Cognitive Function and Urologic Medications for Lower Urinary Tract Symptoms

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Special considerations should be made when selecting medications for the treatment of lower urinary tract symptoms (LUTS) in older patients especially those over 65 years old. This review summarizes the relationship between current treatments for LUTS and cognitive impairment. Although the recently reported association between dementia and tamsulosin is debatable, the effects of α-blockers and pharmacokinetics are not reported in this context. Five-alpha reductase inhibitors appear to affect mood. However, the association between the development of dementia and cognitive impairment is unlikely. Anticholinergic agents, other than trospium, fesoterodine, and imdafenacin have a relatively high distribution in the central nervous system. In particular, oxybutynin is reported to cause cognitive impairment. Several animal studies on the blood-brain barrier permeability of oxybutynin support this. Therefore, care must be taken when they are used in older patients (65 years and older). Beta-3 agonists are an alternative to, or may be used in combination with, anticholinergic drugs for patients with an overactive bladder (OAB). Several phase 2 and 3 clinical studies report high tolerability and efficacy, making them relatively safe for OAB treatment. However, there is a possibility that cognitive function may be affected; thus, long-term study data are required. We have reviewed studies investigating the correlation of urologic medications with cognitive dysfunction and have provided an overview of drug selection, as well as other considerations in older patients (65 years and older) with LUTS. This narrative review has focused primarily on articles indexed in PubMed, Google Scholar, Scopus, and Embase databases. No formal search strategy was used, and no meta-analysis of data was performed.

Keywords: Adrenergic alpha-antagonists; 5-Alpha reductase inhibitors; Cholinergic antagonists; Adrenergic beta-3 agonists; Cognitive dysfunction; Dementia

INTRODUCTION

Announced by the Korea National Statistical Office in 2019, approximately 14.9% of the Korean population is 65 years of age or older. The proportion of people over 65 years of age continues to increase and is predicted to account for 25% of the total population by 2030 [1]. The prevalence and severity of lower urinary tract symptoms (LUTS) are known to increase with age; in addition, the use of drugs to treat LUTS is expected to increase [2-6].

Polymorbidity and polypharmacy are more common among the older than the young populations. In a study using national

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health insurance data from 2010 to 2011 in Korea, the reported prevalence of polypharmacy (taking 6 or more drugs) for patients over 65 years was 86.4% [7]. However, older people are often excluded from clinical studies owing to their age, and there is little evidence to support the safety and effectiveness of drugs in older people [8-10]. Polypharmacy has been reported to increase the probability of drug-drug interaction and to be associated with increased mortality, as well as side effects such as cognitive impairment and falls [11-13].

Therefore, clinicians must consider the potential drug-drug interactions and the decreased body function in old age when prescribing drugs to older patients [14,15].
The Fit fOR The Aged (FORTA) classification was introduced in 2008 with the aim of guiding physicians in their screening process for inappropriate or harmful medications and drug omissions in older patients in an everyday clinical setting [16]. The LUTS-FORTA 2014 study on urological medicine was reported [14]. Consensus was achieved through expert ratings, but the theoretical background is weak owing to insufficient pharmacokinetic evidence.

Although numerous studies have linked cognitive impairment and LUTS drugs, there is no consolidated evidence. Our review compiles scattered reports of this correlation between cognitive impairment and LUTS drugs to present an overall picture, so that treatment selection can be guided in the future.

MATERIALS AND METHODS

For this review, literature reports over 15 years (from January 1994 to January 2020) were searched by using the PubMed, Google Scholar, Scopus, and Embase databases. Keywords, such as "cognition," "cognitive impairment," "dementia," and "Alzheimer's disease," were used to find studies related to cognitive impairment and dementia. In addition, searches using the keywords "adrenergic alpha-antagonists," "5-alpha reductase inhibitors," "cholinergic antagonists," and "adrenergic beta-3 agonists" were performed, along with searches for similar terms and the drugs of each type (e.g., tamsulosin, finasteride, imidafenacin, and mirabegron). We reviewed the abstracts of the results and included only clinical studies about the relevance of drugs to cognitive function. Similar terms were also used in the search to avoid the unintended exclusion of important similar articles from the search. To examine the possibility that the drug pharmacokinetics may affect cognitive function, the following keywords were searched in conjunction with the uro-

logic drugs above: "blood-brain barrier," "permeability," and "pharmacokinetics." All animal studies related to the distribution of urologic medication in the central nervous system (CNS) and the potential for cognitive impairment were included.

ALPHA BLOCKERS

CNS-related side effects of alpha blockers, with the exception of dizziness, have not been reported in over 30 years since the market approval of the first alpha blocker; however, it is still unclear whether dizziness directly affects the brain or is a secondary effect of reduced blood pressure [17]. In particular, selective α1A-adrenergic receptor antagonists, such as silodosin and tamsulosin, were considered to have greater cardiovascular tolerability than other nonselective α-adrenergic receptor antagonists [18].

However, a recent cohort study reported that the group taking tamsulosin had an increased incidence of dementia [19]. In this study, the authors retrospectively analyzed data from patients over 65 years of age with benign prostatic hyperplasia (BPH) from US Medicare records. Data from the tamsulosin cohort (n = 253,136), no-BPH-medication cohort (n = 180,926), doxazosin cohort (n = 28,581), terazosin cohort (n = 23,858), alfuzosin cohort (n = 17,934), dutasteride cohort (n = 34,027), and finasteride cohort (n = 38,767) were extracted. The median follow-up period for this study was 19.8 months. The risk of dementia was significantly higher in the tamsulosin cohort than in the no-BPH-medication cohort (hazard ratio [HR], 1.17) and significantly higher than that in the 5 cohorts for alternative BPH-medication (HR, 1.11–1.26). The dose-response analysis also revealed a higher risk of dementia at higher doses in the tamsulosin cohort (HR, 1.12–1.49). The authors confirmed biological validity from studies that showed that α1A-adrenoreceptors were reduced in the prefrontal cortex of patients with dementia and that tamsulosin suppressed centrally driven bulbospongiosus muscle contraction in a rat model [20,21].

Overall, the results are quite impressive, and appeared to prove to be causal between tamsulosin and dementia. However, there are some questions that remain.

First, from a pharmacokinetic perspective, tamsulosin is a selective drug for the α1A-adrenoreceptor, and it's kind of systemic effect is thought to be less than the nonselective alpha blockers doxazosin, terazosin, and alfuzosin. In other words, other alpha blockers may bind to and affect a variety of subtypes of α-adrenergic receptors, which may have a greater im-

pact on the development of dementia than tamsulosin.

The second question is related to the blood-brain barrier (BBB) permeability. The drugs may affect cognitive function without penetrating the BBB. In other words, if a drug can affect metabolism or regulation of hormones, it may have a secondary effect on the CNS. However, tamsulosin does not have peripheral actions that can adversely affect the brain. Thus, to cause dementia, tamsulosin must penetrate the BBB and act on the α1A adrenoreceptors in the brain [22]. Some studies reported that BBB permeability of tamsulosin was high [20,21], although other animal studies on the BBB penetration of alfuzosin, doxazosin, silodosin, and tamsulosin reported no or very low permeability of the BBB following intravenous or oral ingestion of alpha blockers [23-27]. In one animal study, tamsulosin enhanced memory function by activating N-methyl-D-aspartate receptor-mediated ion currents in the hippocampus [28]. If there is no biological validity, according to the Bradford Hill criteria, a proven association does not appear to indicate a causal relationship [29].

The third question was whether the follow-up period was too short. The associations reported by Duan et al. [19] spanned a median period of less than 2 years. This time period is too short to determine the occurrence of dementia and indicated an accelerated time to diagnosis [30].

In contrast, a recent retrospective cohort study reported that tamsulosin was not associated with the risk of dementia [31]. The authors retrospectively extracted information from the national health insurance service database and performed an analysis of patients over 70 years of age with BPH. In addition, the average age of patients enrolled in this study was higher than that in the study of Duan et al. [19] (76.1–76.7 years vs. 73.3–74.7 years). The median follow-up period was 56.4 months, which was relatively longer [19]. Six cohorts were extracted, and the number of patients in each cohort was as follows: tamsulosin (n = 33,568 subjects), no-medication (n = 3,336), doxazosin (n = 7,012), terazosin (n = 9,443), and alfuzosin (n = 5,904). In their study, the incidence of dementia was higher in the terazosin group than the tamsulosin group (HR, 1.122). However, compared with the no-medication cohort, the BPH-medication cohort had a significantly lower risk of dementia (HR, 0.653–0.721). The authors of this study attributed their findings to the fact that the no-medication cohorts did not represent the general population distribution, rather than the fact that α-blockers lowered the risk of dementia. This large population-based study concluded that BPH drugs did not in-

crease the risk of dementia, and the type of the drug.

Except for the recent debate on the association of dementia with tamsulosin, there appears to be no evidence that the remaining α-blockers (alfuzosin, doxazosin, terazosin, and silodosin) cause cognitive impairment. Some previous animal studies [23-25,27,28] have observed low drug binding in the rat cerebral cortex, suggesting that the drug is unlikely to penetrate the BBB. In addition, doxazosin had a neuroprotective effect in an *in vitro* model of Alzheimer disease [32]. However, terazosin was shown to cause cognitive impairment by decreasing of serotonin level [23]. However, in clinical studies, no association between dementia and cognitive impairment was observed [19,31].

In conclusion, there is little pharmacokinetic or no clinical evidence that alpha blockers promoted cognitive impairment (Table 1). Of course, alpha blockers may lower systemic blood pressure, but at least the possibility of cognitive impairment should not be a concern.

5–ALPHA REDUCTASE INHIBITORS

Finasteride and dutasteride are 5-alpha reductase inhibitors (5-ARIs) used widely for the symptomatic treatment of BPH [17]. These 2 drugs are equally efficient, but finasteride inhibits only type 2 of 5-alpha reductase and dutasteride inhibits both type 1 and 2 of 5-alpha reductase (5-AR) [33]. 5-ARIs are used in the symptomatic treatment of BPH as they inhibit the conversion of testosterone to dihydrotestosterone, reducing prostate volume [34].

Testosterone protects against age-related cognitive decline and dementia in men [35]. In other words, this result is pharmacokinetic evidence that 5-ARI can cause cognitive impairment and dementia. In a very recent animal study, 5-ARIs were reported to increase tau phosphorylation and alter dendritic morphology in the hippocampus of male mice, causing cognitive impairment. In this study, the activity of 5-AR was shown to be involved in the production of neurosteroids, and it was concluded that 5-AR plays an important role in neuroprotective effects [36]. In a population-based retrospective cohort study of male patients 66 years of age or older, 5-ARIs resulted in an increased incidence of self-injury and depression [37].

Contrary to the above results, several studies have reported that the incidence of dementia is not related to 5-ARIs. In a double-blind, placebo-controlled study, testosterone replacement therapy was not associated with improvement in age-re-

Table 1. Literature review of alpha blockers

Agent study	BBB permeability Type of study	Cognitive impairment	Strengths and weaknesses of the study
Alfuzosin	Low		
Rouquier et al. [23]	Animal study	Less likely	*In vivo*, rat/intravenous injection/measured by using extracellular serotonin level
Tae et al. [31]	Big data analysis	No	51.9-Month follow-up/n = 5,904/not associated with a risk of dementia with increased duration
Doxazosin	Low		
Coelho et al. [32]	Animal study	No	*In vivo*, human neuroblastoma cell line/neuroprotective effects in patients with AD
Tae et al. [31]	Population-based study	No	51.9-Month follow-up/n = 3,840/not associated with a risk of dementia
Silodosin	Low		
Yamada et al. [25]	Animal study	Less likely	*In vivo*, rat/no specific binding in the cerebral cortex
Okura et al. [27]	Animal study	Less likely	Ex vivo, rat/oral intake/lower distribution in cerebral cortex
	No clinical trials		
Tamsulosin	Low		
Yamada et al. [26]	Animal study	Less likely	*In vivo*, rat/no specific binding in the cerebral cortex
Kim et al. [28]	Animal study	No	*In vivo*, rat/medication period: 4 weeks/activating NMDA receptor-mediated ion currents
Tae et al. [31]	Population-based study	No	56.4-Month follow-up/n = 33,568/not associated with a risk of dementia
Duan et al. [19]	Population-based study	Yes	19.8-Month follow-up/n = 253,136/increased risk of dementia
Terazosin	Low		
Tae et al. [31]	Population-based study	No	51.9-Month follow-up/n = 4,760/not associated with a risk of dementia
Rouquier et al. [23]	Animal study	Intermediate	*In vivo*, rat/intravenous injection/measured by using extracellular serotonin level

Agents are sorted by alphabetical order.
BBB, blood-brain barrier; AD, Alzheimer disease; NMDA, N-methyl-D-Aspartate.

lated memory impairment in older patients [38]. In addition, a population-based study on the association of tamsulosin with the development of dementia reported that the administration of 5-ARIs was not associated with dementia [19].

In another study, the incidence of dementia was significantly increased in patients taking 5-ARIs. However, it has been reported that 5-ARIs and dementia are not causally linked because prolonged use reduced the risk of dementia [39].

In conclusion, recent results suggest that 5-ARIs are likely to cause affective disorders such as depression. In addition, although the results of clinical studies are positive, there is strong biological evidence that these drugs may affect cognitive function. Therefore, during the use of the 5-ARIs, it should be carefully checked for the development of mood disorders.

ANTICHOLINERGICS

Muscarinic receptors are important for high-level cognitive processes, such as memory and learning [40-43]. The adverse effects of anticholinergics, based on the known function of the muscarinic receptors in the CNS, are a serious concern [44-46].

With increasing age, the likelihood of developing LUTS from OAB increases [5,6], which also increases the need for anticholinergics. However, the pharmacokinetic properties of anticholinergics itself described above are likely to cause cognitive impairment. So, it is necessary to classify the risks of each drug and to carefully select the treatment drug in older patients.

Oxybutynin has been used for the treatment of detrusor overactivity for over 40 years [47] and is reported to promote cognitive impairment in several clinical studies [48-50].

The CNS penetration of drugs is affected by 2 factors: the passive permeability of the BBB [51,52] and the activity of efflux transporters in the brain tissue, such as P-glycoprotein (P-gp) [53,54].

Oxybutynin had the largest passive permeability and the lowest efflux ratio by P-gp in the study of CNS penetration of OAB agents associated with cognitive impairment. In addition, the *in vivo* experiments in this study revealed that it had the highest cerebrospinal fluid (CSF): free plasma concentration ratio of 1.66 [55]. *In vivo* studies using positron emission tomography (PET) and autoradiography also showed that oxybutynin penetrates the BBB in a dose-dependent manner, reducing radioli-

gand binding in rat and monkey brains [44,56,57]. These results provide clinical pharmacokinetic evidence that oxybutynin may affect cognitive impairment. Callegari et al. [55] reported the highest passive permeability for oxybutynin, followed by tolterodine, solifenacin, darifenacin, fesoterodine, and trospium. In particular, trospium is hydrophilic and showed little passive permeability. The efflux ratio by active transporters followed the order fesoterodine (13.7), darifenacin (4.0), solifenacin (1.3), and tolterodine (1.4). *In vivo*, the CSF:free plasma concentration ratios were in the order solifenacin (1.41), tolterodine (0.16), darifenacin (0.06), fesoterodine (0.04), and trospium (0.004). Festoterodine and trospium showed the least CNS penetration. Darifenacin inhibits the contraction of human detrusor smooth muscle through only its antimuscarinic activity and not calcium channel antagonist activity [58,59].

Several *in vitro* and animal studies confirming the brain occupancy of drugs by PET or autoradiography showed that darifenacin may be able to penetrate the BBB to some extent. However, no cognitive impairment was observed after systemic administration [55-57]. A randomized, double-blind, placebo clinical study of volunteers over 65 years of age found no effect on cognitive function after taking darifenacin [60].

Solifenacin has been shown to have a high affinity for M3 receptors mainly in *in vitro* studies of human recombinant muscarinic subtypes. Thus, solifenacin has been reported to selectively act on detrusor muscle contraction [61]. Solifenacin has been reported to have high passive permeability, low active transport efflux ratio in *in vitro* studies, high probability of CNS penetration [55], and greater effects on rat brain as the dose increased in *in vivo* studies [50]. However, some clinical studies showed no significant association with cognitive impairment [50,62]. Furthermore, one study reported that solifenacin could be safely used without aggravating cognitive impairment in patients with Alzheimer disease treated with donepezil [63].

Tolterodine is a nonselective anticholinergic drug used to treat OAB [64]. *In vitro* and radioligand binding studies have determined that tolterodine has a high potential for CNS penetration [55,56]. However, the results of a clinical study showed that the incidence of cognitive impairment was not significantly higher than that in the control group [65].

Trospium and fesoterodine were reported to have significantly lower CNS penetration than other anticholinergic agents in an *in vitro* study [55]. The relatively high molecular weight and low lipophilicity of fesoterodine, hydrophilic trospium, and the active metabolite of fesoterodine, 5-hydroxymethyl tolterodine,

suggest that only very small amounts may cross the BBB [55, 66,67]. A study also reported the effects of taking fesoterodine for 12 weeks in older patients with urge incontinence and revealed no deterioration in cognitive function when subjects were assessed by the mean Mini-Mental Status Examination (MMSE) [68].

Imidafenacin was not likely to affect cognitive function because CNS penetration was not observed in a PET study *in vivo* [44,57]; this is supported by the absence of published clinical studies showing cognitive impairment. In addition, clinical studies using imidafenacin in patients with mild cognitive impairment (MCI) and Alzheimer disease had no effect on cognitive function [69].

Based on these reports, we classified anticholinergics into subcategories according to the effects on cognitive function as follows: class A (safe), low evidence for cognitive impairment based on pharmacokinetic and clinical papers; class B (debate), inadequate pharmacokinetic and clinical evidence on the occurrence of cognitive impairment; class C (cautious) pharmacokinetic and clinical evidence of drug-induced cognitive impairment. Accordingly, anticholinergics were classified (Table 2).

In conclusion, for class C drugs, it is necessary to limit the use in older patients. Class B drugs may cause cognitive impairment owing to their pharmacokinetics. However, there were no clinical studies to support these pharmacokinetic properties, or studies have shown contradictory results. Anticholinergic drugs in class B are suggested to be used with caution at low doses. For class A drugs, pharmacokinetic and clinical reports consistently show a weak association with cognitive dysfunction. Thus, they are thought to be safer than other anticholinergic drugs in older patients.

BETA-3 AGONISTS

There are 3 subtypes of beta-adrenoreceptors: beta-1, beta-2, and beta-3. Of these 3 subtypes, the beta-3 adrenoreceptor is a G protein-binding receptor identified by genome replication in human cells [70].

When the beta-3 adrenoreceptor is activated, it mediates lipolysis in human brown and white fat cells and causes relaxation of smooth muscle in the gallbladder, stomach, small intestine, prostate, colon, and bladder [71,72]. It also controls memory, learning, and appetite [73]. Beta-3 agonists were reported to improve OAB in rat experimental models [74,75], and recently mirabegron was reported as an alternative to anticholin-

Table 2. Literature review of anticholinergics

Agent Study	Class Type of study	Cognitive impairment	Strengths and weaknesses of the study
Darifenacin	B		
Maruyama et al. [56]	Animal study	Less likely	Slight decrease in autoradiography/DDR: no
Callegari et al. [55]	Animal study	Less likely	BBB permeability based on physicochemical properties: significant/*in vitro*: high/*in vitro*: not significant
Yoshida et al. [57]	Animal study	No	*In vivo* PET study/potential adverse effects on the CNS: no
Lipton et al. [60]	Clinical trial	No	RCT/n = 129/mean age: 71.2 years of age/period: 14 days/no difference to control group/DDR: no
Fesoterodine	A		
Dubeau et al. [68]	Clinical trial	No	RCT/n = 562, patients ≥ 65 years of age with urge incontinence/no deterioration in mean MMSE scores
Callegari et al. [55]	Animal study	Less likely	BBB permeability based on physicochemical properties: significant/*in vitro*: moderate/*in vitro*: not significant
Imidafenacin	A		
Yoshida et al. [57]	Animal study	No	*In vivo* PET study/potential adverse effects on the CNS: no
Yamamoto et al. [44]	Animal study	No	*In vivo*, monkey, PET study/mAChR occupancy: some extent/cognitive impairment: no
Sakakibara et al. [69]	Clinical trial	No	N = 187/patients with MCI or AD/average daily dose: 0.19 mg/adverse effect on cognitive impairment: no
Oxybutynin	C		
Callegari et al. [55]	Animal study	Yes	BBB permeability based on physicochemical properties: significant/*In vivo*: moderate/*in vitro*: high
Maruyama et al. [56]	Animal study	Yes	*In vivo* autoradiography/DDR: yes
Yoshida et al. [57]	Animal study	Yes	*In vivo* PET study/potential adverse effects on the CNS: yes
Yamamoto et al. [44]	Animal study	Yes	*In vivo* PET study/occupied central mAChR/cognitive impairment: yes
Katz et al. [48]	Clinical trial	Yes	RCT/n = 12/healthy volunteer/daily doses: 5 mg, 10 mg/cognitive impairment: yes
Esin et al. [65]	Clinical trial	No	Prospective study/n = 43/patients with OAB ≥ 65 years of age/no data about the DDR
Wagg et al. [50]	Clinical trial	Yes	RCT/n = 26/study subjects: ≥ 75 years of age MCI/daily dose: 10 mg
Pietzko et al. [49]	Clinical trial	Yes	Phase I study/n = 12/mean age: 26 years of age/daily dose: 20 mg/change of EEG alpha range: yes
Solifenacin	B		
Maruyama et al. [56]	Animal study	Possible	*In vivo* autoradiography/DDR: yes
Callegari et al. [55]	Animal study	Possible	BBB permeability based on physicochemical properties: significant/In vitro: high/*in vitro*: significant
Wesnes et al. [62]	Clinical trial	No	n = 12/ healthy elderly (mean age: 69.1)/daily dose: 10 mg/no adverse effect on cognitive function
Wagg et al. [50]	Clinical trial	No	RCT/n = 26, MCI elderly (≥ 75 years of age)/DD: 5 mg/adverse effect on cognitive function: no
Tolterodine	B		
Maruyama et al. [56]	Animal study	Yes	*In vivo* autoradiography/DDR: yes
Callegari et al. [55]	Animal study	Yes	BBB permeability based on physicochemical properties: significant/*in vitro*: high/*in vitro*: significant
Esin et al. [65]	Clinical trial	No	Prospective study/n = 21/study subjects: patients with OAB ≥ 65 years of age/DDR: No
Trospium	A		
Pietzko et al. [49]	Clinical trial	No	Phase I study/n = 12/mean age: 26 years of age /daily dose: p.o. 45 mg, i.v. 1.2 mg/change in EEG alpha range: no
Callegari et al. [55]	Animal study	No	BBB permeability based on physicochemical properties: not significant/*In vivo*: low/*in vitro*: not significant
Esin et al. [65]	Clinical trial	No	n = 26/study subjects: patients with OAB ≥ 65 years of age/no data about the DDR

Agents are sorted by alphabetical order.
DDR, dose-dependent response; BBB, blood-brain barrier; PET, positron emission tomography; CNS, central nervous system; RCT, randomized controlled trial; MMSE, Mini-Mental Status Examination; mAChR, muscarinic cholinergic receptor; MCI: mild cognitive impairment; AD, Alzheimer disease; OAB, overactive bladder; EEG, electroencephalography; p.o., per oral; i.v., intravenous.

ergics in patients with OAB, as the first selective beta-3 agonist [76-78]. Several phase 2 and 3 studies have reported its high tolerability and efficacy [79-82]. Therefore, it has emerged as a new treatment option for patients with OAB who cannot take anticholinergic drugs owing to side effects such as dry mouth.

Mirabegron was approved by the U.S. Food and Drug Administration as the first beta-3 agonist in newest category of pharmaceutical treatment for OAB. In addition, it is confirmed by phase III clinical trial evaluating safety and efficacy in patients over the age of 65 years. However, there seems to be very little comment on cognition.

In very recently, a phase 4 placebo-controlled study (PILLAR; NCT02216214) about association between beta3-AR agonist medication and cognition, using Montreal Cognitive Assessment (MoCA) test was conducted [83,84]. The MoCA test was validated in the setting of MCI. Additionally, the sensitivity of the MoCA for detecting MCI is 90%, compared to 18% for other leading cognitive screening tools such as the MMSE [85]. In this PILLAR study, treatment with beta3-AR agonist, mirabegron for 12 weeks had no impact on cognitive function in older patients (65 years and older), as measured by the MoCA.

Although mirabegron has not yet been reported to cause cognitive impairment, it is a potential risk, and long-term studies are required.

CONCLUSIONS

In this review article, we examined the pharmacokinetic and clinical reports of the association between LUTS drugs and cognitive impairment. Alpha blockers are not expected to cause cognitive impairment. Although 5-ARIs have strong pharmacokinetic profiles that may suggest cognitive impairment, the clinical studies have shown that they are less prone to cause dementia. However, they may cause affective disorders such as depression. In the case of anticholinergic drugs, especially class C, the use of each drug should be considered carefully. Beta-3 agonists may replace anticholinergic agents for OAB treatment, but long-term studies are need.

AUTHOR CONTRIBUTION STATEMENT

· Conceptualization: *JHB*
· Formal Analysis: *YJK*
· Investigation: *YJK*
· Methodology: *YJK*

· Project Administration: *BST*
· Writing-Original Draft: *YJK*
· Writing-Review & Editing: *BST*, *JHB*

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