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Erectile dysfunction, anxiety and depressive disorders in arterial hypertension: pathogenetic communication and approaches to treatment

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Summary

Erectile dysfunction (ED) is very common in patients with arterial hypertension (AH), reaching the frequency of 70% according to various authors, and accompanying psychoemotional disorders aggravating the course of sexual and somatic disorders. Associated pathology increases the risk of premature death, worsens the prognosis and reduces social functioning of these patients. Common pathogenetic mechanisms of ED, anxiety and depressive disorders and AH include endothelial dysfunction with decreased nitric oxide production, low levels of androgens, violation of cortico-visceral connections with imbalance of the hypothalamic-pituitary-adrenal system, and sympathicotonia. Complex pathophysiology requires prescription of adequate antihypertensive and psycho-corrective therapy, together with effective ED treatment.

Key words

Erectile dysfunction, anxiety and depressive disorders, arterial hypertension, pathogenetic relationship, Phosphodiesterase type 5 inhibitors, adaptogens.

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Introduction

Combination of erectile dysf unction (ED), anxiety and depressive disorders (ADD) and arterial hypertension (AH), so-called «Mutually reinforcing triad», is rightfully considered one of the most important men's problems of the XXI century. [1]. It is caused by their high prevalence, medical and social importance and several pathogenetic mechanisms common between these conditions [2].

Erectile dysfunction is described as inability to reach and/or support adequate erection necessary for coitus [2]. Around 400mln men have ED and it is predicted this number will reach 900 mln persons that is related to negative influence of a growing number of ED risk factors (AH, smoking, obesity, dyslipidemia, and diabetes mellitus) and increased lifespan of male population that is associated with another important ED risk factor – aging and age-related androgene deficiency [3, 4]. The first large-scale study that assessed ED prevalence was held in 2012 and it demonstrated that 1101 respondents (89.9%) out of 1225 had ED symptoms [5].

Sexual functioning is tightly linked with physical and psychosocial health of men and strongly influences the life quality of men and their families. Significant results of E.O. Laumann e coauthors demonstrated, that erection disorders often accompanied with anxiety, despondence and lack of self-confidence cause 4-fold and 6-fold reduction of physical and psychoemotional component of life quality, respectively [6]. Other authors reported that sexual activity directly correlated with men's lifespan. Results of prospective Cayerphilly study that had lasted 10 years demonstrated that the mortality between men with low sexual activity (less than 1 sexual contact per month) was 50% higher comparing with the men who had sexual contacts twice per week and more often [7].

Individual reports of men and women above 55 years old that had been obtained during recent study held in Florida demonstrated that preserved sexual activity is associated with positive physical, social and emotional health characteristics [8].

Pathogenetic correlation between ED, anxiety/depression and AH

Previously the problems of psychogenic origin had been considered the main reason of ED, nowadays it is established that ED is mostly caused by organic and mixed nature. In any case, concomitant anxiety and depression aggravate the course of sexual and somatic disorders.

Clinical studies demonstrate tight connection between ED and cardiovascular diseases [9]. The study of F.A. Giuliano and coauthors [10] revealed ED in 70% of men with AH, and severe AD was diagnosed in 45.2% of males with AH comparing with 10% frequency of this disorder in general population. Doppler scan of penis vessels reveals ED in 87% of patients with AH [11]. The most important pathogenetic mechanism of AH and ED is endothelial dysfunction and insufficient production of nitrogen oxide (NO), main moderator of systemic and organ blood supply. Elevated blood pressure with senescent background is accompanied with impaired endothelium-dependent vasodilatation and consequent structural remodeling, atherosclerosis development, and stenosis of vessels providing blood supply during erection (Figure 1) [12, 13].

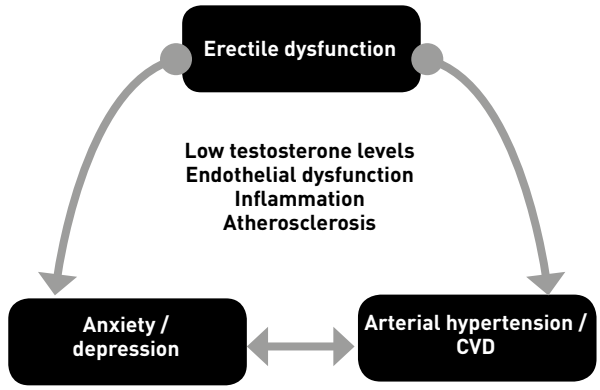


Figure 1. Common mechanisms between ED, ADD, and AH pathogenesis: low testosterone, endothelial dysfunction, slowly progressing systemic vascular inflammation

Chronic vascular inflammation promotes aggravation of endothelial dysfunction and ED development. Increased levels of inflammation markers and mediators (C-reactive protein, intercellular adhesion molecule 1 (ICAM-1), interleukins 6, 10, 1β (IL-6, IL-10, IL-10β, respectively), tumor necrosis factor-α (TNF-α) and endothelial/prothrombotic factors (von Willebrand factor, tissue plasminogen activator, plasminogen activator inhibitor-1, fibrinogen) have been detected in patients with ED [14, 15].

It has been proved that ED is an early marker and predictor of cardiovascular disease. P. Montsori and coauthors demonstrated that ED precedes the development of acute coronary syndrome and angina pectoris in the majority of cases. The average time interval between this events is 12-36 months. It is explained by the fact that diameter of penile artery is 2-3 times less than the diameter of coronary arteries and 3-4 times smaller than the diameter of carotid

arteries, thus manifestations of endothelial dysfunction and atherosclerotic lesions of penile arteries become evident much earlier than the same abnormalities of major coronary and peripheral vessels [16].

Low androgens' level (hypogonadism) is another one important mechanism of combined pathology. Nowadays it has been established that testosterone and its active metabolites not only control adequate sexual functioning but also determine the risk of unfavorable cardiovascular events development and cardiovascular mortality. AH is one of the main cardiovascular disease risk factors and it is connected with low testosterone levels. C. Vlachopoulos and coauthors estimated correlation of low testosterone levels and development of severe cardiovascular event (SCVE) in 228 patients with AH without clinically evident atherosclerosis. They demonstrated that during 44 months observation period 19 participants (8.3%) had developed SCVE like cardiovascular death, myocardial infarction or stroke. Comparing with the patients who did not develop SCVE, men with AH had lower total testosterone (TT) levels (13.5 ± 2.4 nmol/L vs 15.9 ± 5.2 nmol/L, p <0.01) and higher prevalence of hypogonadism (36% vs 16%, p < 0.05) [17]. Testosteron has vasoprotective and cardioprotective effect mediated through NO, its influence on endothelium and inflammation markers, and its deficiency is manifested as cardiovascular disorders like refractory AH, impaired lipid and carbohydrate metabolism, and progressing atherosclerotic remodeling of vessels [18, 19]. Apart from it, androgenic deficiency lowers down psychophysical activity and libido, increases ED and psychoemotional disorders like anxiety and depression that correlates with laboratory test results (TT ⩽ 15nmol/L) [20]. International society of sexual medicine recommends to check TT concentration in patients with ED and/or decreased libido [21].

The presence of anxiety and depression in patients with ED and AH complicates the clinical course of comorbid pathology and becomes a risk factor of premature death, aggravates prognosis and decreases social functioning of these patients [22]. If patients with AH have just depressive disorders, they have 18% higher risk of stroke and 25% higher risk of cardiovascular death [23]. Nowadays several possible common mechanisms of ADD influencing AH, cardiovascular disorders and ED are under investigation. The most important ones are hyperactivation of hypothalamo-pituitary-adrenal system and imbalanced vegetative nervous system with prevailing sympathicotonia [24, 25], impaired functional activity of platelets, increased blood viscosity, endothelial dysfunction [24], and increased chronic inflammatory response [24-26].

Depressive disorders significantly decrease compliance to antihypertensive therapy [27]. These patients do not follow therapeutic regimen and healthy lifestyle in terms of diet, smoking refusal, increased physical activity, and restricted alcohol consumption [28]. European guideline for cardiovascular disease prevention in clinical practice (2016) considers depression and anxiety as significant obstacles for modification of patients' lifestyle in desirable direction that require psycho-correcting work [29].

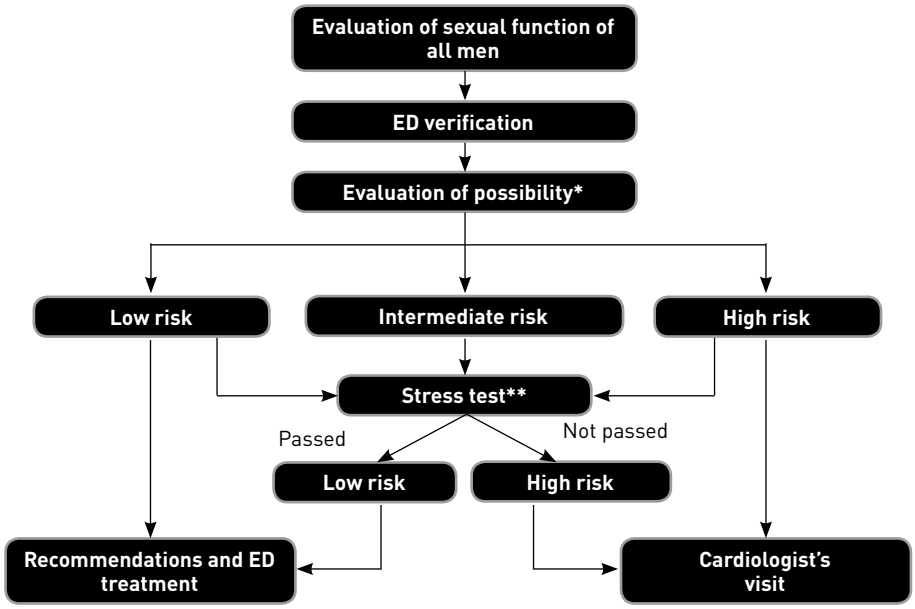
It is necessary to remember that antihypertensive drugs by themselves (non-selective ß-blockers, thiazide diuretics [30-32], and psychotropic drugs like antidepressants and tranquilizers [33]) have a negative impact on ED development. Sings of drug-induced ED include relatively fast development, presence of temporal connection with therapy and reduced intensity or disappearance of ED after drug withdrawal. It explains the fact that ED, ADD and AH triad requires prescription of adequate hypotensive therapy with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) [30-32] and psychotropic treatment with atypical antidepressants like bupropion – selective inhibitor of noradrenalin and dopamine reuptake, trazodone – antagonist of 5-HTA/2C serotonin receptors, agomelatine – MT1 and MT2 melatonergic receptors agonist [33]. The drugs listed above have positive effect on ED without aggravating erectile function.

Treatment of ED and ADD in patients with AH

Complicated pathogenetic connections between ED and ADD in AH require particular treatment approach. Safety of sexual activity in AH is an important question for patients and internal medicine specialists. According with the Princeton Consensus II (Figure 2) [3], patients with controllable AH belong to the low risk group and had can safely continue sexual relationships and use the drugs for ED treatment. Patients with uncontrollable AH having 10-fold increased risk of developing cardiovascular events during coitus and 2 hours after belong to the group of high risk and should visit cardiologist and avoid sexual activity until their condition would be stabilized. Algorithm of management of patients according to cardiac risk is present at Figure 3 [3, 34].

Low risk	Intermediate risk	High risk
• Asymptomatic course or <3 CHD risk factors • Controllable AH • Angina pectoris (FC I-II) • Condition after successful revascularization of coronary arteries • MI without complications (>8 weeks after it) • mild valvular lesions • HF (FC I)	• >3 CHD risk factors • stable angina • MI (2-6 weeks after it) • other manifestations of atherosclerosis (peripheral vascular disorders, transitory ischemic attacks)	• Unstable or refractory angina • Uncontrollable AH • Hf (fC III-IV) • MI or stroke (less than 2 weeks after it) • life-threatening arrhythmias • hypertrophic cardiomyopathy • severe valvular lesions

Figure 2. II Princeton consensus – identification of cardiac risk groups and sexual activity



* Sexual activity is equivalent to walking 1 mile during 20 minutes or going up 2 flights of stairs during 10 seconds
** Sexual activity is equivalent to 4 minutes of Bruce treadmill protocol.

Figure 3. Algorithm of management of patients with ED according to cardiovascular risk [3].

Phosphodiesterase type 5 (PDE-5) inhibitors can be recommended after selection of antihypertensive drugs that are the "golden standard" of ED treatment: sildenafil, tadalafil, valdenafil [35]. At the same time several problems like adverse effects of PDE-5 inhibitors (headache, face hyperemia, dyspepsia, stuffiness in the nose, myalgia) and insensitivity to therapy in 15-40% of patients remain unsolved. It is known that these drugs are able to potentiate relaxing action of NO on smooth muscular cells of trabecular tissue. But central nervous system impulses are required for triggering NO release. Their intensity depends on patient's reaction on sexual stimulus. Due to the lack of substrate of action, monotherapy with PDE-5 inhibitors is not very effective in case of strong reduction of libido and it is heavily suppressed with age. That's why nowadays it is strictly important to optimize clinical usage of PDE-5 inhibitors for treatment of patients with ED [36]. In case of androgen replacement therapy several problems like suppression of endogenous androsteroids production, negative effect on liver and prostate, remain unsolved.

Use of nature—derived drugs, that have minimal number of adverse effects and are capable to increase sexual desire, improve the quality of erection and mood, and stabilize vegetative nervous system, is a good alternative and addition to ED treatment in men with AH. The authors of this article participated in the study of dynamical clinical evaluation of ED and ADD in 78 male patients with AH I-III stage during complex therapy [37-39], which included antihypertensive drugs together with adaptogen Eromax produced in Russia and containing drone brood, pollen pellet, ginseng root, L-arginine, zinc citrate, and pyridoxine hydrochloride. All patients were divided into two groups with comparable age and severity of

Table 1. **Dynamics of testosterone, prolactin, and DHEAS levels in serum during therapy**

Parameters	Day 0		Day 28		Reference values	p
	Group 1	Group 2	Group 1	Group 2		
TT	11.8 ± 4.4	11.4 ± 3.8	17.1 ± 5.7*	13.4 ± 3.1	12.1-38.3 nM/L	<0.02
Prolactin	521 ± 36	517 ± 29	285 ± 60*	460 ± 69	24.5-467 mU/L	<0.02
DHEAS	1.2 ± 0.3	1.3 ± 0.1	1.4 ± 0.7	1.3 ± 0.2	1.0-4.2 μg/mL	>0.054
* Significant differences						

Table 2. **IIEF characteristics' dynamics**

Characteristic	Day 0		Day 28	
	Group 1	Group 2	Group 1	Group 2
ED	13.4 ± 0.7	12.9 ± 0.8	19.8 ± 0.6*	14.8 ± 0.7
Satisfaction with coitus	9.6 ± 0.4	9.8 ± 0.5	14.1 ± 0.7*	12.8 ± 0.4
Orgasm	5.1 ± 0.4	5.7 ± 0.2	8.8 ± 0.2*	5.9 ± 0.8
Libido	6.1 ± 0.5	6.3 ± 0.1	10.9 ± 0.3**	8.1 ± 0.1
General satisfaction	5.8 ± 0.1	5.9 ± 0.7	10.1 ± 0.9**	7.0 ± 0.7
Significant differences - * p<0,05, ** p<0,02.				

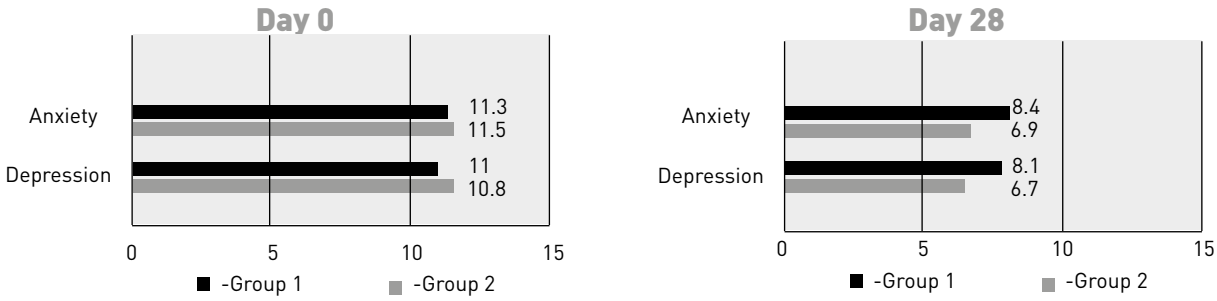


Figure 4. Dynamics of pshycoemotional characteristics

health problems. Patients of the first group (n=55) received hypotensive therapy and adaptogen, the second group (n=23) received only antihypertensive drugs. Small doses of antidepressants (trazodone 50-150 mg/day) were used in both groups in order to reduce evident affective pathology. Common procedures included also individual and/or family cognitive-behavioral psychotherapy. By the moment of the end of treatment, investigation of hormonal status in the first group demonstrated significant increase of TT levels (from 11.8 ± 4.4 to 17.1 ± 5.7 nmol/L, p<0.02) and tendency to increase of dehydroepiandrosterone sulfate (DHEAS) concentration (from 1.2 ± 0.3 to 1.4 ± 0.7 μg/mL, p<0.05) together with decreased prolactin levels (from 521 ± 36 to 285 ± 60 mU/L, p<0.02), whereas the patients of the second group had no significant changes of hormones' levels (Table 1). All parameters of the "International Index of Erectile Function (IIEF) questionnaire increased significantly in the first group (Table 2). Hospital Anxiety and Depression Scale (HADS) revealed more significant reduction of anxiety and depression in the patients of the first group (Figure 2). Before treatment the average level of depression was evaluated as clinical and was comparable in both groups (11.5 ± 0.6 and 11.3 ± 0.7 points, respectively). After treatment this parameter came back to normal values in the patients of the first group (6.9 ± 0.3 points, p<0.02), whereas in the second group its values stayed at subclinical level. Average depression level estimated with the HADS scale was close to clinical level in the beginning of treatment (10.8 ± 0.5 points in the first group versus 11.0 ± 0.2 points in the second group); by the end of treatment (28 days) depression characteristics reached the normal levels only in the first group (6.7 ± 0.3 (p<0.02)) (Figure 4).

Conclusion

ED and ADD are frequently present in men with AH. Combined pathology increases significantly the risk of premature death, aggravates prognosis and lowers down the quality of patients' life. Common pathogenetic mechanisms of ED, ADD, and AH include endothelial dysfunction, low androgene levels, impaired balance of hypothalamo-pituitary-adrenal system, and sympathicotonia. ED is an early marker or prede-

cessor of cardiovascular disorders and appears to be a valuable diagnostic symptom for internal medicine specialists. The triad of ED, ADD and AH requires the prescription of adequate antihypertensive and psychocorrecting therapy, complex restoration of sexual function and consequently becomes the problem of interdisciplinary interaction between cardiologists, psychiatrists, sexologists, urologists and endocrinologists.

Conflict of interest: None declared.

References

1. Goldstein I. The mutually reinforcing triad of depressive symptoms, cardiovascular disease, and erectile dysfunction. The American Journal of Cardiology. 2000;86(2):41–5.
2. El-Sakka AI. Erectile dysfunction, depression, and ischemic heart disease: does the existence of one component of this triad necessitate inquiring the other two? J Sex Med. 2011;8(4):937-40.
3. Hatzimouratidis K, Eardley I, Giuliano F, Moncada I, Salonia A. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. European Association of Urology Web site. http://uroweb.org/guideline/male-sexual-dysfunction/ . Updated 2015.
4. Lewis RW, Fugl-Meyer KS, Corona G, et al. Definitions / epidemiology / risk factors for sexual dysfunction. J Sex Med. 2010;7:1598–607.
5. Pushkar DY, Kamalov AA, Al-Shukri SH, et al. The first pilot epidemiological study of the prevalence of erectile dysfunction in the Russian Federation. Effective pharmacotherapy. Endocrinology. 2013;1(9):28-31. Russian
6. Laumann EO, et al. Sexual dysfunction in the United States: Prevalence and predictors. JAMA. 1999;281:537-44.
7. Smith DG, Frankel S, Yamell J. Sex and death: are they related? Findings from the Caerphilly Cohort Study. BMJ. 1997;315:1641-44.
8. Bach LE, Mortimer JA, VandeWeerd C, Corvin J. The association of physical and mental health with sexual activity in older adults in a retirement community. J Sex Med. 2013 Nov;10(11):2671-8.
9. Gandaglia G, Briganti A, Jackson G, et al. A systematic review of the association between erectile dysfunction and cardiovascular disease. Eur Urology.2014;65:968-78.
10. Giuliano FA, Leriche A, Jaudinot EO, et al. Prevallence of erectile dysfunction among 7689 patients with diabbetes or hypertension, or both. J Urol. 2004;64:1196-201.
11. Vlachopoulos C. Definition and Assessment of Erectile Dysfunction. In: Viigimaa M., Vlachopoulos C., Doumas M. Erectile Dysfunction in Hypertension and Cardiovascular Disease. Springer International Publishing, Switzerland; 2015. pp. 9–17.
12. Clavijo RI, Miner MM, Rajfer J. Erectile Dysfunction and Essential Hypertension: The Same Aging-related Disorder? Rev Urol. 2014;16:167-71.
13. Blick C, Ritchie RW, Sullivan ME. Is Erectile Dysfunction an Example of Abnormal Endothelial Function? Curr Vasc Pharmacol. 2016;14(2):163-7.
14. La Vignera S, Condorelli R, Vicari E, et al. Arterial erectile dysfunction: reliability of new markers of endothelial dysfunction. J Endocrinol Invest. 2011;34(10):314–320.
15. Arana Rosainz Mde J., Ojeda M.O., Acosta J.R., et al. Imbalanced lowgrade inflammation and endothelial activation in patients with type 2 diabetes mellitus and erectile dysfunction. J Sex Med. 2011;8:2017-30.
16. Montorsi P, Montorsi F, Schulman CC. Is erectile dysfuncttion the «tip of the iceberg» of a systemic vascular disorder? Eur Urol. 2003;44:352-4.
17. Vlachopoulos C., Ioakeimidis N, Terentes-Printzios D, et al. Plasma total testosterone and incident cardiovascular events in hypertensive patients. Am J Hypertens. 2013;26:373–81.
18. Novo S, Iacona R, Bonomo V, et al. Erectile dysfunction is associated with low total serum testosterone levels and impaired flow-mediated vasodilation in intermediate risk men according to the Framingham risk score. Atherosclerosis. 2015;238(2):415-9.
19. Spitzer M., Basaria S, Travison TG, et al. The effect of testosterone on mood and well-being in men with erectile dysfunction in a randomized, placebo-controlled trial. Andrology. 2013;1(3):475-82.
20. Lunenfeld B, Mskhalaya G, Zitzmann M, et al. Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. Aging Male. 2015;18(1):5-15.
21. Dean JD, McMahon CG, Guay AT, Morgentaler A, et al. The International Society for Sexual Medicine's Process of Care for the Assessment and Management of Testosterone Deficiency in Adult Men. J Sex Med. 2015;12(8):1660-86.
22. Gathright EC, Goldstein CM, Josephson RA, Hughes JW. Depression increases the risk of mortality in patients with heart failure: A meta-analysis. J Psychosom Res. 2017;94:82-89.
23. Scalco AZ, Scalco MZ, Azul JBS., et al. Hypertension and depression. Clinics. 2005;60 (3):241-50.
24. Nuralieva NF, Napalkov DA. Depression and cardiovascular diseases. Vestn Ross Akad Med Nauk. 2014;(9-10):21-6. Russian
25. Fiedorowicz JG. Depression and cardiovascular disease: an update on how course of illness may influence risk. Curr Psychiatry Rep. 2014;16(10):492.
26. Finnell JE, Wood SK. Neuroinflammation at the interface of depression and cardiovascular disease: Evidence from rodent models of social stress. Neurobiol Stress. 2016;4:1-14.

27. Atlantis E, Shi Z, Penninx BJ, Wittert GA, Taylor A, Almeida OP. Chronic medical conditions mediate the association between depression and cardiovascular disease mortality. Soc Psychiatry Psychiatr Epidemiol. 2012;47(4):615-25.
28. Berntson J, Stewart KR, Vrany E, et al. Depressive symptoms and self-reported adherence to medical recommendations to prevent cardiovascular disease: NHANES 2005-2010. Soc Sci Med. 2015;138:74-81.
29. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37(29):2315-81.
30. Mamedov MN. Men's health issues in cardiology practice 2nd Edition. M: Kardioprogress, 2014. pp. Russian
31. Chrysant SG. Antihypertensive therapy causes erectile dysfunction. Curr Opin Cardiol. 2015;30(4):383-90.
32. Al Khaja KA, Sequeira RP, Alkhaja AK, Damanhori AH. Antihypertensive Drugs and Male Sexual Dysfunction: A Review of Adult Hypertension Guideline Recommendations. J Cardiovasc Pharmacol Ther. 2016;21(3):233-44.
33. DeLay KJ, Haney N, Hellstrom W. Modifying Risk Factors in the Management of Erectile Dysfunction: A Review. World J Mens Health 2016;34(2): 89-100.
34. Nehra A, Jackson G, Miner M, et al. The Princeton III consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2012;87:766-78.
35. Yuan J, Zhang R, Yang Z, et al. Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. Eur Urol, 2013. 63: 902.
36. Kalinchenko SY, Tyuzikov IA, Vorslov LO, et al. Erectile dysfunction: paradoxes and paradigms of modern pathogenetic pharmacotherapy. Consilium Medicum. 2014;16(1):78-82. Russain.
37. Petrova EV, Vakina TN. Therapeutic correction level of dehydroepiandrosterone sulfate and testosterone in sexual dysfunctions. Physician. 2014;1:60-1. Russain
38. Petrova EV, Vakina TN, Burmistrova LA. Sexual dysfunction in anxiety and depressive disorders. Therapist. 2014;5:108-11. Russain
39. Petrova E., Shutov A. Therapeutic correction testosterone deficiency in hypertensive men with erectile dysfunction and depression. J Sex Med. 2016;13(5, Suppl. 2):146. Russain