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Psychological continuum of elderly patients suffering from arterial hypertension with metabolic syndrome, against the background of chronotherapy with a fixed combination of amlodipine, lisinopril and rosuvastatin

Aim	To study the psychological continuum in elderly patients with arterial hypertension associated with metabolic syndrome during the chronotherapy with a fixed combination (FC) of amlodipine, lisinopril, and rosuvastatin.
Material and methods	In the inpatient conditions, 63 patients aged 60–74 years with arterial hypertension associated with metabolic syndrome were treated with chronotherapy with a FC of amlodipine, lisinopril, and rosuvastatin (5/10/10 mg/day in the evening). These patients composed the main group. The control group (58 patients aged 60–74 years with arterial hypertension associated with metabolic syndrome) was treated with the FC of amlodipine, lisinopril, and rosuvastatin at the same dose of 5/10/10 mg/day in the morning.
Results	At one year, the disorders of psychological continuum were significantly decreased with the chronotherapy (evening dosing) with the antihypertensive FC of amlodipine, lisinopril, and rosuvastatin compared to the traditional treatment (morning dosing) at the same dose of 5/10/10 mg/day in both groups. With the chronotherapeutic approach, the dynamic of cognitive disorders in patients aged 60–74 years with arterial hypertension associated with metabolic syndrome was characterized by a significant increase in the Mini-Mental-State-Examination scale score from 17.8±0.3 at baseline to 23.5±0.4 with the evening dosing ($p<0.001$) vs. the increase from 16.9±0.3 to 20.4±0.4 ($p<0.001$) with the morning dosing. The situational anxiety score decreased from 40.0±2.2 to 30.6±1.8 ($p<0.05$) and from 40.8±2.5 to 33.5±1.9 ($p<0.05$), and the trait anxiety score decreased from 48.8±2.0 to 26.4±1.9 ($p<0.001$) and from 44.9±1.9 to 30.7±1.7 ($p<0.01$) with the evening and morning dosing, respectively. Depressive disorders slightly decreased with the chronotherapy by 14.1% vs. 7.7% with the traditional regimen; nevertheless, they were consistent with depressive spectrum disorders in both groups.
Conclusion	The study results showed a higher effectiveness of the chronotherapeutic treatment compared to the traditional treatment with FC of amlodipine, lisinopril, and rosuvastatin in arterial hypertension with metabolic syndrome.

Keywords	Psychological continuum; arterial hypertension; metabolic syndrome; fixed combination of amlodipine, lisinopril, and rosuvastatin; elderly; chronotherapy
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Introduction

The combination of arterial hypertension (AH) and metabolic syndrome (MS) is considered by researchers to be a leading risk factor in cardiovascular and cerebrovascular diseases and complications, especially in elderly patients [1, 2]. AH patients with MS have a two to three-fold increased risk of developing cardiovascular complications, and a five-fold increased risk of diabetes

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mellitus and all-cause death compared to patients without MS [3].

In most countries, 50–60% of elderly people have AH [4], and this age cohort reaches 75–80% in the Russian Federation [1]. The prevalence of MS increases due to increased life expectancy. Epidemiological studies show that the rate of MS increases gradually with age, rises drastically in persons over the age of 50, and reaches a maximum at the age of 60 to 69 [1, 4].

In developed countries, AH in elderly people with MS is now found from 44.9% in Japan [5] to 50.9% in Spain [6]. AH in elderly and senile patients with MS is more severe, with more pronounced carbohydrate metabolism disorders and blood supply disorders [7]. Mixed anxiety-depressive disorders are often diagnosed in patients with AH and MS at 60 to 74 years [8, 9]. In addition to MS, AH plays a significant role in developing cognitive disorders in the elderly. Such disorders, in addition to mixed anxiety-depressive disorders, are rarely analyzed during antihypertensive treatment. Drugs with anticholinergic effects are known to affect the cognitive function in patients aged 80 years and older with essential AH [10]. However, there are no scientific publications on the evaluation of the effects of other groups of antihypertensive agents, including the fixed combination of amlodipine, lisinopril, and rosuvastatin (Equamer), when administered traditionally (in the morning) to AH patients with MS on the psychological domain. There also no reports on changes in the mental status of elderly AH patients with MS when the above FC is used as chronotherapy (administered in the evening).

Aim

To study the psychological continuum in elderly AH patients with MS during the chronotherapy with amlodipine/lisinopril/rosuvastatin.

Material and methods

In a clinical setting, 63 AH patients with MS at the age of 60–74 (treatment group) received chronotherapy with amlodipine/lisinopril/rosuvastatin (Equamer) at the dose of 5/10/10 mg in the evening (8 p.m.). The control group of AH patients with MS at the age of 60–74 received amlodipine/lisinopril/rosuvastatin in the morning (traditional therapy) at the same dose of 5/10/10 mg. Both groups were comparable in the main clinical and demographic characteristics (Table 1).

The diagnosis of MS included the criteria set out in the Expert Guidelines of the Russian National Scientific Society of Cardiologists for Diagnosis and Treatment of Metabolic Syndrome, revised version 2 [11]. Central (abdominal) obesity (waist circumference more than 80 cm in female patients and more than 94 cm in males) was the main criterion for the diagnosis of MS [11]. Additional criteria of MS were as follows: AH (BP>130/85 mmHg); elevated triglycerides (>1.7 mmol/L); decreased high-density lipoprotein cholesterol (HDL–C) (< 1.0 mmol/L for male patients and<1.2 mmol/L for female patients; elevated low-density lipoprotein cholesterol (LDL–C) (>3.0 mmol/L); fasting hyperglycemia (fasting plasma glucose >6.1 mmol/L); impaired glucose tolerance (plasma glucose >7.8 and<11.1 mmol/L 2 hours after a glucose challenge).

MS was diagnosed in the presence of central obesity and two additional criteria [11].

Diagnosis of AH was based on the National Guidelines of the Russian National Scientific Society of Cardiologists for Prevention, Diagnosis, and Treatment of Arterial hypertension, revised version 4 [12].

Exclusion criteria were: age <45 and >74 years; diabetes mellitus type 2; AH grade III–IV degree; dementia, mental illness and incapacity; renal and hepatic failure, malignancy; history of acute MI; coronary artery bypass grafting, percutaneous coronary intervention; cerebrovascular accident; acute inflammatory process within the past six months; severe cognitive impairments, senile asthenia.

Cognitive impairment was studied before, and 1 year after the treatment, using the Mini-Mental State Examination (MMSE) score [13]. The severity of cognitive dysfunction was evaluated as follows: 0–10 – severe, 11–19 – moderate, 20–23 – mild, 24–27 – no cognitive impairment [13].

State and trait anxiety was assessed by the State-Trait Anxiety Inventory (STAI) [14]. The level of state and trait anxiety was determined by the total score: 20–35 – low, 36–50 – average, 51–60 – increased, 61–70 – evident, and 71–80 – high. Depression was assessed by the Center

Table 1. Main pretreatment clinical and demographic characteristics of patients of both groups

Parameter	Control group	Treatment group
Age, years	70.2±2.2	69.4±2.4
BMI, kg/m^2	31.9±1.1	30.2±1.3
Male/female	28/30	28/35
Duration of AH, years	10.6±2.5	9.8±2.7
AH grade 1, n (%)	38.6	36.5
AH grade 2, n (%)	61.4	63.5
Office SBP, mm Hg	163.8±3.8	162.8±3.7
Office DBP, mm Hg	98.7±1.8	100.9±1.7
HR, bpm	76.0±1.0	77.6±1.1

BMI, body mass index; AH, arterial hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

for Epidemiologic Studies – Depression (CES – D) score [15]: <18 – no depression; from 18 to 24 – depressive disorders;>24 – depression.

The study was conducted following the Declaration of Helsinki and the Good Clinical Practice [16].

The data obtained was processed using Statistica 10.0 and White's non-parametric t-test.

The data is expressed as mean and the standard errors. The differences were statistically significant at p≤0.05.

Results

In both groups the initial cognitive impairments were moderate according to the MMSE score (Figure 1).

The 12-month chronotherapy with amlodipine/lisinopril/rosuvastatin lead to a significant reduction in cognitive deficits in the included patients, regardless of the mode of use of amlodipine/lisinopril/rosuvastatin, yet more significantly in the treatment group. After evening administration of amlodipine/lisinopril/rosuvastatin, cognitive impairments were absent according to the MMSE score in 12.3±4.1% of patients in the treatment group and 7.5±4.3% of patients in the control group with the traditional treatment (p>0.05). However, the post-treatment improvements in cognitive function in elderly AH patients with MS were significantly higher in the treatment group (32.4±3.2% vs. 20.7±5.3% in the control group; p<0.05).

Chronotherapy with amlodipine/lisinopril/rosuvastatin significantly reduced state anxiety in both groups (Figure 2), while the mean baseline score changed to low after treatment. However, in the study groups, the amlodipine/lisinopril/rosuvastatin treatment modes did not have statistically significant effects on the state anxiety scores.

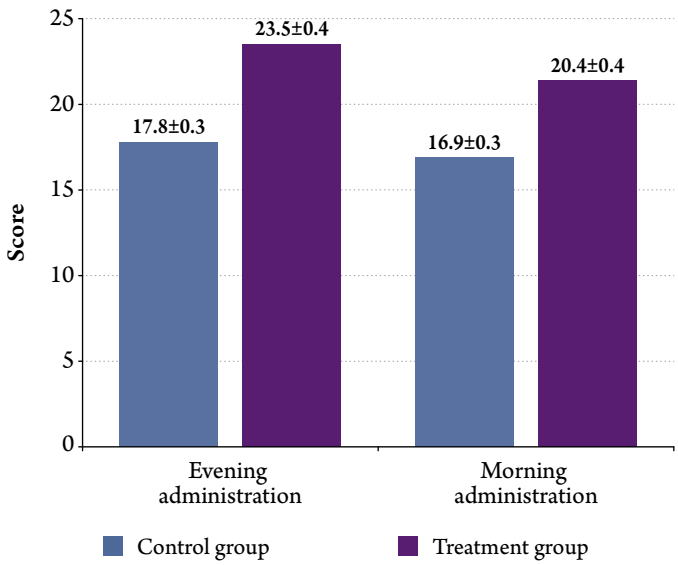
The beneficial effects of the chronotherapy with amlodipine/lisinopril/rosuvastatin in elderly AH patients with MS were also shown by the trait anxiety assessment score (Figure 3). This reduced significantly (p<0.05) by the end of follow-up.

During chronotherapy with amlodipine/lisinopril/rosuvastatin, the degree of depressive disorders decreased significantly (p<0.05) according to the CES-D score in AH patients with MS in both groups (Figure 4). However, neither treatment mode normalized depressive status, which was regarded in both groups as depressive disorders at the beginning of treatment and at the end of follow-up.

Discussion

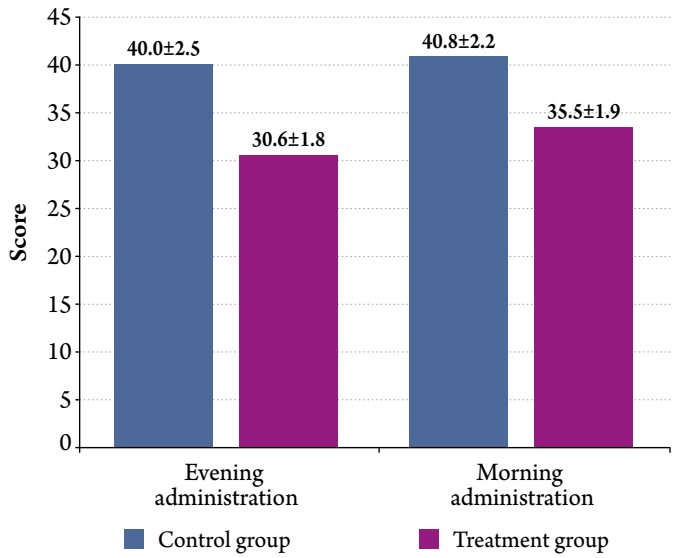
The effects of amlodipine/lisinopril/rosuvastatin on cognitive changes in elderly AH patients with MS, as well as patients of other age, are not reported in scientific publications. The review of literature did not find any information on the effects of this fixed combination in patients with only AH. After six months of using a free combination of rosuvastatin and nimodipine, 60 patients with cardiovascular pathology and moderate cognitive impairments caused by small cerebral vessel disease had a better mental status with more significant improvement (p<0.05), than in the control group (nimodipine mono-

Figure 1. Changes in cognitive impairments as measured by the mean MMSE score when amlodipine/lisinopril/rosuvastatin were used in elderly AH patients with MS in the evening and in the morning (M±m)



AH, arterial hypertension; MS, metabolic syndrome.

Figure 2. Changes in state anxiety according to the STAI score for amlodipine/lisinopril/rosuvastatin used in elderly AH patients with MS in the evening and in the morning (M±m)



AH, arterial hypertension; MS, metabolic syndrome; STAI, State-Trait Anxiety Inventory.

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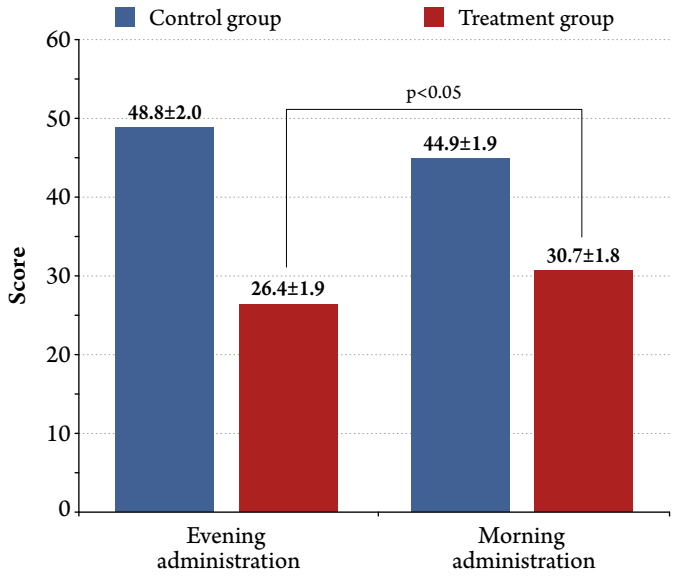
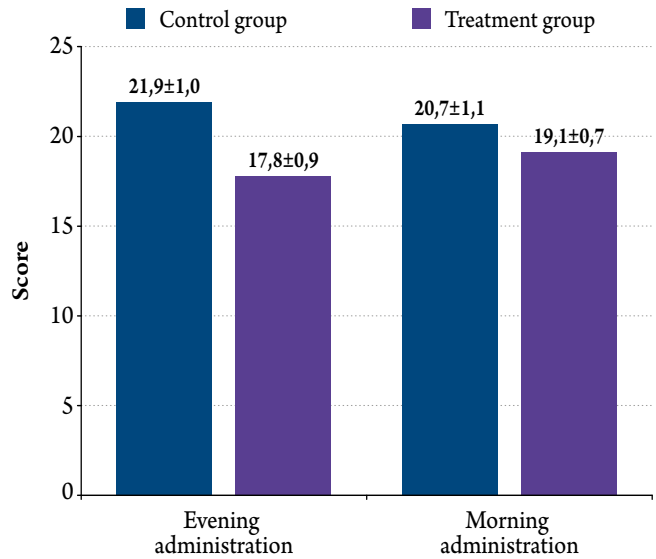
Figure 3. Changes in trait anxiety according to the STAI score for amlodipine/lisinopril/rosuvastatin used in elderly AH patients with MS in the evening and in the morning (M±m)



AH, arterial hypertension; MS, metabolic syndrome; STAI, State–Trait Anxiety Inventory.

Figure 4. Changes in the depressive impairments as measured by the CES-D score for amlodipine/lisinopril/rosuvastatin used in elderly AH patients with MS in the evening and in the morning (M±m)



AH, arterial hypertension; MS, metabolic syndrome.

therapy; n=60) [17]. The authors concluded that the combination of rosuvastatin and nimodipine is safe and effective in treating cognitive impairments in patients with cardiovascular diseases.

Ostroumova et al. [10] analyzed cognitive function in patients of 80 and older with essential AH, who took anticholinergic drugs compared to those who did not take this class of drugs. They detected a more pronounced decrease in cognitive function according to the MMSE score, the Boston Naming Test, and the ADAS-cog subscore. For example, the mean MMSE score was 21 and 22.5 ($p<0.040$), the Boston Naming Test score was 27 and 30 ($p<0.014$), while the mean ADAS-cog score was 16.7 and 12.7 ($p<0.030$) in patients with essential AH receiving and not receiving anticholinergic drugs, respectively. Other cognitive scores tended to show a cognitive decline, but the results did not reach statistical significance. There were no significant differences in the GDS-15 scores between the study groups.

Conclusion

The use of the fixed combination of amlodipine, lisinopril, and rosuvastatin in elderly patients, as the chronotherapy or traditional therapy, improves the psychological continuum. However, a more significant exacerbation of cognitive deficits, trait anxiety, and depressive disorders is observed during the chronotherapy. Both dosing regimens of the fixed combination of amlodipine, lisinopril, and rosuvastatin produce no significant effects on the changes in state anxiety in both study groups of patients with arterial hypertension and metabolic syndrome. Therefore, chronotherapy with this fixed combination in 60–74-year-old patients with arterial hypertension and metabolic syndrome will help maintain psychological and functional activity.

No conflict of interest is reported.

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