline of MMSE score. Esin et al showed that Tolterodine group had -1.60 (-3.04,-0.16; 95% CI) points less than control group. The decline was considered clinically insignificant.

Fesoterodine is one of the antimuscarinic agents which shows minimal CNS adverse effects. It has been investigated that the lipophilicity of 5-hydroxymethyl tolterodine, was 10 times less lipophilic than those for tolterodine, solifenacin, or oxybutynin. Therefore, fesoterodine had least propensity of CNS effects.[20-21] The result of this study showed that Fesoterodine had no effect towards MMSE score between intervention group and control group which is in line with its pharmacological profile.

Solifenacin was shown to have a favorable outcome towards MMSE score in Elderly. Two previous studies showed a higher MMSE score in Solifenacin group compared to placebo. Compared to other muscarinic agents, Solifenacin was shown to have the best safety profile on cognitive impairment in elderly. The MMSE score in Solifenacin group was 0.92 (0.56, 1.28; 95% CI) points higher than placebo.

Sakakibara et al.[9] investigated the role of Imidafenacin on bladder and cognitive function in neurologic OAB patients.[9] The study included sixty-two subjects (25 men, 37 women, mean age 70 years with OAB due to neurologic diseases) which mostly had mild cognitive decline (mean MMSE 21.8). It was shown that Imidafenacin significantly ameliorated urinary urgency, nighttime urinary frequency, and quality of life index ($p < 0.05$) without cognitive worsening, with a trend of prefrontal activation. Three cognitive measures (MMSE, FAB, ADAS-cog) did not change significantly in a 3-months period.[9]

In 2014, Sakakibara et al.[10] investigated the effect of Imidafenacin on cognitive safety and overall tolerability in clinical use. The patients enrolled in the study were assessed for their total MMSE score at baseline, 24-, and 48- weeks after treatment. There were 187 patients enrolled in the study. There was no significant decrease noted in the MMSE scores in the patients during follow up. Furthermore, the absence of

evidence suggesting any safety issues in the study provide confirmation that Imidafenacin can be used safely for cognitively vulnerable patients with OAB.10 In this study, the use of Imidafenacin was shown to have a favorable outcome. Compared to placebo, MMSE score in Imidafenacin group was higher by 0.79 (-0.26, 1.84, 95% CI) points.

CONCLUSION

The use of most but not all antimuscarinics medication has little to no effect on the cognitive function in the management of overactive bladder in elderly patients. However, Oxybutynin, Darifenacin, and Tolterodine was shown to have significant decrease in cognitive functions, as shown in the decline of total MMSE score.

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