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Influence of current state of executive function and working memory on adherence to antimuscarinic therapy in older women with OAB

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ABSTRACT

Aim: Evaluation of the executive function and working memory influence, as well as the general state of memory, on adherence to treatment with antimuscarinic drugs in elderly women with overactive bladder (OAB).

Background: Antimuscarinic are effective and safe for the treatment of OAB, but adherence to treatment remains low. Demographic, socioeconomic, and medical factors which influence the medication adherence have been explored; however, the impact of executive function and working memory on adherence has not been evaluated yet.

Methods: In total 417 women from 65 to 88 years old with the diagnosis overactive bladder were selected to participate in the study. They were prescribed AM drugs: trospium 15 mg / day (n = 138), or Solifenacin 5 mg / day (n = 132), or Darifenacin 7.5 mg / day (n = 147). The observation was carried out for 12 weeks. The urodynamic state was investigated using the questionnaire OABq-SF, uroflowmetry was performed at the start and end of the study, voiding diary - during the whole time of observation. The state of mental health was investigated using MMSE and GDS. The assessment of executive function and working memory, as well as general memory estimation, was carried out using the Wisconsin Card Sorting Test, Wechsler Memory Scale subscale, and the California Verbal Learning Test. Hierarchical and simultaneous regressions were calculated to study the effect of executive function and working memory on medication adherence.

Results: The urodynamic state of patients significantly improved after the treatment, the cognitive functions did not change. The analysis of hierarchical and simultaneous regressions made it possible to establish that the predictor variables significantly influencing medication adherence of elderly women with OAB to AM treatment are executive function and working memory composite (β = .39, $p < .05$), severe symptoms of lower urinary tract (β =. -. 31, $p < .05$), and age (β =. -. 25, $p < .05$).

Conclusion: The status of executive function and working memory, as well as the age and severity of the pathological symptoms of lower urinary tract should be considered when predicting adherence to AM treatment in elderly patients with OAB.

Introduction

More than 16% of women on average suffer from symptoms of overactive bladder (OAB), and up to 27-46% of women of all ages "at least sometimes" experienced the symptoms of hyperactivity [1,2]. In recent decades in most of the national populations the percentage of older people has increased. The prevalence of OAB increases significantly with age. The prevalence of overactive bladder symptoms among women over 65 years of age is 61% or more [3]. These symptoms adversely affect the quality of life associated with health [4,5]. Obsessive and irritating symptoms, such as pollakiuria, imperative urges to urinate and urge urinary incontinence can lead to depression, reduced social mobility, and may be associated with significant financial costs [6–8].

Management of overactive bladder symptoms is currently being done mainly using the line of antimuscarinic drugs (AM). AM of the last generation, such as trospium, solifenacin, and darifenacin, are highly selective anticholinergic agents that do not affect cognitive status and are the drugs of choice for elderly patients [9,10]. Among anticholinergic drugs most widely used in the present time, trospium has the least selectivity. Solifenacin has larger affinity to M3-cholinergic receptors of bladder than to muscarinic receptors of the second type, darifenacin is M_3-selective. Selectivity of solifenacin and darifenacin in respect of M_3-cholinergic receptors,

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low lipophilicity of trospium decreasing the probability of its penetration through hematoencephalic barrier make possible its use for elderly patients. Nevertheless, low penetrating capability of trospium through hematoencephalic barrier does not mean complete absence of influence on encephalic structures that possibly can adversely affect the state of frail elderly patients, persons with increased individual sensitivity to this preparation, elderly persons already having cognitive disorders or central nervous system diseases. Besides, in the most of studies of trospium effectiveness and safety there are data that for a small percentage of patients taking this medicine, side effects and symptoms of disorder of the function of central nervous system are still noted. They are: accommodation disorder, dizziness, mydriasis, anxiety, activation, tiredness, headache, drowsiness or sleeping disorder. From this point of view, the influence of long-term taking trospium on cognitive functions in elderly patients may, to our opinion, give additional information about trospium safety. Besides, in earlier studies we had paid attention to low adherence to trospium treatment of elderly women with urinary incontinence [15]. The reason may be absence of result, side effects, dosage regime and many other factors, but the influence of memory disorder on the adherence to trospium treatment of elderly women, to our opinion, also has been studied insufficiently.

Appearance of new advanced medicinal products, for example β3-receptor agonists, makes it possible to increase effectiveness of treatment in case of persistent symptoms preservation. Mirabegron is the first β3-adrenoreceptor agonist permitted for use in GMP, and in a series of studies it has recommended itself as a preparation with good safety profile. Certainly, the preparation is one of the most advanced alternative medicinal products. At present time its effectiveness as a monotherapy or in combination with AM for severe forms of idiopathic overactive bladder is being widely discussed. But its effectiveness and safety in treatment of neurogenic bladder has not been researched comprehensively. Besides, investigation of influence of the preparation in usual and increased doses on PQ interval, heat rate, and the level of arterial pressure in elderly patients is being continued.

It is known that the effectiveness of OAB therapy is directly related to observance of the regime of taking AM. Medication adherence is defined as taking a medication prescribed by a doctor at the prescribed dose, at the appropriate time and in the right way. According to the available data, adherence to treatment with AM is rather low and roughly corresponds to the patients' resistance to prostaglandins and antidiabetic agents [11]. Many factors can influence medication adherence in women with OAB. These include: the effectiveness of treatment / lack of expected outcome, treatment regimen, side effects, and duration of treatment [12]; patient awareness, polymorbidity [13]; patient's age, availability of insurance and other socio-economic factors [14]. In our earlier studies we also studied adherence to AM treatment and found that the percentage of patients with severe lower urinary tract symptoms (LUTS), minor and short-term side effects, or their absence, is high among all the stable patients. Stable patients were characterized by living in an urban district, living with a spouse, high individual annual income, as well as a high level of social functioning, role-emotional functioning and mental health [15–18].

At the same time there is poor information in modern literature about the state of cognitive functions and their effect on adherence to AM treatment. It is known that elderly people have a high risk of disrupting cognitive processes that can lead to inaccurate and inconsistent performance of the doctor's appointments, even when the patient realizes the need for treatment and seeks to receive it. The theoretical basis for understanding the types of cognitive processes that are most important for successful performance of prescriptions is presented in prefrontal cortex theory [19]. According to this theory, there are two main types of cognitive processes which are associated with precise performance of prescriptions. These are executive function and working memory, and one that involves memory storage and retrieval [20]. Compliance with the drug regime is associated with the executive function, as it ensures the generation and execution of a specific action plan aimed to comply with the doctor's prescriptions. Compliance with the drug regime also correlates with the working memory as often the patient should keep the intention to take the medicine while performing other actions. And even in case of remembering about the need for taking medication, the patient is often forced to postpone this action until appropriate conditions arise. Besides dependence from the executive function and working memory, medication adherence can also be associated with the coding and storage of health information [21].

There is evidence in the literature, that cognitive function is an independent factor of medication adherence among elderly people with chronic diseases [22]. At the same time, it is known that cognitive functions are not violated when using AM of recent generations in elderly women with OAB [23]. Thus, the purpose of our study was to assess the relationship between the executive function and working memory, as well as the general state of memory with adherence to antimuscarinic therapy in elderly women with OAB.

Materials and methods

The study was conducted in the Far Eastern Federal University and Vladivostok City Polyclinic No. 3 from 01. 12. 2015 to 01.06.2017. The sample size was calculated taking into account the confidence probability of 95% and the confidence interval of ± 5%. Cases with individual data were depersonalized by assigning random numbers obtained from the random number generator.

The sample size was determined based on the idea of sufficiency of confidence probability 95%, correct dispersion distribution and form, and probable loss of a part of population not more than 10-15% in the most part of similar studies carried out before [1,3,7,11 et al]. This made it possible to use statistic approach to the calculation of the volume of sampled population, and to calculate the total volume of population based on the formula: $n=(Z\,\delta/\,e)^{2}$, where Z is the value of Z-statistics in one-sided Z-test, at confidence level 95% equal to 1,96, δ – standard deviation, and e- acceptable error of study. The total sample population was 388 people. Taking into account the probable loss of number in the process of study, in total 417 people were enrolled, uniformly distributed in three subgroups.

After 12 weeks of taking preparations, 364 patients (87.3%) were left in the sampling that made it possible to correctly carry out correlation analysis between the values of different cognitive and urodynamic parameters, as well as comparative analysis between the subgroups with acceptable certainty level. We used Wald test as a method of parameters limitation test. Using Wald statistics, we calculated non-shifted variance with Fisher asymptotic distribution. We could not detect any certain differences between the samples with complete and incomplete data set.

Women who independently applied for help in the urological department of the polyclinic and who were prescribed AM preparations: Trospium 15 mg / 2 times daily (Group A; n = 138), or Solifenacin 5 mg / day (Group B; n = 132), or Darifenacin 7.5 mg / day (Group C; n = 147) were involved in the study. The distribution into groups was random. In enrollment of the groups we used the method of adaptive stratified randomization implying provision of approximately equal number of patients in groups during all the procedure of randomization and after its completion. In the beginning of enrollment patients were distributed equally probable, using random number generator, into three groups. Then, before it is determined to

which group another patient is classified, the enrollment and age composition of already created groups were assessed. If the enrollment of one of the groups exceeded the others, the probability to be included in this group decreased. To "blind" a member of the research group carrying out statistical analysis of obtained data sets, data files were impersonalized by assigning random numbers using tabular method, personal information was removed from them. The information, which preparation is taken by a patient in treatment of OAB, was not disclosed to patients.

Exclusion criteria: taking AM during the last 6 months before the study; taking other anticholinergic drugs, as well as glaucoma, urethral obstruction, acute microbial-inflammatory diseases, hyperthyroidism and decompensate arrhythmias.

Most of the women had a high index of comorbidity (3.93 (0.94)) and took other drugs for the supporting treatment of chronic diseases. Before the start of the treatment each of the patients received a container with an electronic cap opening recorder and was instructed how to use it for the next 12 weeks. Medication adherence was defined as the percentage of days when the patient took the drug at the prescribed dosage. In our study we proceeded from the assumption that although electronic control does not guarantee the correct dose of the drug, it allows to determine that the patient remembered about the need to take the prescribed drug.

We studied the marital status, the number of full years of study, and the financial well-being of the participants before starting the study. Financial well-being was defined as: 1 - not able to make ends meet, 2 - barely make ends meet, 3 - have enough money, 4 - have enough money to do whatever you want [21]. The data on the age and sex of patients, place of residence were taken from the Outpatient's card (Form 025y). The data on the education level (higher: university/secondary general/secondary professional) were provided by patients themselves. Also, we took from the Outpatient's card the data on Charlson Comorbidity Index, character of previous OAB treatment, medicinal drugs taken by the patient.

The state of the urodynamics of lower urinary tract was monitored by the overactive bladder questionnaire (OABq SF) and uroflowmetry at the beginning and end of the study. The OABq SF scales include the evaluation of Daytime urinary frequency, Nocturnal frequency / nocturia, Urgency, Urge urinary incontinence with scoring. During the uroflowmetry we assessed Average (urine) flow rate (Q_{aver}, ml / sec), Maximum (urine) flow rate (Q_{max}, ml / sec), post void residual (urine volume). The procedure of uroflowmetry was carried out according to standard scheme: patient with full bladder was offered to urinate on the uroflowmeter located in an isolated room of the urodynamic laboratory. Then the patient was placed on gynecological examination chair, and one-channel catheter (UROBAR, Helmbrechts, Germany), was inserted via urethra to bladder cavity, the bladder emptied and the released urine was measured. [24]. In addition, women were asked to keep the Bladder diary throughout the study, in which they noted Daytime urinary frequency, Nocturnal frequency / nocturia, Urgency, Urge urinary incontinence [25]. Under the severe symptoms of LUTS we understood the presence on average of 2 or more incontinence episodes per day and more than 16 points on the OABq SF scale [26].

All elderly women filled the geriatric depression scale (GDS) [27] and the subscale of the physical activity questionnaire [28] at the start and end of the study. GDS was evaluated as follows: 0 - 9 points - the norm, 10 – 19 points – moderate depression, and 20 - 30 points – severe depression. We used the Mini-mental State Examination (MMSE) scale for a screening assessment of mental status [29].

Executive Function was studied using the Wisconsin Card Sorting Test (WCST), which makes it possible to evaluate the ability to abstract thinking and switching cognitive strategies when receiving feedback information (subscales Perseverative responses and Categories Completed) [30]. The Wechsler Memory Scale 3 (WMS III) allowed us to study the processes of storage and processing of information and the state of working memory (subscales Mental Control, Digit Span Backward, and Letter Number Sequencing). The total memory assessment was performed using WMS III (subscales Logic memory 1, 2 recall and Logic memory 2 recognition), as well as the California Verbal Learning Test - CVLT (subscales Short and Long Delay Cued Recall; Recognition measures) [21,31–33].

It is commonly believed that working memory is a cognitive resource taking part in storage and operative processing of information. In scales created for assessment of working memory usually investigation of the volume of remembered information, or simultaneous investigation of the level of preservation and processing of information is used. Before the researchers classified these tasks as a simple or complex span. Information integrity is usually investigated using simple tasks, while use of complex tasks implies the possibility of use and realization of information. Scales WMS III, WCST, CVLT make it possible to investigate the elements of preservation and manipulating with information. We obtained composite assessment of «Working Memory and Executive Function» by averaging Z assessment for each participant using the key parameters of these scales.

Then we carried out composite assessments of the Executive Function and Working Memory, as well as total memory score, using these data. The procedure of calculation of the composite assessments was equivalent to assessment of units of weighted coefficients. In specific weighing of multidimensional structures, the stability of results for independent selections increases, that makes it possible to increase the adequacy of interpretation [33]. We also performed calculation of hierarchic regression with assessment of the strength of influence of predictor variables. For check of variations significance, at first the model not including the variations for a specific predictor was calculated, then- one including these. Then the models were compared using dispersion analysis ANOVA.

Results

In total 417 women aged 65 to 88 years with the established diagnosis: overactive bladder (ICD-9-CM: 596.51 or ICD-10-CM N32.81) participated in this study. The mean age was 74.8 years.

During the study 53 (12.8%) participants were discontinued for various reasons. Twenty-five patients refused to take medication because of dissatisfaction with the result (6.0%). Among them 14 patients (4.4%) refused to receive trospium, 9 (2.1%) patients refused to receive solifenacin, and two (0.5%) – to receive darifenacin. Also, 19 participants (4,5%) refused because of intolerable side effects. Nine participants stopped taking medication due to reasons not related with the study: two (0.5%) died because of acute cardiac failure, two removed to a new place, two lost the control cap, and three refused from participation without any explanations. Of 19 participants who refused because of side effects, 12 (2.9%) people complained of strong headache, dizziness, nausea, 5 (1.2%) participants noted intolerable skin itching, two-diarrhea. Among the patients that refused from medication for this reason, 10 (2.4%) had received trospium, 6 (1.4%)- solifenacin, 3 (0.7%)- darifenacin.

In whole, 71 person complained of side effects, but 52 patients continued their participation in the study. 31 (7.4%) patients felt nauseous; 13(3.1%) felt dryness of the mouth; 11 (2.6%) noted headache, 9 (2.1%)- blurred vision, 3 (0.7%)- diarrhea, 2- disorientation in space (some of the patients felt several side symptoms simultaneously or successively). Among the patients

Table 1
Demographic, socio-economic and medical characteristics of women with overactive bladder before and after of treatment (N = 417).

Before of treatment (n = 417)				After of treatment (n = 364)			
Variables	Mean	SD	Range	Mean	SD	Range	P value
Age, in years	74.8	7.9	65-88	73.6	8.1	65-88	.386
Education, in years	13.1	4.8	8-17	13.3	3.6	8-17	.414
Financial well-being	2.89	0.72	1-4	2.85	0.68	1-4	.475
Charlson Comorbidity Index	3.93	0.94	1-10	3.88	0.84	1-9	.213
Severe symptoms (EUI ≥ 2/day)	2.71	0.72	0-5.3	1.54	0.51	0-2.8	.037*
Depression (GDS)	4.18	1.25	0-21	2.93	0.92	0-18	.061
Activity subscale (busyness)	28.83	8.90	9-27	28.01	8.12	9-27	.287
Medication adherence (% of days)	–	–	–	76.91	6.17	2.7-100	

Note: GDS: Geriatric Depression Scale; EUI: episodes of urinary incontinence.

who received trospium (n = 138) side effects were noted for 28 (6.7%), among the persons who received solifenacin- 17(4.1%), among those who received darifenacin- 7 (1.7%). The described side effects had short time frame and either disappeared spontaneously, or taking the medication was suspended for 1- 4 d.

We did not find significant differences before and after treatment (n = 417/364) in terms of age, education, financial well-being, Charlson comorbidity index, geriatric depression scale, activity subscale (Table 1). The GDS scale score was 4.18 (1.25) prior to the study that corresponds to the norm; after the treatment the score did not change significantly: 2.93 (0.92), $p > 0.05$.

The average percentage of the number of days of taking medication in accordance with the prescription was 76.9 (6.2), and any significant differences between the persons who took different medications were not detected ($p > 0.05$ in all compared cases). The percentage of days of receiving trospium was 73.1 (5.9), solifenacin- 76.3 (7.9), darifenacin- 80.1 (8.9). The level of adherence to medication during 85% and more of the time of observation was noted in 71.1% of women. Patients whose adherence was less than 85% of days of observation were uniformly distributed in the range 0- 84%.

Table 2 presents data on the changes in cognitive status and the status of lower urinary tract in women with OAB before and after a three-month AM therapy. There were no significant changes in the parameters characterizing Working Memory and Executive Function ($p > 0.05$ in all cases). Parameters characterizing the evacuation function (Q_{aver}, Q_{max}) also did not change reliably ($p > 0.05$, $p > 0.05$, respectively). However, there was a significant improvement in the parameters characterizing the memory function of the bladder after the first month of treatment and till the end of therapy. Fig. 2 illustrates the changes in the number of urination, urgency and incontinence during the treatment. The number of Daytime urinary frequency and Nocturnal frequency / nocturia, as well as episodes of Urgency (urinary) incontinence, decreases significantly. According to Bladder diary, the values of Daytime urinary frequency (9.1 (1.7) / 5.1 (2.0), $p < 0.05$), Nocturnal frequency (1.9 (0.6) / 0.4 (0.4), $p < 0.01$), urgency (3.4 (0.8) / 1.2 (0.9), $p < 0.05$), urgency (urinary) incontinence (1.6 (1.5) / 0.5 (0.5), $p = 0.071$) significantly decreased too. The data obtained using the OAB-SF questionnaire comply well with these results. The average value of Postvoid residual (urine volume) at the start of the study was 29, 7 ml, at the finish – 37, 5 ml, the differences to be non significant ($p \geq 0.05$).

Table 2
Descriptive statistics of the Working Memory, Executive Function, and functional status Lower Urinary Tract in women with overactive bladder before and after treatment antimuscarinic drugs (N = 417/364).

Parameters of cognitive status (score points)	Before of treatment M (SD)	After of treatment M (SD)	P value
Mini-Mental State Examination	26.6 (5.3)	26.1 (4.1)	.171
WMS III Mental Control	5.6 (2.0)	5.4 (1.7)	.293
WMS III Digit Span Backward	11.7 (0.9)	10.5 (3.2)	.137
WMS III Letter Number Sequencing	13.8 (2.7)	13.2 (3.5)	.368
WMS III Logic memory 1 recall	35.6 (7.7)	36.4 (12.0)	.417
WMS III Logic memory 2 recall	22.3 (6.7)	20.4 (11.5)	.197
WMS III Logic memory 2 recognition	23.4 (5.1)	25.1 (4.5)	.242
CVLT Short Delay Cued Recall	12.7 (7.0)	13.0 (5.3)	.375
CVLT Long Delay Cued Recall	11.7 (1.9)	11.5 (2.3)	.216
CVLT Recognition measures	24.0 (2.3)	23.9 (2.8)	.130
WCST Perseverative responses	27.3 (5.8)	26.9 (6.9)	.345
WCST Categories Completed	25.2 (4.2)	25.8 (5.1)	.153
Urinary storage symptoms (OABq SF, points) [R1Q5]			
Frequency	4.1 (1.3)	1.0 (1.1)*	.031
Nocturia	3.2 (1.5)	0.6 (0.3) *	.042
Urgency	4.4 (0.9)	0.9 (0.5)*	.019
Urgency (urinary) incontinence	3.7 (1.2)	1.5 (0.7)*	.036
Frequency volume (Bladder diary, episodes/day)			
Daytime urinary frequency	9.1 (1.7)	5.1 (2.0)*	.044
Nocturnal frequency/nocturia	1.9 (0.6)	0.4 (0.4)*	.009
Urgency	3.4 (0.8)	1.2 (0.9)*	.037
Urgency (urinary) incontinence	1.6 (1.5)	0.5 (0.5)	.071
Urodynamic investigation (uroflowmetry)			
Postvoid residual (urine volume), ml	36.7 (15.3)	31.5 (11.5)	.214
Q_{aver}- Average (urine) flow rate, ml/sec	16.3 (3.7)	18.6 (10.2)	.291
Q_{max}- Maximum (urine) flow rate, ml/sec	19.4 (5.6)	19.1 (7.6)	.692

WMS III: Wechsler Memory Scale 3; CVLT: California Verbal Learning Test.
WCST: Wisconsin Card Sorting Test; M: mean; SD: standard deviation.
* $p < .05$.

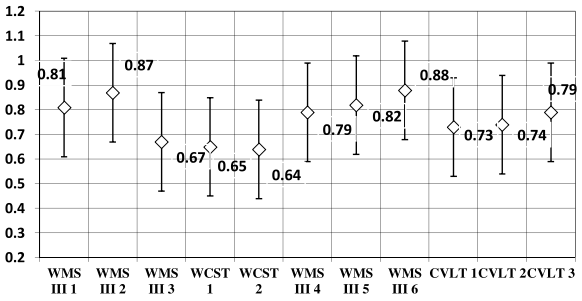

Fig. 1. The correlation (Part Whole) of Each Scale to the Executive Function and Working Memory and the Memory Composite Scores (N = 417).
Notes: WMS III = Wechsler Memory Scale III; WMS III-1: Mental Control; WMS III-2: Digit Span Backward; WMS III-3: Letter Number Sequencing; WMS III-4: Logic memory 1 recall; WMS III-5: Logic memory 2 recall; WMS III-6: Logic memory 2 recognition.
WCST = Wisconsin Card Sorting Test; WCST 1 - Perseverative responses, WCST 2 - Categories Completed.
CVLT = California Verbal Learning Test; CVLT 1 - Short Delay Cued Recall; CVLT 2 - Long Delay Cued Recall; CVLT 3 - Recognition measures.

We have analyzed part–whole correlations for the relationship between the composite scores for executive function–working memory and memory and the component parts (Fig. 1). This method of analysis is recommended for use with smaller sample sizes for which a formal factor analysis might not be advisable [21]. Each of the estimates was strongly related ($r = 0.65$-0.88, $p < 0.05$) to the composite scores. Thus, we confirmed high validity of the composite scores for the executive function and working memory (extensive function and working memory).

Zero order correlations between separate parameters of the sample after completion of treatment are represented in Table 3. A high level of medication adherence among patients was associated with age ($r = -0.51$, $p < 0.01$), education level ($r = 0.45$, $p < 0.05$), severity of lower urinary tract symptoms ($r = 0.48$, $p < 0.05$), and the MMSE scale score ($r = 0.29$, $p < 0.05$). The executive function and working memory composite, as well as the cued recall and recognition memory composite, also showed a strong level of interrelation with medication adherence / fulfilling doctor's prescriptions ($r = 0.47$, $p < 0.01$ and $r = 0.53$, $p < 0.05$). The association of other variables with adherence to treatment was not found.

In Table 4 the results of plotting of hierarchic and simultaneous regressions for the sampled population after completion of the course of treatment are represented. In accordance with the previously obtained results, we introduced the variables in the hierarchical regression in the following order: age, severity of symptoms, executive function and working memory composite score, education, mini-mental state exam score, cued recall and recognition memory composite, activity subscale, geriatric depression scale, financial well-being, Charlson comorbidity index. Analysis of the results allowed us to establish that such model parameters as age (increment $R2 = .06$), severe symptoms ($R2 = .06$), executive function and working memory composite ($R2 = .08$), education ($R2 = .06$), cued recall and recognition memory composite ($R2 = .07$) add a unique variance.

When simultaneous regression was performed (with simultaneous introduction of all variables), it was established that executive function and working memory composite ($\beta = .39$, $p < .05$), severe symptoms of lower urinary tract ($-.31$, $p < .05$), and age ($-.25$, $p < .05$) are reliable predictor variables.

Table 5 represents the number and percentage of patients with high level of correlation between the number of days of taking medicinal drugs and the values of different parameters which we assessed in this study. As it is seen from the table, all the group turned out to be homogenous enough according to this criteria: in any case we did not find significant differences between the percentage of patients in subgroups A, B and C. High correlation between adherence and the age was noted in group A for 56% of patients, but in the general group this indicator was significantly high only for 35% of patients. In 79% of the patients of total the sample high level of correlation of adherence was found; with total score MMSE, in 77% - with executive function and working memory composite score, in 73% - with Charlson Comorbidity Index. Also, more than in 60% of patients a strong correlation of adherence and memory sum (73%), severe symptoms of urinary incontinence (64%) and depression level was also found. So, strong correlation of medication adherence and the parameters investigated in the first turn (EFWM, Memory sum) turned out to be characteristic for the most part of patients (73-77%), not depending on which exactly antimuscarinic drug they were taking during the treatment.

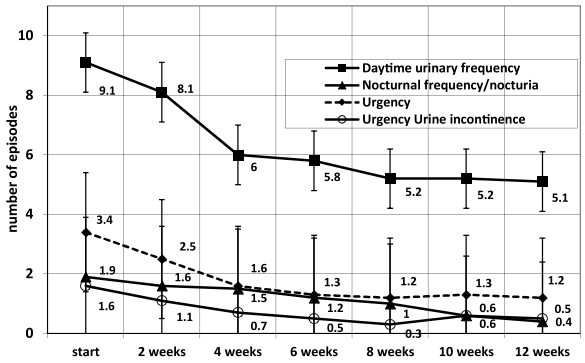

Fig. 2. Changes in score of symptoms overactive bladder in women, who took trospium 15 mg/day (n = 138), or Solifenacin 5 mg/day (n = 132), or Darifenacin 7.5 mg/day (n = 147).
Note. The according to voiding of diary (total number n = 417).

Discussion

In planning this study we wanted to assess the interrelation between adherence to treatment with AM in elderly women and executive function and working memory, as well as the general state of memory, taking into account the influence of all other factors. During three months we performed observation of the state of urodynamics of patients who received trospium, solifenacin and darifenacin, after completion of the study we examined the parameters of cognitive status related to behavioral features in taking the decision on performance of the doctor's prescriptions.

At the first stage we found that the storage symptoms (according to OABq SF and voiding diary) significantly decreased, the voiding symptoms did not change (according to uroflowmetry). The state of cognitive functions remained stable, and the MMSE and GDS tests showed no symptoms of depression in most of the patients. Medication adherence was an average of 76.9% and did not differ in women taking different AM. Thus, functional state of the lower urinary tract and cognitive functions of patients after the treatment were fully consistent with the literature data and the results of our own earlier observations [15, 16, and 23].

At the second stage we studied the influence of executive function and working memory, as well as the general state of memory on medication adherence, taking into account all other factors. We found out that composite assessments of executive and working memory are valid and correlate with each of the individual variables that characterize these cognitive functions. Next, we performed zero order correlations, and found that medication adherence directly correlates with the severity of lower urinary tract symptoms ($r = 0.48$, $p < 0.05$), executive function and working memory composite ($r = 0.47$, $p < 0.01$), education level ($r = 0.45$, $p < 0.05$), MMSE scale index ($r = 0.29$,

Table 3
The correlation matrix of the variables that affect adherence to treatment by antimuscarinic drugs.

Variables		Demographic and Socio-economical status				Medical Status		Mental Health Psychic status Cognitive function			
	Ad	Age	Educ	AS	FWB	CCI	SS	GDS	MMSE	EFWM	CRRM
Age	-.51**										
Education	.45*	.10									
AS	.18	-.43**	-.12								
FWB	.14	-.29*	.17	.08							
CCI	.09	.51**	.13	-.23	.14						
Severe sym	.48*	.43*	.03	.15	.07	.16					
GDS	.17	.20	.18	-.21	.23*	.34*	.37*				
MMSE	.29*	-.15	.28*	.24	.07	-.14	-.19	-.18			
EFWM	.47**	-.14	.49**	.19	.17	-.11	-.08	-.21	.45**		
CRRM	.23*	-.19	.39*	.14	0.15	-.01	.06	-.16	.61**	.49**	

Notes: Ad – adherence, Educ - educational level; AS - activity subscale (busyness); FWB - financial well-being; GDS - Geriatric Depression Scale; MMSE - Mini-Mental State Exam; CCI - Charlson Comorbidity Index; SS, Severe sym - severe symptoms (EUI ≥ 3/day); EFWM - executive function and working memory composite score; CRRM - cued recall and recognition memory composite.
* $p < .05$.
** $p < .01$.

Table 4
Hierarchical and simultaneous regression predicting antimuscarinic adherence.

	Hierarchical regression			Simultaneous regression	
Variables	R^2 Increments	*F* Change	Degree of Freedom	Standardized β	*t*
Age	.06*	3.79	430	-.25*	1.78
SS	.06*	6.12	420	-.31*	2.01
EFWM	.08*	8.29	410	.39*	2.14
Education	.06*	5.33	400	.17	.83
MMSE	.05	5.04	390	.19	.53
Memory sum	.07*	6.98	380	.11	.90
AS	.01	0.86	370	.04	.42
GDS	.01	1.67	360	-.09	1.03
FWB	.02	1.95	350	.01	.13
CCI	.04	4.66	340	.15	.97
Total	.46**	3.84	340		

Notes: SS - severe symptoms (EUI ≥ 3/day); AS - activity subscale (busyness); EFWM - executive function and working memory composite score; MMSE - Mini-Mental State Exam; Memory sum - cued recall and recognition memory composite; AS - activity subscale (busyness); GDS - Geriatric Depression Scale; FWB - financial well-being; CCI - Charlson Comorbidity Index.
* $p < .05$.

Table 5
Number and percentage of patients in each group with high level of correlation between medication adherence and social-demographic, cognitive, urodynamic parameters.

Variables	Group A (n = 138/115) N %	Group B (n = 132/118) N %	Group C (n = 147/131) N %	Total (n = 417/364) N %
Age	56 (56.5)	39 (33.0)*	35 (27.1)*	130 (35.7)
SS	71 (61.7)	79 (66.9)	84 (65.1)	234 (64.3)
EFWM	88 (76.5)	92 (77.9)	102 (70.1)	282 (77.5)
Education	59 (51.3)	71 (60.2)	66 (51.2)	196 (53.8)
MMSE	101 (87.8)	95 (80.5)	93 (72.1)	289 (79.4)
Memory sum	87 (75.6)	89 (75.4)	91 (70.5)	267 (73.3)
AS	21 (18.2)	18 (15.2)	17 (13.2)	56 (15.4)
GDS	68 (59.1)	75 (63.5)	77 (59.6)	220 (60.4)
FWB	41 (35.6)	63 (53.4)	46 (35.6)	150 (41.2)
CCI	79 (68.7)	95 (80.5)	93 (72.1)	267 (73.3)

Notes:
SS - severe symptoms (EUI ≥ 2/day).
AS - activity subscale.
EFWM - executive function and working memory composite score.
MMSE - Mini-Mental State Exam.
Memory sum - cued recall and recognition memory composite.
GDS - Geriatric Depression Scale.
FWB - financial well-being.
CCI - Charlson Comorbidity Index.
Significance of differences*$p < .05$.

$p < 0.05$), as well as cued recall and recognition memory composite ($r = 0.23$, $p < 0.05$). A negative correlation of medication adherence with age was also found ($r = -0.51$, $p < 0.01$). After constructing the hierarchical and simultaneous regressions it was established that the predictor variables significantly influencing medication adherence of elderly women are executive function and working memory composite (β = .39, $p < .05$), severe symptoms of lower urinary tract (-.31, $p < .05$), and age (-.25, $p < .05$). This result is well congruent with prefrontal cortex theory which describes the relation of the executive function and working memory with observation of prescriptions [19,20]. The working and prospective memory supports temporal integration and makes it possible to

realize the model of behaviour assuming high adherence to execution of doctor's prescriptions and treatment in whole (with understanding by the patient its significance and necessity, that is with optimal motivation). The data received also confirm already existing data that executive function affects the capacity for self-care [34]. At the same time, the total memory score in our study appeared to be not related with medication adherence. But in everyday life for the most part of patients, as a rule, it is not difficult to remember about the necessity of taking medications. Possibly, understanding of the information about their disease, about the ways of treatment and the significance of exact following the instructions is more significant for poorly educated patients. In our opinion, poor understanding of cause-and-effect relationship and absence of necessary motivation can have a significantly larger effect on behavioral features of such women. Such assumptions have been expressed in literature before, too [21].

In the process of study it was found that for the most part of patients (56-79%) strong correlation dependence was noted between medication adherence and such parameters as EFWM, Memory sum, CCI, UI and a series of others. This result, in particular, confirms the thesis that executive function and working memory without doubt affect the adherence to treatment with antimuscarinic drugs in elderly women, and their state shall be taken into account when making choice of AM.

We also did not find interrelation between the condition of mental status according to MMSE and medication adherence. But it had been shown before that the executive interview developed for assessment of executive function is more sensitive to cognitive changes related to executive function and working memory [35].

In our opinion, a significant effect of executive function and working memory on medication adherence in women with OAB can be attributed to the strengths of this study. Such a study was never conducted for patients of this profile. No less important, in our opinion, is the new information about the absence of a strong relationship between the total memory score and patient resistance. In addition, we have confirmed the significant importance of age and severity of symptoms for medication adherence in elderly women with OAB.

This study has some restrictions. We did not study the duration of the disease of the patients, the use of physiotherapeutic methods of treatment before the study and their effectiveness. We also did not study changes in the intensity of the factors that influence decision-making by patients during the observation. These questions require further evaluation.

Nevertheless, the findings can be used in daily practice by urologists, therapists, family doctors for assessment of the risks reducing the effectiveness of OAB treatment in older women due to low medication adherence. A preliminary assessment of executive function and working memory, along with other factors, may allow rationalizing the treatment algorithm, including special measures to control drug administration.

Conclusions

Adherence to AM in women with OAB is 76.9% on average and does not differ with the administration of standard dosages of trospium, solifenacin and darifenacin. The pathological symptoms of LUT significantly decrease after 4-8 weeks of AM treatment. The state of cognitive functions of the patients against the background of AM administration does not change.

The executive function and working memory affect the adherence of elderly women with OAB to doctor's prescriptions and, along with other factors of influence, such as the age and severity of lower urinary tract pathological symptoms, should be considered when developing the treatment algorithm.

Declaration of Competing Interest

The authors confirm that there is no conflict of interest.

References

[1] Ju R, Garrett J, Wu JM. Anticholinergic medication use for female overactive bladder in the ambulatory setting in the United States. Int Urogynecol J 2014 April;25(4):479–84.

[2] Coyne KS, Margolis MK, Kopp ZS, Kaplan SA. Racial differences in the prevalence of overactive bladder in the United States from the epidemiology of LUTS (EpiLUTS) study. Urology 2012 January;79(1):95–101.

[3] Sexton CC, Coyne KS, Thompson C, Bavendam T, Chen CI, Markland A. Prevalence and effect on health-related quality of life of overactive bladder in older americans: results from the epidemiology of lower urinary tract symptoms study. J Am Geriatr Soc 2011 August;59(8):1465–70.

[4] Haab F. Chapter 1: The conditions of neurogenic detrusor overactivity and overactive bladder. Neurourol Urodyn 2014 July;33(Suppl 3):S2–5.

[5] Patrick DL, Khalaf KM, Dmochowski R, Kowalski JW, Globe DR. Psychometric performance of the incontinence quality-of-life questionnaire among patients with overactive bladder and urinary incontinence. Clin Ther 2013 June;35 (6):836–45.

[6] Melotti IGR, Juliato CRT, Tanaka M, Riccetto CLZ. Severe depression and anxiety in women with overactive bladder. Neurourol Urodyn 2018 January;37 (1):223–8.

[7] Bradley CS, Nygaard IE, Hillis SL, Torner JC, Sadler AG. Longitudinal associations between mental health conditions and overactive bladder in women veterans. Am J Obstet Gynecol 2017 October;217(4)430 e1-430.e8.

[8] Onukwugha E, Zuckerman IH, McNally D, Coyne KS, Vats V, Mullins CD. The total economic burden of overactive bladder in the United States: a disease-specific approach. Am J Manag Care 2009;15(4 Suppl):S90–7.

[9] Esin E, Ergen A, Cankurtaran M, Yavuz BB, Halil M, Ulger Z, et al. Influence of antimuscarinic therapy on cognitive functions and quality of life in geriatric patients treated for overactive bladder. Aging Ment Health 2015;19(3):217–23.

[10] Sakakibara R. Cognitive adverse effects of anticholinergic medication for overactive bladder in PD/DLB. Rinsho Shinkeigaku 2013;53(11):1389–92.

[11] Basra RK, Wagg A, Chapple C, Cardozo L, Castro-Diaz D, Pons ME, Kirby M, Milsom I, Vierhout M, Van Kerrebroeck P, Kelleher C. A review of adherence to drug therapy in patients with overactive bladder. BJU Int 2008 September;102 (7):774–9.

[12] Veenboer PW, Bosch JL. Long-term adherence to antimuscarinic therapy in everyday practice: a systematic review. J Urol 2014 April;191(4):1003–8.

[13] Brubaker L, Fanning K, Goldberg EL, Benner JS, Trocio JN, Bavendam T, Jumadilova Z. Predictors of discontinuing overactive bladder medications. BJU Int 2010 May;105(9):1283–90.

[14] Harpe SE, Szeinbach SL, Caswell RJ, Corey R, McAuley JW. The relative importance of health related quality of life and prescription insurance cover age in the decision to pharmacologically manage symptoms of overactive bladder. J Urol 2007;178(6):2532–6.

[15] Kosilov K, Kuzina I, Loparev S, Gainullina Y, Kosilova L, Prokofyeva A. Influence of the Short-term Intake of High Doses of Solifenacin and Trospium on Cognitive Function and Health-Related Quality of Life in Older Women With Urinary Incontinence. Int Neurourol J 2018;22(1):41–50.

[16] Kosilov K, Loparev S, Kuzina I, Shakirova O, Zhuravskaya N, Lobodenko A. Treatment compliance of working persons to high-dose antimuscarinic therapies: a randomized trial. Ter Adv Urol 2016 August;8(4):239–48.

[17] Kosilov K, Loparev S, Kuzina I, Shakirova O, Zhuravskaya N, Ankudinov I. Social, economic, and medical factors associated with solifenacin therapy compliance among workers who suffer from lower urinary tract symptoms. Int Neurourol J 2016;20(3):240–9.

[18] Kosilov K, Loparev S, Ivanovskaya M, Kosilova L. Maintenance of the therapeutic effect of two high-dosage antimuscarinics in the management of overactive bladder in elderly women. Int Neurourol J 2013 December;17 (4):191–6.

[19] Fuster JM. The prefrontal cortex–an update: time is of the essence. Neuron 2001 May;30(2):319–33.

[20] Raz NB. Aging of the brain and its impact on cognitive performance: Integration of structural and functional findings. In: Craik FIM, Salthouse TA, editors. The handbook of aging and cognition. Mahwah, NJ: Erlbaum; 2000. p. 1–90.

[21] Insel K, Morrow D, Brewer B, Figueredo A. Executive function, working memory, and medication adherence among older adults. J. Gerontol: Ser B 2006 March;61(2):P102–7.

[22] Alosco ML, Spitznagel MB, van Dulmen M, Raz N, Cohen R, Sweet LH, et al. Cognitive function and treatment adherence in older adults with heart failure. Psychosom Med 2012 November December;74(9):965–73.

[23] Geller E, Crane A, Wells E, Robinson B, Jannelli M, Khandelwal Ch, et al. Effect of anticholinergic use for the treatment of overactive bladder on cognitive function in post-menopausal women. Clin Drug Investig 2012 October;32 (10):697–705.

[24] Shy M, Fletcher SG. Objective evaluation of overactive bladder: which surveys should i use? Curr Bladder Dysfunct Rep 2013 March;8(1):45–50.

[25] Amundsen CL, Parsons M, Cardozo L, Vella M, Webster GD, Coats AC. Bladder diary volume per void measurements in detrusor overactivity. J Urol 2006 December;176(6 Pt. 1):2530–4.

[26] Wu JM, Fulton RG, Amundsen CL, Knight SK, Kuppermann M. Patient preferences for different severities of and treatments for overactive bladder. Female Pelvic Med Reconstr Surg 2011 July;17(4):184–9.
[27] Yesavage JA. Development and validation of a Geriatric Depression Screening Scale: a preliminary report. J Psychiatr Res 1982;17:37–49.
[28] Park DC, Hertzog C, Leventhal H, Morrell RW, Leventhal E, Birchmore D, et al. Medication adherence in rheumatoid arthritis patients: older is wiser. J Am Geriatrics Soc 1999;47:172–83.
[29] Skoog J, Backman K, Ribbe M, Falk H, Gudmundsson P, Thorvaldsson V, et al. A longitudinal study of the mini-mental state examination in late nonagenarians and its relationship with dementia, mortality, and education. J Am Geriatr Soc 2017 June;65(6):1296–300.
[30] Tanabe MK, Whitaker AM, O'Callaghan ET, Murray J, Houskamp BM. Intellectual ability as a predictor of performance on the Wisconsin Card-Sorting Test. Appl Neuropsychol Child 2014;3(4):275–83.
[31] Kent PL. Evolution of Wechsler's Memory Scales: content and structural analysis. Appl Neuropsychol Adult 2017 May-Jun;24(3):232–51.
[32] Davis JJ, Wall JR. Examining verbal memory on the Word Memory Test and California Verbal Learning Test-Second Edition. Arch Clin Neuropsychol 2014 December;29(8):747–53.
[33] Figueredo AJ, McKnight PE, McKnight KM, Sidani S. Multivariate modeling of missing data within and across assessment waves. Addiction 2000 November;95(Suppl. 3) S361-80.
[34] Royall DR, Palmer R, Chiodo LK, Polk MJ. Declining executive control in normal aging predicts change in functional status: the Freedom House Study. J Am Geriatr Soc 2004 March;52(3):346–52.
[35] Allen SC, Jain M, Ragab S, Malik N. Acquisition and short-term retention of inhaler techniques require intact executive function in elderly subjects. Age Ageing 2003 May;32(3):299–302.