NEW POSSIBILITIES OF PHYTOTHERAPEUTIC CORRECTION OF SLEEP DISORDER

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The problem of stress and stress-related diseases is one of the leading problems in modern medicine. The pathological influence of long-term chronic psycho-emotional stress, which is at the basis of the formation of various "civilization diseases", among which neuroses and psychosomatic pathologies take the leading place, becomes especially relevant. One of the most important symptoms accompanying the mentioned pathological conditions is sleep disturbance [1, 2, 46-52].

According to the International Classification of Sleep Disorders 2005 (ICSD-2) [2], there are 6 types of sleep disorders, such as insomnia, sleep apnea, hypersomnias, circadian rhythm sleep disorders, parasomnias and sleep-related movement disorders. At the same time, in routine medical practice, when it comes to sleep disorders, first of all, insomnia is considered.

Insomnia is a clinical syndrome characterized by the presence of disturbances in the initiation, duration, consolidation or quality of sleep, which develop despite a sufficient amount of time and conditions for sleep and manifested by various disturbances in daytime activities.

Insomnia is 1.5 times more common in women than in men. In elderly over 75 years of age, the incidence of insomnia is doubled compared to middle-aged people. Sleep disorders are most often identified in people with low education and socioeconomic status, unemployed people or those who work on a variable schedule. Due to comorbid disorders, mental illnesses or chronic pain syndrome, sleep is disturbed in 50-75% of cases. 40% of patients with insomnia have one or more mental disorders, compared to 16% of people without sleep disorders [46-53].

Sleep disorder symptoms are as follows:

- fatigue, impaired concentration or memorization of information;
- social dysfunction, mood disorder, irritability, daytime sleepiness, low motivation and initiative, tendency to make mistakes at work or when driving vehicles;
- muscle tension, headache, gastrointestinal disorders and concern about sleep [1, 49,50].

Sleep is a special genetically determined state of the body, characterized by a regular sequential change of certain polygraphic patterns in the form of cycles, phases, and stages.

Physiologically normal sleep consists of two successive phases – slow and fast phases of sleep that are strictly distinguished by the character of the electroencephalogram (EEG) and the activity of various mediator systems of the brain [51].

The first stage of slow sleep (Non-rapid eye movement sleep (NREM sleep) or sleep onset) is a passive process characterized by a decrease in the tonic activity of excitatory systems as a result of the accumulation of "neuronal metabolites": somatoliberin, adenosine, gamma aminobutyric acid (GABA), glycine, prostaglandin-D2, interleukin-1β, tumor necrosis factor-α in the brain [51].

After sleep onset, a person transmits into the 2nd phase of slow-wave sleep, which is formed due to an active process mediated by the preoptic anterior hypothalamus (POAH), which includes neurons of the ventrolateral preoptic nucleus (VPN) and GABAergic neurons of the anterior hypothalamus and the cerebral hemispheres. At the same time, the excitatory systems of the brain significantly reduce their activity. VPN cells, secreting the inhibitory GABA mediator, are the main source that suppresses the functioning of brain regions that maintain a state of excitement: the blue spot, seam cell nuclei, pedunculopontine (PPN) and laterodorsal tegmental nuclei (LDT), ventral tegmental area (VTA), mammillary nuclei. Figure 1 shows the mechanisms of NREM sleep [51].

Rapid eye movement sleep (REM sleep) is characterized by the active (desynchronized) cortical EEG; the pronounced atony of the muscles maintaining the posture; the rapid eye movement; the tetrarhythm in the hippocampus; the pronounced fluctuation of the cardiorespiratory rhythm and central body temperature [51].

Separate groups of neurons localized in the brain stem are responsible for each manifestation of the described stages of REM sleep: muscle atony is mediated by the activation of neurons of the blue spot alpha (Lcα), rapid eye movements are the result of the activity of neurons located near the nuclei that abduct (VI pair) the cranial nerves of the formation; the hippocampal teta-rhythm is generated due to the work of neurons of the oral nucleus of the pons; muscle contractions appear as a result of the discharges of neurons of the medulla oblongata giant cell nucleus (especially the caudal part); an increase in brain temperature and cardiorespiratory fluctuations is caused by the activation of neurons of the parabrachial nucleus of the pons [51].

Neuronal networks controlling REM sleep are modulated by numerous neurotransmitter systems [51]. During REM sleep, acetylcholinergic neurons of PPN and LDT are activated, increasing the activity of groups of cells responsible for the manifestations of the characteristics of the REM phase. Acetylcholine stimulates the blue spot glutamatergic neurons, which activate inhibitory interneurons of the spinal cord, suppress the activity of mononeurons, resulting in muscle atony. In addition, projections of the blue spot neurons stimulate acetylcholinergic cells of the basilar nucleus of the forebrain. Acetylcholine that affects cortical neurons, disrupts their synchronous electrical activity and enhances glutamatergic transmission.

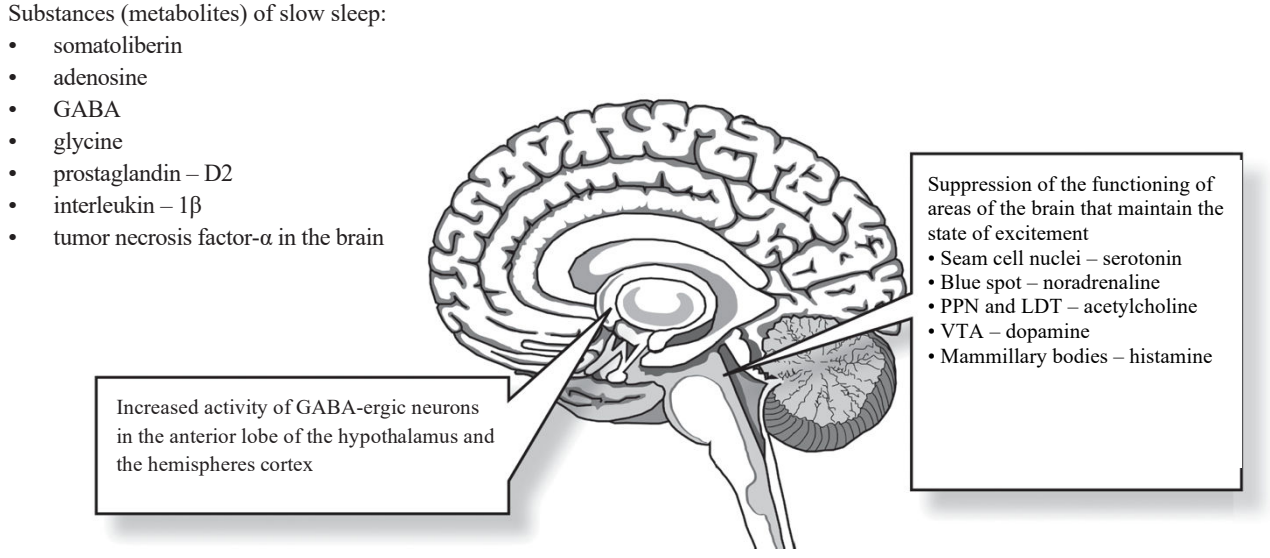

Fig. 1. *The mechanism of slow-wave sleep (NREM-sleep)*

Melatonin-concentrating hormone (MCH) is involved in the maintenance of REM sleep, the main effect of which is post- and presynaptic inhibition, which is mediated by the binding of MCH to MCH receptors of type 1 and 2, combined with Gi, Gq, Go subtypes of signaling proteins. MCH weakens the amplitude of glutamate-induced excitatory currents, and suppresses currents by means of potential-dependent calcium channels, in addition, 85% of MCH-ergic cells of the hypothalamus are also GABA-ergic [51].

Along with noradrenaline, the activity of MCH neurons is reduced by serotonin, dopamine, and acetylcholine. MCH suppresses the neurons of the seam nuclei, and promotes falling asleep and the development of REM sleep due to a decrease in aminoergic tone. Figure 2 shows the mechanisms of REM sleep [51].

It should be noted that modern approaches to the therapy of insomnia should be based on the use of both pharmacological and non-pharmacological methods of treatment. Non-pharmacological treatments include stimulation therapy, sleep restriction, relaxation, sleep hygiene, and cognitive therapy. Pharmacological treatment, in turn, should be a supplement to non-drug therapy, with an emphasis on cognitive-behavioural, anti-stress and anti-depressive aspects [53].

For the treatment of insomnia, various pharmacological groups drugs, which exhibit both the main or additional hypnotic effect, are used, [5, 11, 28, 29, 43, 46, 49, 53]. Among the drugs that contribute to the improvement of sleep, it is necessary to distinguish:

- Z-drugs are non-benzodiazepine agonists of benzodiazepine receptors and GABA receptors. They have a short half-life (1 to 5 hours), and help to quickly fall asleep and maintain the physiological duration of sleep. In addition, they have a relatively acceptable safety profile [26];
- benzodiazepine drugs affect all types of subunits of the GABA-receptor complex, providing hypnotic, anti-anxiety, anticonvulsant, sedative and muscle-relaxing effects. Their use (first of all, drugs of the first generations with a long half-life) correlates with high risks of side effects, which limits their use as hypnotics;
- melatonin drugs bind to specific MT_1 and MT_2 receptors, the maximum density of which is observed in the suprachiasmatic nuclei of the hypothalamus, providing a positive effect on the act of falling asleep, the duration and quality of sleep, but in general they have a rather weak hypnotic effect, providing, for the most part, central adaptogenic, but not actually hypnotic effect [24];
- antidepressants improve parameters of awaking, with the exception of a noticeable increase in daytime sleepiness by 82%, which is a limiting factor in their use, and disrupt the physiological structure of sleep as well [45];
- histamine receptor blockers (H1-blockers) block H1-histamine receptors in the central nervous system (CNS), reducing the activity of one of the main activating systems - histaminergic.

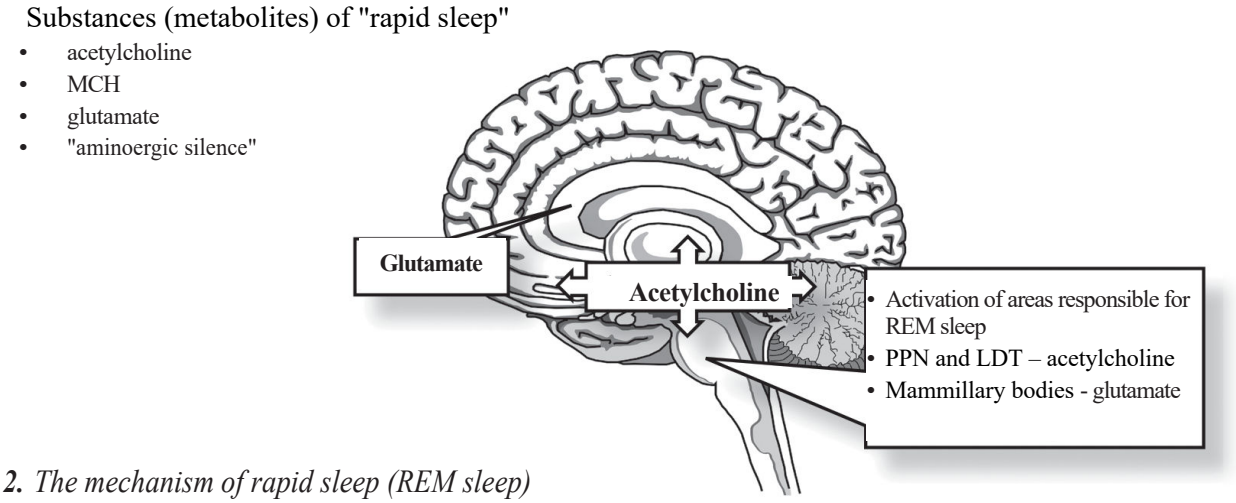

Fig. 2. *The mechanism of rapid sleep (REM sleep)*

The second most pronounced effect is cholinolytic. Due to this fact the possibilities of their prescription are limited if glaucoma and prostate adenoma are suspected. The positive effect on sleep is manifested in the maintenance of sleep without affecting onset sleep [48]. They have a pronounced post-somnic effect, which significantly reduces their value as sleep aids.

Phytotherapy. Currently, phytotherapy is successfully used for sleep disorders, increased anxiety and irritability, it is well tolerated and has a high level of adherence among patients. According to the World Health Organization (WHO), about 40% of the population prefers medicinal products containing natural (plant) components [2].

According to evidence-based medicine, the medicinal plants taken their place in the prevention and treatment of insomnia include:

- Humulus lupulus L. is a popular component of medicinal preparations used as a sedative hypnotic. Mechanisms of influence on sleep have not been fully studied. It contains volatile oils, valerian acid, estrogen-like compounds, tannins and flavonoids. Taking preparations based on Humulus lupulus L. is associated with risks of depression, sedation during the day (you should avoid driving vehicles and working with potentially dangerous mechanisms), increased risk of breast cancer, and hematological abnormalities [1, 37].
- Valeriana officinalis is widely used as a sleeping and daytime sedative. Valeriana contains valepotriates, valeric acid, essential oils (borneol acetate, sesquiterpenes) and various water-soluble components that have a sedative effect. Valeriana has hypnotic, sedative, anxiolytic effects due to the effect on GABA receptors in the central nervous system, as a result, it is contraindicated for people with depression and other disorders accompanied by depression of the nervous system, those who drive vehicles and work with potentially dangerous mechanisms . The therapeutic dose of valerian extract should be 400 mg to 1 g per 1 dose. The doses below 400 mg have a placebo effect. Long-term use of valerian preparations is associated with risks of cardiovascular complications, liver damage, confusion and delirium [1, 37].
- Passiflora contains alkaloids, maltol, ethylmaltol and flavonoids. It is used as a sedative in patients with neurasthenic and depressive states, stress, anxiety, nervousness, sleep disorders, climacteric and pre-climacteric period. The evidence base of Passiflora, from the point of view of its clinical use, is contradictory, and reliable data on the effect on sleep are not fully substantiated [1, 37].

The worldwide experience of using drugs for the treatment of insomnia has made it possible to formulate requirements for "perfect" sleep aids, which should not only regulate the speed of falling asleep, the depth and duration of sleep, reduce the number of night awakenings, but also eliminate disorders related to insomnia, such as stress, depression and cognitive dysfunction [53].

Among the phytopreparations that have become widespread in world clinical practice and have polymodal pharmacodynamic and provide an effect not only on sleep and its quality, but also on accompanying deviations in the form of stress-mediated diseases, the following should be highlighted: *Withania somnifera, Bacopa monnieri, Centella asiatica, Convolvulus pluricaulis, Nardostachys jatamansi, Rubia cardifolia, Celastrus paniculatus, Acorus calamus.*

The study by Kumar A. (2008) has established that Withania somnifera has soporific, anti-stress (central adaptogenic), antioxidant and neuromodulating effects. From the point of view of somnology, Withania somnifera has a modulating effect on GABA and GABA-ergic neuromediation. Activation of GABA-ergic processes is necessary to ensure the falling asleep, normalization of the physiological structure of sleep without accompanying complications inherent to benzodiazepines (headache, dizziness, cognitive impairment, development of addiction) and Z-drugs (postsomnia syndrome).

As part of the treatment of stress-dependent insomnia, a beneficial effect of Withania somnifera on various sleep parameters, such as acceleration of falling asleep, increase in the total duration of sleep and the stage of deep sleep, has been established [22].

Withania somnifera, in contrast to known sleeping aids, has a positive effect on the cognitive sphere - memory, concentration of attention and mental performance, due to the stimulating effect on cholinergic processes in the cortex and hippocampus, the reduction of free radical oxidation processes, which is observed in conditions of chronic stress (antioxidant action) [21].

Table 1. *The pharmacodynamic properties of Withania somnifera, Bacopa monnieri, Centella asiatica, Convolvulus pluricaulis, Nardostachys jatamansi, Rubia cardifolia, Celastrus paniculatus, Ácorus calamus*

Plants	Falling asleep	NREM sleep	REM sleep	Reducing the number of awakenings	Anti-stress effect	Antidepressive effect	Anxiolytic effect	Improving the cognitive sphere
Withania somnifera [6,8,21,22]	+	+	+	+	+	+	+	+
Bacopa monnieri [17,23,25,32,34,38,44]	+	+	+	+	+	+	+	+
Centella asiatica [15,39]	+	–	–	+	+	+	–	+
Convolvulus pluricaulis [9,10,13]	+	+	+	–	+	+	+	–
Nardostachys jatamansi [33,36]	+	+	-	–	+	–	+	+
Rubia cardifolia [12,18,30]	+	+	+	–	+	–	–	+
Celastrus paniculatus [7,16]	+	–	–	–	+	–	+	+
Ácorus calamus [31,35]	–	–	+	–	–	–	+	+

In addition, Withania somnifera activates the processes of neuroplasticity by increasing the number of interneuron connections – the morphological basis of cognitive processes [22]. Also, it should be noted that Withania somnifera has an independent anxiolytic effect, which allows to eliminate concomitant anxiety manifestations [6, 8].

In clinical practice, Bacopa monnieri has proven to be an effective hypnotic agent that increases the duration of sleep, normalizes sleep structure, and reduces the number of night awakenings [17, 23].

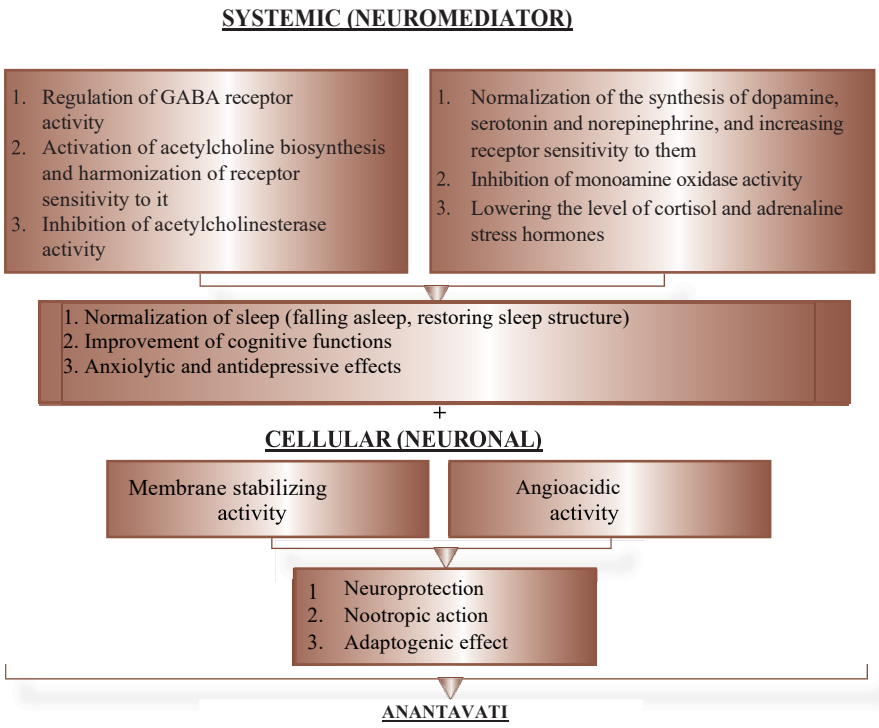

Fig. 3. *Mechanism of action of Anantavati*

Any sleep disorders lead to changes in the cognitive sphere, that is why the nootropic effect of Bacopa monnieri, which is expressed in the improvement of memory and attention processes, is so important [25, 44]. The multimodal effect of Bacopa monnieri on memory processes is based on the ability of the plant's biologically active substances to optimize the processes of monoamine potentiation (serotonin and dopamine), synthesis and receptor binding of acetylcholine and GABA. This allows to harmonize the processes of short-term and long-term memory,

reaction speed, concentration of attention, cognitive interest, cause and effect relationships, ability to learn, memorization, concentration, and the speed of switching attention [19, 25, 32, 38, 42].

In addition, Bacopa monnieri exhibits a clinically pronounced antidepressive effect associated with the "classical" mechanism of action of antidepressants – inhibition of reuptake of serotonin and noradrenaline, which is not characteristic of other herbal preparations [32], and activation of catecholamine biosynthesis as well [34].

There has been established that Centella asiatica exhibits nootropic and neuroprotective effects due to the reduction of free radical oxidation and glutamate-dependent reactions (excitotoxicity) [15, 39], and a pronounced adaptogenic effect due to the normalization of the natural protective potential of the brain under the conditions of the development of stress dependent reactions.

The combination of nootropic, anxiolytic, antidepressive, hypnotic, and adaptogenic effects should be noted among the clinical and pharmacological effects of Convolvulus pluricaulis [3, 9, 10, 13, 40]. **Normalization of the structure of sleep under the influence of Convolvulus pluricaulis is realized due to the active effect of its components on the GABA receptors, with a pronounced weakening of the manifestations of anxiety, restlessness, and tension [10].**

Rubia cardifolia combines nootropic and anti-stress effects. The mechanism of implementation of the pharmacological effect occurs due to the activation of GABA biosynthesis by increasing the concentration of this neurotransmitter in the central nervous system and is associated with a decrease in the development of stress-dependent reactions, including insomnia [18, 30]. The GABA-ergic mechanism also determines the nootropic effect of Rubia cardifolia [12].

Celastrus paniculatus. The biologically active compounds of Celastrus paniculatus mediate antioxidant and antiglutamatergic effects, expressed in a nootropic effect that actives the process of memorization and improvement of short-term memory, which is primarily impaired by stress and aging, and an antiserotonin effect, which allows to reduce the manifestations of anxiety and the progression of insomnia [7, 16].

Nardostachys jatamansi has complex nootropic, anxiolytic, and hypnotic effects due to its antioxidant properties and effect on GABA receptors [33, 36].

Acorus calamus has a complex effect on the realization of nootropic and anxiolytic effects by inhibiting acetylcholinesterase (ACE), adreno- and serotonergic processes in the central nervous system [31, 35].

Summarizing the positive clinical experience of the use of Withania somnifera, Bacopa monnieri, Centella asiatica, Convolvulus pluricaulis, Nardostachys jatamansi, Rubia cardifolia, Celastrus paniculatus and Acorus calamus, it should be noted that their combination allows to significantly normalize the central mechanisms of cardiovascular regulation and the psycho-emotional sphere, and to optimize the treatment schemes of patients with sleep disorders, including those with accompanying stress-related diseases, due to synergism and the presence of anti-stress, antidepressive, anxiolytic effects, and positive effect on the cognitive sphere (Table 1). Anantavati is one of such remedies on the pharmaceutical market of Ukraine. Anantavati is a unique combination containing all the above-mentioned plants.

To date, Anantavati has a positive clinical experience for anxiety-depressive disorders in combatants in the anti-terrorist operation zone, during the recovery period, with the following dosage regimen: 1 tablet once a day for 1 month after meals.

The study by S.M. Moroz (Regional Clinical Hospital named after I. I. Mechnikov, Dnipro) has demonstrated [52]:

- a decrease in the level of irritability when taking Anantavati, which was associated with the effect of withanone contained in Withania somnifera. It balanced the processes of inhibition and excitation in the central nervous system due to a decrease in the level of stress hormones (cortisol, adrenaline) and an increase in anti-stress hormones (dehydroepiandrosterone sulfate) [6, 52]. An anti-stress effect was also exerted by Rubia cardifolia, Nardostachys jatamansi, Acorus calamus and Celastrus paniculatus [12, 52].
- the elimination of insomnia is due to the presence of such plants as Convolvulus pluricaulis, Bacopa monnieri and Withania somnifera, which mildly inhibit monoamine oxidase, contribute to slowing down the breakdown of monoamines (serotonin, norepinephrine, dopamine) and normalize sleep stages [6; 9, 44, 52].
- antidepressive effect of medicinal plants contained in the phytocomplex: Centella asiatica

has an anxiolytic effect due to inhibition of phospholipase A2 activity by asiaticosides [15, 52]. Withania somnifera exhibits an anxiolytic effect, similar to lorazepam, due to a decrease in the level of the endogenous inhibitor of monoamine oxidase in the brain – tribulin, which is a clinical marker of anxiety [8,52]

All components of Anantavati have complementary effects on the psycho-emotional and cognitive spheres. Their influence on the mechanisms of the development of insomnia is so multifaceted that it allows to ensure the correction not only of sleep disorders, but also of the entire complex of maladaptive processes underlying the pathological effects of chronic stress, in contrast to "classical" sleep aids – benzodiazepines, doxylamine, Z-drugs (Figure 3).

The action of Anantavati is characterized by much more favourable safety characteristics – the absence of daytime sleepiness, changes in psychomotor reactions, habituation and addiction, withdrawal syndrome, potentiation of the alcohol effects. Due to these facts Anantavati can be used without disrupting the usual rhythm of social activity and the risk of side effects. You should take 1 tablet in the evening (after dinner). If it is necessary to correct accompanying psycho-emotional disorders (anxiety, tension, depressed mood, depression), you should take 1 more tablet in the morning or in the middle of the day after meals for a course of 45-60 days.

With the appearance of Anantavati in domestic medical practice, new opportunities arise for multimodal correction of stress-dependent disorders of the central nervous system, including sleep disorders.

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