

Efficacy of etifoxine versus phenazepam in the treatment of patients with adjustment disorders (open randomized controlled trial)

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In the article, based on the study of 90 patients with symptoms of adjustment disorders, the results indicate a pronounced anxiolytic effect of etifoxine in the absence of a benzodiazepine-type muscle relaxant and inhibitory effect characteristic of phenazepam and other tranquilizers of the benzodiazepine group. This allows attributing etifoxine to the number of daytime tranquilizers.

Key words: etifoxine, phenazepam, adaptation disorders

Efficacy of etifoxine versus phenazepam in the treatment of patients with adjustment disorders (open-label randomized controlled trial)

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The adjustment disorder (AD) is defined as "the state of subjective distress and emotional anxiety, usually affecting the performance of social functions and performance, during the period of adaptation to a major change in life or a stressful event in the life of the patient" (ICD-10 code F43.2). AD is a frequent cause of primary treatment of patients for help to doctors of different specialties [2, 14]. According to a number of researchers, in general medical practice, 10% of patients show AD, usually evaluated in the group of patients with anxiety disorders. In the treatment of AD, in addition to psychotherapy, anxiolytics are widely used, among which benzodiazepines are used most often [11]. The original domestic anxiolytic phenazepam, a benzodiazepine derivative, is most often prescribed in Russia for the treatment of patients with AD and anxiety disorders. At the same time, as in the treatment with other benzodiazepine anxiolytics, many patients experience cognitive impairment, and in a number of cases, withdrawal and addiction syndrome [3, 13], which adversely affect the quality of life of patients. The high demand for tranquilizers in the treatment of mental disorders and the likelihood of the formation of adverse events in the long-term administration of benzodiazepine tranquilizers served as a basis for the search for tranquilizers that did not have these drawbacks. These drugs include the anxiolytic non-benzodiazepine structure of etifoxine, produced by Biocodex (France) under the trade name Stresam. Between 1995 and 2007, etifoxine was used in 40 countries to treat more than 11.3

million patients. In Russia, the drug was registered in 2008. An analysis of the results of special studies of the drug Stresam conducted in various clinics in France (in psychiatric institutions, as well as in the psychoneurological and cardiological departments of multi-profile hospitals) attests to its proven high anxiolytic effectiveness and safety [8, 9, 15]. The investigators associate the high efficacy and safety of Stresam with its specific dual mechanism of action directed toward GABA receptors and stimulation of neurosteroids [7, 12].

The aim of the study was to compare the effectiveness and safety of the use of etifoxine and phenazepam in patients with an adaptation disorder.

Material and methods

To conduct an open, randomized controlled trial, 90 patients were selected in 3 psychiatric centers in Moscow and St. Petersburg. The study included patients aged 18 to 65 years male and female with symptoms of adaptation disorder, as defined by ICD-10 (code F43.2), lasting at least 4 weeks. The level of anxiety on the Hamilton scale was to exceed 20 points, and on the scale MADRS - be no more than 20 points. The criteria for excluding patients from the study were: concomitant psychiatric illness, chronic disease or a threat to life, alcohol abuse, drug addiction or the period of stopping the use of drugs, as well as pregnancy.

The study did not include patients treated with benzodiazepines during the previous 4 weeks, who took medications that were able to influence the metabolism of the test compounds (carbamazepine, phenytoin, primidone, rifampicin, griseofulvin, phenobarbital, probenecid) during the last month before or during the study, as well as beta-blockers and other drugs, the effect of which on the central nervous system could affect the results of the study. Patients were randomized into two groups who received oral phenazepam 0.5 mg twice daily (morning and evening) or etifoxine at a dose of 150 mg per day (50 mg in the morning and 100 mg in the evening). The treatment was conducted for 6 weeks. Efficiency and safety were assessed on the 7th and 42nd days of course therapy. The withdrawal syndrome was assessed 1 week after the end of the study (day 49).

The level of anxiety was recorded in accordance with the Hamilton anxiety scale (HAM-A) at baseline, on the 7th and 42nd days. The overall development of the disease was assessed using the CGI (Global Clinical Improvement Scale) scale: global clinical improvement on days 7 and 42, disease severity at baseline, on days 7 and 42, and therapeutic index for The 7th and 42nd days.

Side effects diagnosed independently or during observation were recorded throughout the study. The withdrawal syndrome after the end of therapy was assessed on the 49th day on the HAM-A and CGI scales and was defined as the difference between the results of the indicators of the 49th and 42nd day.

The Hamilton anxiety scale (HAM-A) [6] was used in clinical trials of medications, it assessed both psychiatric and somatic manifestations of anxiety. The Global Clinical Improvement Scale (CGI) was used to conduct a reliable overall assessment of the patient's condition at each examination (scores on "severity of the disease" and "global clinical improvement"), and to assess the risk-benefit ratio of therapy [10].

The randomization list for each center was created before the study began to determine its design. Each center assigned patients numbers sequentially, in accordance with the chronological order of inclusion in the study.

Statistical methods

For the analysis, the following patient populations were considered: a safety list including all patients randomized in the study and authentically receiving at least one dose of the study drug; a complete analysis list (SPA), including all patients randomized in the study, provided that any information is known of the outcome of follow-up; the protocol list (NGN), which includes all patients from the SPA group, for which no serious violation of the protocol was registered.

The statistical analysis was carried out using SAS software version 9.2 for Windows OS and consisted of descriptive statistics and hypothesis testing.

The lack of superiority of phenazepam compared with etifoxine was assessed by calculating 95% CI (confidence interval) on the average difference in anxiety level detected by the Hamilton scale between the two treatments. The 95% confidence interval was based on the ANOVA model. It was found that etifoxine is no less effective than phenazepam if the upper limit of 95% did not exceed 2.5 points. The ANOVA model was also used to compare the efficacy index in two therapeutic groups for each time point studied. Comparison of the results on the CGI scale was carried out using Cochran-Mantel-Haenszel tests. For comparison, we used the Fisher test for binary variables and the Cochran-Mantel-Haenszel test for ordinal variables. These tests were carried out with a bilateral restriction with a significance level of 5%.

The effectiveness analysis took into account the incidence of side effects and withdrawal syndrome. For this purpose, individual data on side effects were analyzed. A comparison of the two therapeutic groups was performed using the Cochran-Mantel-Haenszel test. The analysis of the withdrawal syndrome consisted of descriptive statistics of changes in anxiety according to the Hamilton scale and CGI scores from the 42nd to the 49th day, as well as in the distribution of the incidence of withdrawal syndrome. A comparison of the two therapeutic groups was carried out using the exact Fisher test.

Results

The study included 90 patients, selected and randomized to receive treatment with etifoxine (44 patients) and phenazepam (46 patients). 8 patients from the phenazepam group withdrew from the study due to the development of side effects. In both groups, there was a high compliance rate with an average of 99.0% (SD = 3.2%) in the etifoxine group and 99.8% (SD = 3.0%) in the phenazepam group.

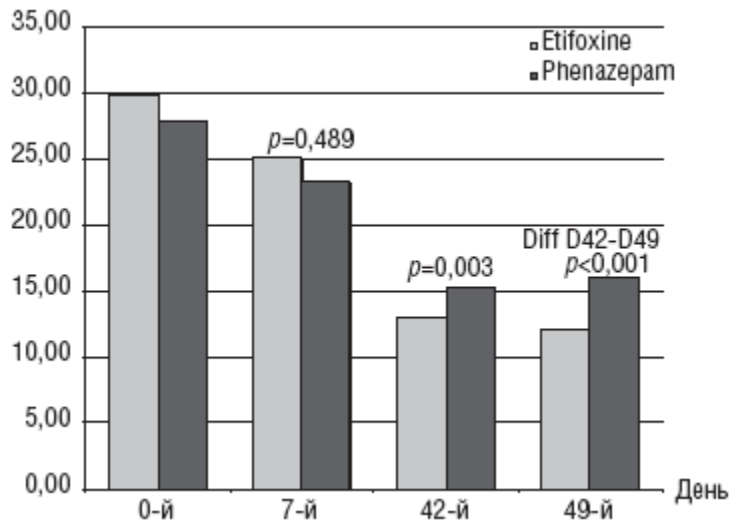
Patients at baseline are presented in the table. The average age of the patients was 45 years (from 21 to 64 years). Most of them led an active lifestyle (78%). The baseline on the HAM-A scale was 29.73 ± 7.62 points in the etifoxine group and 27.83 ± 5.95 points in the phenazepam group. The severity of the disease on the CGI scale was 4.32 ± 0.74 points in the etifoxine group and 4.28 ± 0.69 points in the phenazepam group.

Initial patient data

Initial data	Etifoxine	Phenazepam	Total
Number of patients, people	44	46	90
Including men,	27.27	32.61	30.00
Average age (SD)	44.17 ± 11.59	46.35 ± 11.65	45.28 ± 11.61
HAM-A (SD)	29.73 ± 7.62	27.83 ± 5.95	
The severity of the CGI (SD)	4.32 ± 0.74	4.28 ± 0.69	
Activity (% of employees)	77.27	78.26	77.78

The indicators of anxiety level on the HAM-A scale decreased in both groups (Fig. 1). The average anxiety index on the 42nd day was 12.98 ± 4.16 in the etifoxine group and 15.21 ± 6.02 in the phenazepam group, which corresponds to a 56.44% decrease in the HAM-A score in the etifoxine group and 45.35% in the group of phenazepam. The mean difference (etifoxine-phenazepam) was -3.17 (CI 95% $[-5.25, -1.09]$). Based on the results of the HAM-A scale, it was concluded that there was no superiority in the therapeutic effect of phenazepam compared with etifoxine. Attention was drawn to the greater efficacy of etifoxine compared to phenazepam ($p = 0.003$). On the 7th day, the average anxiety index was 25.09 ± 5.77 in the etifoxine group and 23.24 ± 5.40 in the phenazepam group. The mean difference (etifoxine-phenazepam) was 0.37 (CI 95%: $[-0.70, 1.44]$). On the 7th day, etifoxine was no less effective than phenazepam. Therefore, in the three studied periods of the therapeutic course, the upper limit of 95% CI (confidence interval) of the smallest square of the mean discrepancy between etifoxine and phenazepam was less than 2.5, which suggests that there is no superiority in the effectiveness of any drug compared to each other. The ANOVA model did not demonstrate a significant result of treatment on day 7 (0.489), while on day 42 the result of treatment was highly significant ($p = 0.003$).

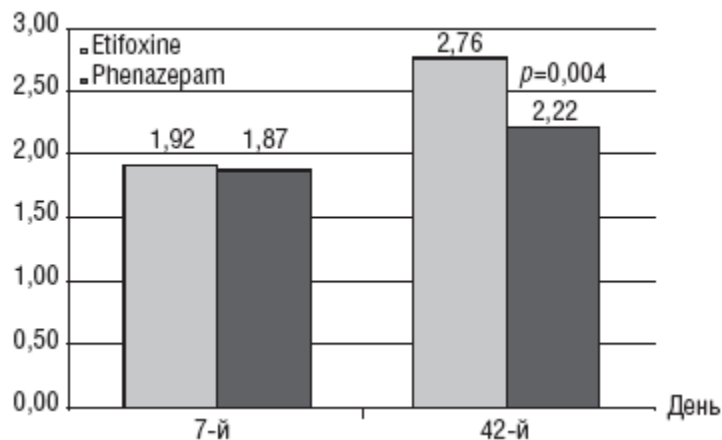
Fig. 1. Indicators on the Hamilton scale (patients included in the study)



The severity of the disease decreased in both groups on the 7th day by 0.84 in the etifoxine group compared to 0.52 in the phenazepam group ($p = 0.081$); on the 42nd day - by 2.34 in the etifoxine group and by 1.97 in the phenazepam group ($p = 0.004$). From the point of view of improving the condition on the 7th day of action, etifoxine was comparable to phenazepam (etifoxine: 2.93 ± 0.73 as compared to phenazepam: 3.00 ± 0.63 , $p = 0.205$); but etifoxine showed greater efficacy on the 42nd day (etifoxine: 2.27 ± 1.45 compared with phenazepam: 2.45 ± 0.98 , $p < 0.001$). During this period, 60% of patients in the CGI group of phenazepam had a "very strong improvement" or "a strong improvement", while the rest of the patients noted a "minimal improvement".

In the etifoxine group, more than 75% of patients rated their condition as "very strong improvement" or "strong improvement," 10% as "minimal improvement," and in 10% the result of the evaluation was "deterioration." The difference between the two therapeutic groups was statistically significant on the 42nd day. At the same time, the efficacy index in patients in the etifoxine group on the 42nd day of therapy was higher than in the phenazepam group (2.76 ± 0.87 in the etifoxine group compared to 2.22 ± 0.95 in the phenazepam group; $p = 0.004$) (Figure 2).

Fig. 2. Therapeutic index



During the study, 22 side effects were noted: 1 of them was associated with etifoxine and 21 - phenazepam. In the group of phenazepam, side effect was noted in 15 patients (32.61% of the examined). Effects such as drowsiness, dizziness, somnolence, awakening difficulties (18.18% of patients), muscle weakness, headache, loss of attention, myasthenia gravis and abdominal pain (one patient in the etifoxine group) have been reported. There was a statistically significant difference between the etifoxine and phenazepam groups in the number of side effects that caused the interruption of treatment (8 versus 0; $p = ,002$).

The withdrawal syndrome, defined as an increase in the HAM-A score between the 42nd and 49th days, was more common in the phenazepam group compared with the etifoxine group (26 vs. 3, $p < 0.001$). The mean discrepancy between the results on the HAM-A scale between the 49th and 42nd days was negative in the etifoxine group and positive in the phenazepam group (day 49-day 42: -0.88 ± 2.05 vs. $0,89 \pm 2.25$, $p < 0.001$).

Discussion

The results of the study indicate that etifoxine is effective in the treatment of AD. During the therapy, anxiety scores on the HAM-A scale decreased on the 7th day and subsequently decreased steadily until the 42nd day of treatment. These indicators were compared with the data of anxiolytic action of phenazepam in patients of the comparison group. The presented data can be supplemented with information available in the literature on the results of psychophysiological studies of a single oral etifoxine intake. They noted a slight effect of the drug on the objective and subjective indices of psychomotor reactions and cognitive functions compared with the placebo effect [8].

The high efficacy of etifoxine in AD, which is not inferior (in some cases, superior) to phenazepam, and the practical absence of side effects, suggests that an anxiolytic agent equal in effect to the most potent tranquilizers from the benzodiazepine group appeared in clinical practice. This assumption was confirmed upon acquaintance with the results of a special comparative study of the anti-anxiety effect of etifoxine and lorazepam, which is, as is well known, as well as phenazepam, one of the most effective tranquilizers of the benzodiazepine group [9]. It turned out that the decrease in anxiety scores on the

HAM-A scale when prescribing etifoxine to patients with anxiety disorders was 52.3% and lorazepam 54.6% ($p = 0.0006$).

At the same time, clinical improvement, according to the general clinical impression (CGI) score, the Social Adaptation-Self Assessment Score (SAS-SR) and the Shihan Scale, was observed with both etifoxine and lorazepam. However, a significant improvement ($p = 0.003$) and a significant therapeutic effect without undesirable phenomena were registered in a larger number of patients taking etifoxine ($p = 0.04$). In addition, a smaller number of patients taking etifoxine (1 vs. 8) experienced a relapse of the disorder. According to the present study, etifoxine is better tolerated than phenazepam (1 side effect in the etifoxine group versus 21 in the phenazepam group). Similar results were obtained when etifoxine and lorazepam were compared.

The results of this study confirm the high anxiolytic efficacy of etifoxine and its good tolerability.

These data give grounds to recommend it for wide application in medical practice. Taking into account the revealed features of the clinico-pharmacological effect of etifoxine, it can be attributed to the group of daytime tranquilizers.

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