

The drug Dormiplant in the treatment of nervous diseases and pediatrics  
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1. Introduction

Any herbal (galenic) medicinal product (MP), due to its complex chemical composition and production technology, has a wide range of types of pharmacological action directed not only to the target organ, but also to the conjugated systems of the body [1-3, 6]. However, when compiling and approving, in accordance with the procedure established in the Russian Federation, "Instructions for the medical use of the drug" (hereinafter - "Instructions") for herbal preparations, these features of phytopharmaceutical drugs (and clinical phytotherapy in general) are practically not taken into account. As a rule, the range of types of pharmacological (therapeutic) action of such drugs, included in the "Instruction", is artificially narrowed in accordance with ICD-10 by analogy with allopathic drugs.

The appointment of such drugs, of course, should be carried out in strict accordance with the approved "Instruction", but, from the point of view of traditional medicine, it is highly advisable to reliably inform doctors and pharmaceutical workers about the herbal ingredients included in the drug and the specificity of the action of the phytopreparation in the treatment of various nosological forms of the disease ...

If a practitioner is not familiar with the peculiarities of the phytotherapy method [6], the basics of phytochemistry and the technology for the production of herbal medicines, unfortunately, he cannot always correctly assess the types of action of a particular drug observed in the clinic, which can be explained by the presence of a wide spectrum of biologically active substances (BAS). Pharmaceutical workers dispensing OTC drugs from pharmacies, on the contrary, have a fairly high qualification in the field of pharmacognosy, phytochemistry and phytotechnology, but they cannot always offer the pharmacy visitor scientifically based information about the results and features of the use of a galenic drug in clinical practice.

Problem. Common treatment regimens for insomnia include benzodiazepines or benzodiazepine receptor agonists (zopiclone, zolpidem). The most serious side effects from their use include the development of drug dependence and tolerance to drugs, inhibition of the respiratory center, changes in the structure of sleep, the formation of parasomnia, the development of daytime sleepiness and a decrease in the ability to concentrate with prolonged use of drugs, etc. [10, 12, 13, 16, 23, 28].

Given the widespread prevalence of sleep disorders in the human population (about a third of the adult population suffers from various kinds of sleep disorders), the urgent task is to find effective and safe analogues (including of plant origin) for the treatment of insomnia.

The purpose of this work was information and analytical research results of domestic and foreign clinical trials of the drug Dormiplant (manufacturer: "Dr. Wilmar Schwabe", Germany) in the treatment of nervous diseases and sleep disorders, as well as substantiation of the possibilities of its use both in adult and pediatric practice for various nosological forms of diseases.

The objects of the study were the results published in the open press clinical studies of the drug Dormiplant, carried out in accordance with the requirements

GCP in various countries of the world, including the territory of the Russian Federation. Of particular interest were publications containing the results of comparative studies of Dormiplant with synthetic drugs used in neurology and psychiatry, subject to prescription.

Dormiplant (abroad the drug is registered under the name Euvegal® forte) is a herbal medicine that, in accordance with the "Instruction" approved in the Russian Federation, has a sedative effect. Composition of the preparation: dry extract of valerian roots (160 mg) and dry extract of lemon balm leaves (80 mg). Indications for use (in accordance with the "Instructions"): increased nervous irritability, difficulty falling asleep. The drug is approved for use in the Russian Federation in children from 6 years of age.

## 2. Discussion of the results of clinical trials of the drug Dormiplant and its ingredients

Historical reference. Pronounced sedative and hypnotic effect of mint extracts and lemon balm have been known to mankind since ancient times. More than 2,000 years ago, Valerian root extract was used to relieve stress and correct sleep disorders. Since the middle of the 18th century, valerian and lemon balm extracts have been widely used as hypnotics in a number of European countries, and due to the low incidence of side effects, these drugs were dispensed without a doctor's prescription [10]. Subsequently, a number of domestic and foreign scientific studies have confirmed the presence of sedative and hypnotic effects of valerian extract, along with a weak anticonvulsant and antispasmodic effect. At the same time, none of the studies conducted revealed statistically significant side effects, even with a 20-fold excess of the recommended therapeutic dosage [15, 17, 33, 35].

Valerian extract. The mechanism of action of valerian drugs on the central nervous system is still unclear. Some authors note changes in the activity of GABA neurons [29], others do not exclude the possibility of influencing the secretion of melatonin [27]. Interesting results have been obtained when comparing the effects of valerian with those of synthetic tranquilizers and hypnotics such as benzodiazepines. These works are especially relevant in the context of the constantly expanding spectrum of side effects from the intake of synthetic hypnotics [15-17, 20, 22, 23, 28].

A number of foreign studies are devoted to the study of the effect of valerian extract on the structure of sleep [8, 10, 12, 20, 21, 31]. F. Donath et al. (randomized, double-blind, placebo-controlled study; 16 patients with long-term insomnia, mean age 49 years) sleep structure as an objective criterion was assessed using polysomnography, and subjective parameters (sleep quality, duration of falling asleep, morning feeling of alertness, etc.) were studied with using special questionnaires [10]. After a single application of the extract, no changes were noted in either the structure or the quality of sleep. However, after long-term use (14 days), a statistically significant improvement in the studied parameters compared with the placebo group was revealed. In the structure of sleep, after taking valerian extract, the proportion of slow-wave sleep (SWS) decreased, there was an improvement in subjective indicators compared with placebo: the time to fall asleep decreased, the quality of sleep and the patients' morning well-being improved. The extremely low level of side effects was especially noted - 1 migraine attack and 1 exacerbation of gastroenteritis.

Thus, it was found that valerian extract has a positive effect on the structure of sleep in patients with insomnia and does not have the side effects characteristic of benzodiazepine receptor agonists. According to the results of the study, the extract was recommended for the treatment of insomnia. Dormiplant. H. Dressing et al. the results of a double-blind, placebo-controlled study on the effect of the drug on sleep quality in 68 patients with mild insomnia are presented [12]. Patients

received 2 tablets of Dormiplant in the morning and in the evening; other sleeping pills and psychotropic drugs were canceled.

The main parameters were recorded: sleep quality, daily well-being or motivational status, as well as secondary parameters: time to fall asleep, total sleep duration, ability to concentrate, aftereffect and anxiolytic effect of the drug. The main parameters were investigated using scales placed in separate questionnaires, where patients in the morning assessed each parameter on a 10-point system. As a result of the studies, statistically significant improvements in the main indicators were obtained in comparison with the placebo group.

The most pronounced effect was noted in the subjective well-being of patients. In group 2 (with good drug tolerance and no side effects), the average time required to fall asleep was statistically significantly reduced from 53.4 minutes. up to 36.9 minutes (in the placebo group - 52.7 and 41.7 minutes, respectively). An increase in the total duration of sleep, the disappearance of nightmares was noted. All effects persisted for 1 week of follow-up. It has been shown that Dormiplant is a therapeutic alternative to the treatment of insomnia with synthetic drugs or can be used as an adjunct to the general treatment regimen.

Very interesting is another study by Dressing H. et al., In which for the first time the effectiveness of Dormiplant was compared with the effectiveness of a synthetic drug for the treatment of insomnia (0.125 mg Triazolam) under the control of a placebo group [13]. Study: duration 9 nights; 20 healthy volunteers aged 30-50 years. Result: in the group of patients receiving Dormiplant, sleep productivity increased significantly, as well as the duration of the deep sleep stage, the time to fall asleep and the total awakening time per night decreased. The effects of Dormiplant were completely comparable to those of Triazolam, but after taking Dormiplant, there was no addiction, daytime sleepiness, impaired concentration, etc. Subjectively, all patients noted an improvement in their well-being the next day after taking Dormiplant. Thus, the comparability of the therapeutic effects of Dormiplant and Triazolam was statistically significant with the complete absence of side effects inherent in benzodiazepines in Dormiplant, i.e. Dormiplant is an effective and safe alternative to synthetic drugs (benzodiazepines, etc.) in the treatment of various sleep disorders.

In a multicenter study, Schmidt U. et al. studied the effectiveness of Dormiplant in the treatment of psychosomatic disorders. The psychosomatic symptom complex includes sleep disorders, gastrointestinal syndrome, neurocirculatory disorders [30]. Most often, according to the authors of the study, tranquilizers (preferably benzodiazepines) are used in the treatment of psychosomatic disorders, which are addictive, significantly inhibit cognitive functions (especially in children and the elderly) and reduce interest in life, but herbal preparations with well tolerated and not having the listed side effects. The study included patients with complaints of increased emotionality (91.0%), sleep disorders (82.2%), fatigue (75.3%) and anxiety (53.1%). Dormiplant was used as a herbal preparation, 1-2 tablets twice a day for 4 weeks. As a result of Dormiplant therapy, a statistically significant improvement in the patients' condition was obtained (table).

table

The results of Dormiplant therapy (according to Schmidt U. et al. [30])

Нарушения	Количество пациентов		
	до лечения, чел.	после лечения, чел.	с положительными результатами лечения, %
Повышенная эмоциональность	1270	514	59,5
Нарушения сна	1146	441	61,5
Утомляемость	1050	295	71,9
Тревожность	741	245	66,9

In addition, as a result of the use of Dormiplant, the incidence of psychovegetative disorders such as headaches and heart pains of various origins, lumbar pains, gastrointestinal disorders, hot flashes and sweating has significantly decreased.

Thus, it was shown that the drug Dormiplant is effective in the treatment of psychosomatic disorders and, along with sedative, has anxiolytic and mild antispasmodic effect, that is, it is a real alternative to synthetic tranquilizers.

In a randomized, double-blind, placebo-controlled study by Albrecht M. et al. no effect of Dormiplant in recommended dosages on the ability to drive a car, as well as on psychomotor functions and mental abilities when drinking alcohol was found (that is, unlike tranquilizers, the drug does not potentiate the effect of alcohol) [7].

### 3. Discussion of the results of clinical trials of the drug Dormiplant and its ingredients in children's practice

The question of finding a safe analogue to synthetic tranquilizers is especially acute in pediatrics, since the side effects of psychomimetics (depression of cognitive functions, decreased ability to concentrate, etc.) are considered unacceptable in the clinic of childhood diseases.

A fairly common problem in childhood is neurosis, neurosis-like disorders, as well as sleep disorders, which are most often associated with increased stress and lack of physical activity. These disorders are of a functional nature and do not require rigid medical correction. Given the widespread prevalence of sleep disorders in children and the presence of side effects from the use of synthetic hypnotics (the expediency of taking which in this case is highly questionable), the search for herbal sedatives is urgent.

According to the majority of clinicians, most often children have problems with falling asleep [9,24–26], and the maximum frequency of such problems occurs at an early age and gradually decreases with increasing age of the child.

Valerian extract. WorkAJP Francis et al. is devoted to sleep disorders in children with an intellectual disability [14], since it is they who have the greatest difficulties in the selection of sedative therapy [14, 34].

Studies have shown that, in general, sleep disturbances in these children are of the same nature as in normally developing children. The study involved 5 children aged 7-14 years with IQ <70, suffering from sleep disorders. Children received tablets containing 500 mg of dried and crushed valerian root at a dose of 20 mg / kg body weight, 1 hour before bedtime. For the reliability of the results obtained, each child alternately received the active drug or placebo for 8 weeks.

The estimated parameters were the time required to fall asleep, the total waking time per night, and the quality of sleep. The parents of the children were instructed how to maintain special scales in which the indicated parameters were noted. As a result of this study, statistically significant therapeutic effects of valerian root were found.

Compared with placebo, total sleep time per night was reduced, total sleep duration increased, and parental ratings of sleep quality improved. The results of a number of studies on the effectiveness of the use of valerian root extract and preparations based on it for sleep disorders in children [9, 10, 11, 18, 19, 32, 34] suggest that they are effective, well tolerated and safe for use in children. practice. Extraction preparations based on valerian root have not only a sedative, weak anticonvulsant, but also a mild anxiolytic effect, which is especially important in the treatment of childhood fears. In addition, studies have shown the ability of such drugs to positively influence the structure of sleep in children.

Dormiplant. In addition to these problems, in modern neurology, unsolved the problem of tics relief in children remains, which, according to most authors, are the most common form of childhood hyperkinesis.

Most often, psychotropic and neuroleptic drugs are used in the treatment of tics, causing hypersomnia and a number of endocrine and extrapyramidal complications. Given the severity of complications and the ambiguity of the results of prolonged conventional therapy for tics, the search for natural and safe analogues of drugs for the treatment of childhood hyperkinesis remains relevant today.

In the study of M.A. Lobov. et al., carried out on the basis of MONIKI them. Vladimirsky, evaluated the effectiveness of Dormiplant in 20 children (5 to 12 years old) with acute (6 children) and persistent (14 children) tics [5]. All children received Dormiplant 1 tablet 2-3 times a day in combination with Glycine for 2 months. During the study, no side effects of the drug were identified. After the treatment, it was possible to achieve cessation of tic hyperkinesis in 5 children with acute tics; stable remission was achieved in 3 children with persistent tics. In 6 children, the incidence of tics significantly decreased. The greatest efficacy of the drug was revealed in relation to mild tics - single at rest and during exercise.

Another common disorder in childhood neurology is minimal cerebral dysfunction (MMD), which is considered a special form of functional immaturity of the brain [4]. One of the most common manifestations of MMD is attention deficit hyperactivity disorder (ADHD), which leads to impaired social adaptation of the child and a decrease in school performance. Traditional drug treatment regimens for MMD and ADHD include antidepressants, CNS stimulants, antipsychotics, and nootropics.

At the moment, the question of the possibility of correcting this kind of neurological disorders in children with the help of herbal medicines remains important. On the basis of MONIKI, a study was conducted to assess the effectiveness of the drug Dormiplant in the correction of ADHD [4]. The study included 20 children aged 7-9 years with ADHD and concomitant neuropsychological disorders (asthenoneurotic disorders, tension headaches, tics, and sleep disturbances). Almost all children experienced difficulties in school.

All children received Dormiplant 1 tablet 2-3 times a day for 2 months in combination with Glycine. In this case, no side effects were found from

use of the drug. 15 out of 20 children showed improvement in behavior characteristics, regression of hyperactivity and impulsivity, improvement in memory and attention indicators. In the course of the study, the Bourdon test was used to objectively assess the scope of attention. Initially, the accuracy index was  $14.7 \pm 2.4$ , at the time of completion of the study, this indicator was  $21.3 \pm 3.1$  and indicated a statistically significant improvement in attention indicators. 10 children improved their school performance.

It should be especially noted that neuropsychological disorders disappeared in all children who took Dormiplant according to the indicated scheme.

EEG data indicated a tendency for the indicators to return to the age norm, as well as to the restoration of the zonal distribution of rhythm in most children. So, before taking Dormiplant, EEG indices corresponded to the age norm only in 4 children, after the end of the course of drug use, normal EEG parameters were recorded in 8 children.

Thus, the following were revealed: 1) distinct sedative and moderate relaxing effects of the drug Dormiplant in the complete absence of any side reactions; 2) the positive effect of the drug on cognitive functions (memory, attention, intelligence) in children, which makes it practically irreplaceable in children with poor school performance.

Based on the results of the study, Dormiplant can be considered as an effective and safe drug for the treatment of astheno-neurotic disorders in children, as well as for the correction of behavioral disorders in ADHD. The authors of the publication consider it possible to use the drug both as monotherapy and in combination with other psychotropic and neurometabolic agents.

#### 4. Conclusions

1. Dormiplant is a herbal preparation based on extracts of valerian and lemon balm, possessing, according to clinical studies, a pronounced sedative, hypnotic and mild anxiolytic effect; can serve as a real alternative to synthetic tranquilizers in the treatment of various kinds of sleep disorders and psychosomatic disorders in adults.

2. The ability of the drug has been proven to positively influence the structure of sleep, improving the morning well-being of patients. None of the studies revealed statistically significant side effects from taking the drug, even with a 20-fold excess of the recommended therapeutic dosage.

3. The comparability of therapeutic effects is statistically significant. Dormiplant and benzodiazepines in the absence of the side effects characteristic of benzodiazepines. The effect of Dormiplant in recommended dosages on the ability to drive a car, as well as on psychomotor functions and mental abilities when drinking alcohol, was not found.

4. The drug has real prospects for use in pediatrics:

- has a sedative, anxiolytic, relaxing, anticonvulsant and mild antispasmodic effects; has a positive effect on the structure of sleep and cognitive functions (memory, attention, intelligence) in children;
- can be indicated as monotherapy for mild tic hyperkinesis degree, and also as an adjunct to other psychotropic drugs in the treatment of severe tic disorders;
- is an effective and safe drug for the treatment of astheno-neurotic disorders in children, as well as correction of behavioral disorders in ADHD;
- scientifically substantiated is its use as monotherapy for the listed disorders, as well as in combination with other psychotropic and neurometabolic drugs.

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