Efficacy and safety of a daytime anxiolytic containing technologically processed antibodies to the S100 protein. Overview of clinical studies

Perez M.[1], Zavadenko N.N.[2], Skipetrova L.A.[3], Smirnov I.I.[3], Nesterovskiy Yu.E.[2]

[1]Medical Faculty Autonomous University Nuevo Leon, Monterrey, Mexico; [2]Academician L.O. Badalyan Department of Neurology, Neurosurgery and Medical Genetics, Faculty of Pediatrics, Pirogov Russian National Research Medical University, Moscow; [3]Center for Speech Pathology and Neurorehabilitation, Moscow

[1]Av. Francisco I. Madero S/N, Mitras Centro, 64460 Monterrey, N.L., Mexico; [2]1, Ostrovitianova St., Moscow 117997, Russia; [3]20, Nikoloyamskaya St., Build. 1, Moscow 109240, Russia

The review presents the results of clinical studies of the efficacy and safety of Tenoten and Tenoten children's in the treatment of anxiety, neurotic, stress-related and somatoform disorders and adjustment disorders.

Technologically processed antibodies to the S100 protein in Tenoten and Tenoten children's drugs change the conformation of the S100 protein, which is considered as a pathological link in the development of anxiety states, as well as neurodegenerative diseases.

Tenoten is a well-studied daytime anxiolytic that combines a favorable safety profile with high anxiolytic activity. The efficacy of Tenoten in the treatment of anxiety disorders is comparable to that of benzodiazepine drugs. Tenoten has no inhibitory and muscle relaxant effects, does not cause drug tolerance, addiction, "withdrawal" syndrome, as well as drug interactions. Tenoten for children has been shown to be effective in the treatment of anxiety in children, including those with somatic manifestations, attention deficit hyperactivity disorder, and learning disabilities.

Keywords: *Tenoten; Tenoten children's; neurotic and neurosis-like disorders; anxiety disorders; neuroinflammation; daytime anxiolytic.*

Contact: *Nikolay Nikolaevich Zavadenko;* ***zavadenko@mail.ru***

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Anxiety disorders are one of the most common emotional disorders among all age groups [1, 2]. They became even more prevalent lately, as a result of COVID-19 pandemic and subsequent global financial and political upheavals. According to a study conducted by NAFI (multiprofile analytical center), the majority of people in Russia (70%) experience some degree of anxiety, while only 30% of Russians manage to maintain emotional balance and keep their level of anxiety under control in the current social and economic situation [3]. According to Kommersant newspaper, the events of spring 2022 followed by a new wave of sanctions caused a multiple increase in demand for anti-anxiety medicines in Russia. Thus, total sales of anxiolytics in pharmacies exceeded 525 million rubles in the first week of March, which is four times more than a year earlier. The demand for anti-anxiety medicines has grown more than for medicinal products in general [4].

Based on data published in The Lancet, the number of depressions and anxiety disorders increased by 26% worldwide, in the first year of the pandemic [5]. Residents of the countries of Central Asia and South America suffered the most, with a number of depression and anxiety cases increasing by 30 to 35% [5].

Anxiolytics, antidepressants, some antipsychotics as well as non-drug therapies are used to treat anxiety disorders [1, 6–8].

Among the multitude of medicinal products, domestic products based on technologically processed affinity-purified antibodies (TPA AB) to S100 protein (NPF Materia Medica Holding LLC, Russia) stand out: Tenoten for patients over 18 years of age, and Tenoten for children, for pediatric patients over 3 years of age, used in therapeutic practice for more than 15 years.

It should be noted that many years of experience in the use of medicinal products based on TPA AB to S100 has been accumulated in Russia, as well as in the CIS countries, Southeast Asia, and Mexico.

Purpose of this study: review of clinical trials of Tenoten and Tenoten for children used for the treatment of anxiety conditions in adults and in pediatric practice.

Materials and methods

Data search and selection strategy

Information about clinical trials (CT) was searched in open sources (on the Internet, in the medical library) using the keywords Tenoten and Tenoten for children. The information search strategy included accessing official websites, such as domestic and foreign CT registries and databases, electronic libraries, including State Register of Medicines (grls.ru); US National Library of Medicine ClinicalTrials.gov (clintrials.gov); International Clinical Trials Registry Platform (ICTRP), WHO (www.who.int/ictrp/search/en), electronic research library eLIBRARY.RU, PubMed, Cochrane Library, Russian scientific electronic library CyberLeninka (cyberleninka.ru).

To improve the representativeness of data on efficacy and safety (the information was obtained within the scope of pharmacovigilance), reports on the results of clinical trials were requested from the manufacturer.

Criteria for selecting clinical trials to be included in the review:

1) study design: CT with control group, prospective randomized clinical trial (RCT), cohort study.
2) RCT participants: male and female patients aged 18 years and over with a diagnosis of mixed anxiety-depressive disorders, neurotic, stress-related and somatoform disorders for Tenoten, and male and female patients aged 3 years and older with a diagnosis of anxiety disorders (AD), consequences of perinatal CNS damage, learning impairments, attention deficit hyperactivity disorder (ADHD) for Tenoten for children.

RCTs that did not meet the inclusion criteria, duplicate publications of RCT results, and trials with insufficient data for analysis were excluded from the review.

To assess the methodological quality of RCTs, the risk of bias was assessed.

In accordance with the recommendations of the Cochrane Collaboration, the following criteria were considered: randomization method, presence/absence and type of blinding in the trial, compliance of the results with the endpoints/efficacy criteria, and degree of representation of the results, followed by an assessment of the risk of bias in the trial as a whole as low, medium, high, or undefined [9, 10].

The safety of therapy was assessed taking into account the number and nature of adverse events (AEs), their relationship with the product, deviations in laboratory and vital signs while taking the medicinal products. When preparing the review, modified/adapted elements from PRISMA 2020 were used, such as a checklist and a flow diagram for new systematic reviews, including searches in databases, registries and other sources [11].

Statistical methodology

Continuous findings (symptoms duration) in individual trials were compared using Student's t-test. Fisher's exact test was used to evaluate differences in the frequency scores of individual trials.

Results

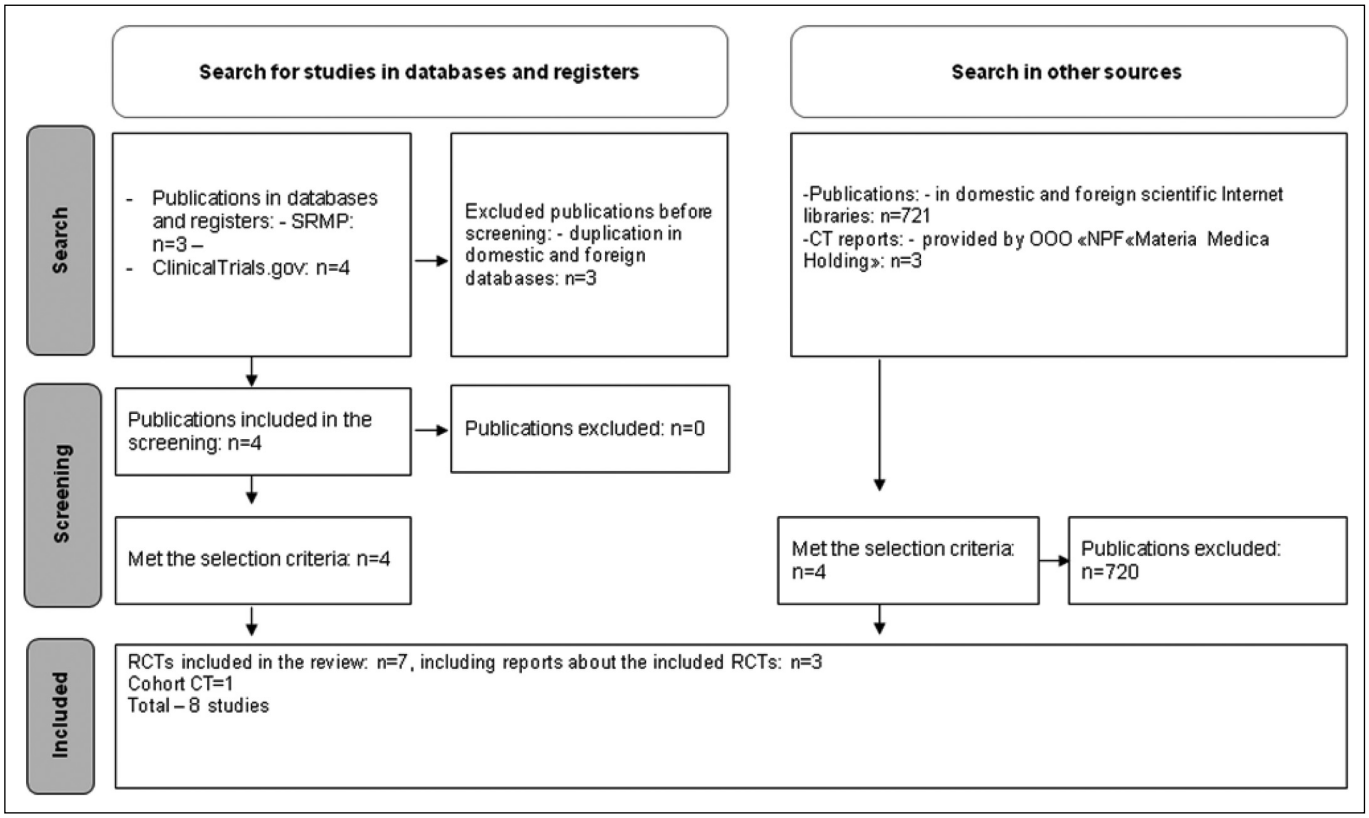
Trials selection. 721 publications were found in open sources by keywords; additional 3 reports on clinical trials were provided by the sponsoring company. The review includes data from 7 RCTs and 1 cohort study (Figure).

Bias risk assessment in trials

Data on the assessment of the risk of bias in trials are presented in Table 1.

The results of published studies included in the review are shown in Table 2.

A part of the results of clinical trials of Tenoten and Tenoten for children were presented on ClinicalTrials.gov website and in the reports of marketing authorization holder, and were not previously published. The results of these studies included in the review are presented in Table 3.



Scheme for selecting clinical trials for review (adapted from PRISMA statement [11])

Discussion

The etiology of anxiety disorders a matter of discussion. The mainstream theory considers the appearance of anxiety as a disruption in the functioning of the GABA-ergic system, which is involved in enabling inhibition processes in the CNS.

A decrease in its activity leads to phobias, apprehension, anxiety and panic attacks. Increased constitutional propensity for anxiety and depressive reactions are also primarily due to insufficient activity of the GABA-ergic system [17].

At the same time, there is increasing evidence that impaired immune regulatory mechanisms may contribute to the development of anxiety and depression [18, 19]. Many immune cells, including macrophages, neutrophils, and eosinophils, are involved in the development of neuroinflammation by producing inflammatory mediators [20].

The current theory of neuroinflammation explains the development of mental disorders by an increase in pro-inflammatory cytokines, an excess of which can directly affect certain areas of the brain involved in the regulation of emotional response: the amygdala, hippocampus, hypothalamus and cerebral cortex [21]. In clinical and experimental studies, it has been shown that pro-inflammatory cytokines such as tumor necrosis factor alpha [TNF-α], or interleukin [IL]-6 can lead to neuronal damage, contributing to the progression of depression and anxiety disorders [22].

The S100 protein is considered in the context of pathological link for the development of neuroinflammation, leading to the appearance of anxiety, depression, and neurodegenerative diseases, such as Parkinson's and Alzheimer's disease [23].

The research has shown that an increased level of S100 protein is able to enhance the expression of NO-synthase and pro-inflammatory cytokines (IL-6, IL-1β, TNFα) in microglia and macrophages [24], which leads to pathological changes in neurons, their death and the release of hyperphosphorylated tau protein, starting the process of neuroinflammation [25]. The S100B protein also increases the expression of the β-amyloid peptide precursor (APP), which in turn induces the production of S100B, thus completing the vicious circle of neurotoxic effects of S100B [26, 27].

Anxiolytics are widely used in medical practice, but, despite their diversity, not all of them have a pronounced anxiolytic effect combined with reliable safety, especially in patients with concomitant diseases [28]. Among anxiolytics, benzodiazepine derivatives enhancing GABA-ergic transmission in the CNS hold the top position. However, benzodiazepine therapy is not suitable for everyone due to its numerous side effects (drowsiness, decreased concentration, impaired coordination) and the fact that benzodiazepines may cause drug dependence [17]. The high incidence of adverse events also limits the use of antidepressants, especially in cases of somatoform dysfunction, for which they have insufficient efficacy [29].

Daytime anxiolytics are better in meeting safety requirements for the pharmacological therapy of anxiety. This group of medicinal products has minimal sedative or hypnotic effects, and do not suppress cognitive functions. Therefore, such products can be prescribed for daytime use on an outpatient basis and taken during the working day [30, 31].

One of the promising approaches in developing daytime anxiolytics involves working on the brain-specific protein S100 that modulates the functional state of the GABA-ergic system and a number of other CNS neurotransmitter systems associated with it. This protein is one of the regulators of the brain's integrative activity and is actively involved in synaptic processes [32].

The effect on S100 B protein also makes it possible to regulate the course of neuro-inflammatory processes in the CNS.

The S100 protein directly interacts with the GABA-benzodiazepine chlorine-ionophore receptor complex, mainly with its chloride channel, stimulating the entry of chlorine into the cell [33, 34].

A modern way to use S100B protein as a target for the production of anxiolytic drugs is the use of antibodies to it. It was found that with a certain technological treatment (preparation of high dilutions using a patented technology), antibodies to the S100 B protein exhibit an anti-anxiety effect without concomitant damaging effect from the psyche [33, 34].

Table 1. *Bias/Bias Risk Assessment Results*

Study	Randomization method	Distribution masking (+/–)	Blinding (+/–)/ type (if applicable)	Presentation completeness of results in accordance with the efficacy criteria in the RCT (+/–)
RCT 1 (N.N. Zavadenko, et al., 2015) [12]	Block, IVS	No data	+/double	+
RCT 2 (E.S. Keshishyan, et al., 2019) [13]	No data	No data	+/double	+
RCT 3 (N.N. Zavadenko, et al., 2020) [14]	Simple	No data	+/double	+
RCT 4 (N.N. Zavadenko and N.Y. Suvorinova, 2010) [15]	Simple	No data	+/double	+
Open Comporative RCT 5 (2004) unpublished	No data –	–	–	+
RCT 6 (2007) unpublished	Block, IVS	No data	+/double	+
RCT 7 (2021) unpublished	No data	No data	+/double	+
Cohort Study 8 (A.L. Vertkin, et al., 2021) [16]	Not applicable	–	–	–

Note. IVS – interactive voice system.

Table 2. *Design and results of included studies*

Study	Design	Results
Observational program for evaluating the use of Tenoten in patients with arterial hypertension (AH) and anxiety-depressive spectrum disorder TEATR [16]	6933 patients with hypertension and anxiety-depressive spectrum disorders from 18 to 70 years of age participated in the trial; the follow-up period lasted 12 weeks. Vital signs (heart rate, systolic and diastolic BP), severity of anxiety, depressive or mixed disorder according to HADS, and the physician's clinical impression of the patient's condition on the Clinical Global Impression-Severity (CGI-S) scale were assessed. Charlson comorbidity index was calculated	After 12 weeks of taking Tenoten, 82% of patients had no symptoms of anxiety and depressive disorder. The mean combined HADS-A and HADS-D scores decreased by 63.5% and 56.5%, respectively (p<0.0001). The average decrease in SBP (systolic blood pressure), DBP (diastolic blood pressure) and heart rate was 11.2%; 10% and 8% (p<0.0001). The mean CGI-S score decreased by 1.66±1.23 (p? 0.0001). Based on the results of variance analysis, the change in SBP and DBP was significantly affected by the degree of hypertension (SBP and DBP – p<0.0001), the nature of emotional disorder (SBP – p=0.03; DBP – p=0.005) and their interaction (SBP – p=0.04; DBP – p=0.0002). The change in heart rate was influenced only by the degree of hypertension (p<0.001) and the interaction of factors (p=0.03). 48.75% of all assessed patients had zero comorbidity index. Less than 1% of the study participants had a comorbidity index of 7 to 15. As a result of the All-Russian observational program TEATR, the efficacy and safety of Tenoten in patients with emotional disorders and grade 1 to 3 hypertension was demonstrated in real clinical practice
Multicenter, double-blind, placebo-controlled, randomized study of the efficacy and safety of Tenoten for children in children and adolescents with anxiety disorder [12]	12 weeks' follow-up of 98 children and adolescents from 5 to 15 years of age with a confirmed diagnosis of anxiety disorder according to ICD F93. The severity of anxiety disorder was determined using rating scales in children and adolescents by G.P. Lavrentieva and T.M. Titarenko and SCAS	The use of Tenoten for Children for 12 weeks was effective in the treatment of children and adolescents with AD and contributed to reducing the severity of AD. After 4 weeks of treatment, the proportion of children with a high level of anxiety in the main group (Tenoten) decreased from 59 to 33% (versus 65 and 46% in the placebo group). By the end of 12-week course of therapy with Tenoten for Children, the proportion of children with severe anxiety disorders was 20% (versus 35% in the placebo group), and the proportion of patients with an average level of anxiety increased to 78% (versus 65% in the placebo group). This demonstrated the anxiolytic efficacy of the product. Based on self-assessment of children of 8 to 15 years of age, performed with SCAS (Spence Children's Anxiety Scale) subscales, a pronounced anxiolytic effect of Tenoten for children was observed on the Panic attacks and agoraphobia subscale: the severity of symptoms decreased from 5.4±4.2 to 3.5±3.7 within 12 weeks. The Separation Anxiety subscale showed a decrease in the initial score from 6.9±3.8 to 4.6±3.6, and the level of social phobia decreased from 8.5±4.0 to 5.7±3.4 (p= 0.014). In children of the younger age group, the mean values of AI (anxiety index) decreased by 11.9 (in the placebo group 8.3 (p=0.04) during 12 weeks of treatment with Tenoten for Children
Multicenter, double-blind, placebo-controlled, randomized clinical trial of the efficacy of Tenoten for children in a liquid dosage form [13]	184 children (aged 29 days to 9 months) with consequences of perinatal CNS damage were included. The trial lasted 12 weeks. Psychomotor development indicators were assessed by the Zhurba–Mastyukova scale	As a result of the 12 weeks' therapy, 77.5% of patients who took Tenoten for Children showed an improvement in psychomotor development by 4 or more points on Zhurba–Mastyukova psychomotor development scale (similar improvement was observed in 60.5% patients in the placebo group; the difference from placebo was significant, with p=0.02 on Fisher exact test). The proportion of patients with normal (age-appropriate) psychomotor development in the main group was 43.8% after 4 weeks and 87.5% after 12 weeks of taking Tenoten (33.7 and 79.1% in the comparison group, respectively, p=0.01). It has been established that Tenoten for Children in liquid form was safe in the treatment of patients on the 1st year of life
Multicenter, double-blind, randomized, placebo-controlled clinical trial to study the efficacy and safety of Tenoten for children in the treatment of specific learning disorders [14]	Within 12 weeks, 240 children aged 7 to 9 years with disorders of reading, spelling, arithmetic skills development, as well as mixed learning disorders were examined. During the visits, the study physician assessed learning skills according to the method developed by T.A. Fotekova, T.V. Akhutina and WAIS test	As a result of the treatment, the total score of learning skills increased by 18.55±15.87 (from 61.39±12.04 to 79.94±18.22) in the group that took Tenoten for Children (versus 60.46±11,04 and 74.56±18.75 in the placebo group, respectively, nonparametric Wilcoxon test p=0.0113). During therapy, no cases of interaction of Tenoten for Children with medicinal products used as concomitant therapy were observed
Treatment of Attention Deficit Hyperactivity Disorder with Tenoten for Children: Results of a Double-Blind, Placebo-Controlled, Randomized Trial [15]	The 12-week trial included 50 ADHD patients aged 6 to 12 years. The following methods were used to assess their condition: the ADHD Symptoms Rating Scale (ADHDRS-IV) to be completed by the investigator based on the parents' report, the ADHD Severity Rating Scale (CGI-ADHDSeverity) to be completed by the investigator, the Conners ADHD Symptom Rating Scale to be completed by the parents	Positive trends in the condition of patients treated with Tenoten for Children were achieved after 1 month and continued to develop over the next two months of treatment. By the end of 12 weeks, the total score of ADHD symptoms severity in Tenoten for Children group decreased by 11.2, and by 7.2 in the placebo group, or 36.4% and 21.4%, respectively (significance of differences compared with the baseline p<0.001, significance of differences compared with the placebo group p<0.05). The group of children taking Tenoten for Children showed the most pronounced improvement in hyperactivity that decreased by 41.9% over 3 months of therapy, while the placebo group showed a decrease by 25.5% (p<0.001) in this parameter.The observation showed good tolerance of Tenoten, comparable with placebo. Adverse events were reported in 1 patient in Tenoten group (headaches during the first month of treatment) and 1 patient in the placebo group (sleepwalking in the 1st month of observation)

Table 3. *Design and results of unpublished studies included in the review*

Study	Design	Results
Double-blind, placebo-controlled RCT to study the anxiolytic activity of Tenoten on the basis of the Scientific Center of Neurology of the Russian Academy of Medical Sciences (2007)	62 patients with anxiety disorders due to Parkinson's disease and chronic cerebrovascular diseases were assessed. During 4 weeks of treatment, the anxiolytic activity of Tenoten was evaluated at a dosage of 8 tablets per day. The primary efficacy endpoints were the percentage of patients responding to therapy (more than 50% reduction in total HAM-A score from baseline) and the mean reduction in anxiety on the HAM-A scale assessed after 1, 2, 4 and 4 weeks. weeks after drug withdrawal	By the end of the 4-week therapy, there was a pronounced positive trend for decrease in the anxiety syndrome in patients with neurological disorders. The severity of anxiety assessed on the HAM-A scale decreased by 45.63±2.61% in the group on average, and by 13.09±3.38% in the placebo group. Differences in the groups were statistically significant ($p<0.05$). The anxiolytic effect of the product was persistent, as the effect of the therapy continued 4 weeks after the end of treatment. At the end of the therapy, the proportion of patients who responded to therapy in Tenoten group (a decrease in the total HAM-A score by more than 50% from the baseline) was 41.3%, vs. 6.7% in the placebo group ($p<0.05$). At the end of the therapy, the proportion of patients who responded to therapy in Tenoten group (a decrease in the total HAM-A score by more than 50% from the baseline) was 41.3%, vs. 6.7% in the placebo group ($p<0.05$). By the end of the observation, this percentage was 44.6% in Tenoten group vs. 0% in the placebo group ($p<0.05$). The reduction of anxiety was also supported by the Hospital Anxiety and Depression Scale (HADS) Anxiety subscale data both at the end of treatment and 4 weeks after the end of treatment, vs. placebo
Double-blind, placebo-controlled RCT to study the safety and efficacy of Tenoten in the treatment of anxiety in adults. Based on 23 medical centers of the Russian Federation and Kazakhstan (2021)	390 outpatients aged 18 to 45 years with an anxiety level of more than 11 points on the HADS-A scale and more than 18 points on the HAM-A scale against the background of diseases: somatoform disorders (F45), including somatoform dysfunction of the autonomic nervous system (ADNS) (F 45.3), reaction to severe stress and adjustment disorders (F43), as well as other neurotic disorders (F48.8, F48.9). Participants were randomized into 4 groups. Patients in groups 1 and 3 received Tenoten as 2 tablets 2 times a day or 2 tablets 4 times a day, respectively. Patients in groups 2 and 4 received a placebo Tenoten regimen. The primary endpoint was the change in mean HAM-A total score from baseline in groups 1 and 3 after 12 weeks of treatment	After 12 weeks of therapy, a decrease in the mean total HAM-A score was 7,26±4,63 [7,12±4,65] in Tenoten-1 group, and 6.40±4.02 [6.08±3.78] in Tenoten-3 group (versus 8.48±5.13 [8.31±4.51] in Placebo group; ANCOVA, p group 1/placebo = 0.0055 [0.0155], p group 3/placebo < 0.0001 [0.0001]). The mean score changes were 11.25 [11.23] in Tenoten-1 group, 11.91 [12.36] in Tenoten-3 group, and 9.71 [9.94] in Placebo group. An equivalence analysis of therapy did not reveal any differences between the Tenoten groups with different regimens (ANCOVA, p=0.008 [0.008]). After 4 weeks of treatment with Tenoten (secondary endpoints), the absence of anxiety (<14 HAM-A scores) was observed in 46% of patients in group 1 and 48.5% of patients in group 3. After 12 weeks, the proportion of patients with recovery increased to 88.1 % in group 1 and 96.2% in group 3. The efficacy of Tenoten at a dose of 8 tablets per day was superior to placebo (Fischer's test, p group 3/placebo = 0.007). Trends in the HAM-A mean total score after 4 weeks of treatment. The average total score on the HAM-A scale decreased to 13.31±4.7 [13.33±4.8] in group 3 compared with baseline values (versus 13.85±5.34 [13.99±4.91] in the Placebo group, ANCOVA t-test, p=0.044 [0.047]) (Fig. 2). The change in mean HAM-A was 4.37 [4.35] in Tenoten-1 group and 3.29 [3.64] in Placebo group. The analysis showed no difference between Tenoten-1 and Placebo groups (ANCOVA t-test, p=0.08 [0.14]). The change in mean HAM-A was 4.37 [4.35] in Tenoten-1 group and 3.29 [3.64] in Placebo group. The analysis showed no difference between Tenoten-1 and Placebo groups (ANCOVA t-test, p=0.08 [0.14]). Trends in the HAM-A mean total score after 8 weeks of treatment. Taking Tenoten had a positive effect on the trends in the severity of anxiety in group 3. In these patients, the decrease in the mean HAM-A score to 9.88±4.93 [9.82±4.97] was statistically significant (vs. 10.81±5.16 [9.82±4.97] in the Placebo group, ANCOVA t-test, p group 3/placebo = 0.027 [0.033]). The proportion of patients responding to treatment (⩾50% reduction in HAM-A score). After 4, 8 and 12 weeks of treatment, the proportion of patients who responded to treatment was 12.7%, 34.9% and 69.8% in Tenoten-1 group, respectively. In Tenoten-3 group, the response rate was 13.8% at week 4, 42.3% at week 8, and 73.8% at week 12 of the therapy. Significant differences between the Tenoten and Placebo groups were observed only after 12 weeks (Fischer test, p group 1/placebo = 0.01, p group 3/placebo = 0.001). Additionally, 70 patients with SAD were divided into two subgroups and assessed. The main group (n=35) took 8 tablets Tenoten per day, the comparison group (n=35) took placebo on the same scheme. The groups were comparable in demographic and clinical characteristics. The decrease in the mean total HAM-A score in the Tenoten group after 12 weeks of treatment reached 11.4, and the placebo group's score decreased to 8.9 points. The difference in changes in the total score between the groups was 2.4, which was statistically and clinically significant (p=0.026). The data of the ITT analysis are shown, with the results of PP efficiency analysis in square brackets
Multicenter open comparative RCT (with Diazepam), 4 research centers in Moscow and St. Petersburg (2004)	272 patients from 18 to 65 years old, with manifestations of anxiety and phobic disorders, as well as neurasthenia, adjustment disorder, generalized anxiety disorder, mixed anxiety and depressive disorder. Within 28 days, two observation groups received: Tenoten 6 tablets per day and the second group Diazepam – 15 mg per day. The effectiveness of the anti-anxiety effect was assessed by the change in the total score on the HAM-A scale, the Spielberger anxiety scale (State-Trait Anxiety Inventory, STAI) and the proportion of patients who responded to treatment (criteria for a positive response to treatment: a decrease in the total HAM-A score by 50% and more) or achieved remission (remission criterion: decrease in the total HAM-A score to 7 or less).	The initial total HAM-A score was 27.1±0.5 in Tenoten group, and 29.0±0.4 (p=0.2) in Diazepam group. After 4 weeks, the level of anxiety significantly decreased in both groups, reaching 11.6±0.4 in Tenoten group vs. 9.9±0.4 in the comparison group (p=0.1). No statistically significant differences between the levels of anxiety in the groups of patients taking Tenoten or Diazepam were found on Days 1, 7 and 28 of observation. The proportion of patients with a positive response to treatment (a decrease in the total HAM-A score ⩾50%) was 72.6% in Tenoten group, and 65.8% in the comparison group. The remission (NAM-A decrease to ⩽7%) was observed in 12.8% of patients in Tenoten group, and in 22.1% of patients in the comparison group. In each of the groups, the total score significantly differed both from the baseline ($p<0.001$) and from the data of the previous assessment ($p<0.001$) on all the set days of assessment (days 7, 14, 28), which indicated a pronounced anti-anxiety effect of the medicinal products. Positive dynamics on the State-Trait Anxiety Inventory did not differ in groups (Table 1). At the end of the trial, patients in both groups gave evidence of increased activity, improved mood and well-being (assessment on the scale of Well-being-Activity-Mood. Tenoten had a significantly more favorable safety profile than Diazepam: the proportion of patients with adverse events (AEs) in Tenoten group was 5.6% versus 39.2% in Diazepam group; the number of AE cases per 100 patients in Tenoten group was 20.4 versus 299.2 in Diazepam group. The study showed that the anxiolytic effect of Tenoten was not inferior to the effect of Diazepam, with a significantly lower frequency of adverse events ($p<0.01$)

Neuroprotective effect of TPA to S100B may be associated with the suppression of neuroinflammatory process inhibition of lipid peroxidation processes, and a decrease in the buildup of reactive oxygen species that have a damaging effect on neurons [35, 36].

By modifying the functional activity of the S100 protein, TPA to S100B have a neuroprotective effect in case of intoxication and/or hypoxia, and in conditions after acute cerebrovascular disturbance [36].

The introduction of Tenoten into clinical practice was preceded a preclinical studies that demonstrated their stress-protective, anxiolytic, antidepressant, antiamnesic, and neuroprotective effects [37].

The safety of Tenoten, absence of addiction or interaction with other drugs, demonstrated in the TEATR program [16] and previous clinical and experimental studies, make it possible to use the product in the therapy of emotional disorders in patients with medical pathology, minimizing the likelihood of adverse reactions. Possessing a favorable ratio of safety and efficacy, Tenoten may become a medicinal product of choice for the treatment of anxiety-depressive reactions in patients with hypertension.

Tenoten for children is widely used to reduce anxiety in children, including those with somatic symptoms and impaired development of school skills [14, 38].

The safety of the medicinal products is confirmed, as they do not cause adverse events, do not influence the course of the underlying disease, do not to cause addiction or drowsiness, and laboratory findings remain stable in the course of the treatment.

The mechanism of anti-anxiety action of Tenoten and Tenoten for Children is explained by its influence on the GABA-ergic system [36]. At the same time, Tenoten has an effect on situational anxiety, somatovegetative syndrome, and on the condition of patients with underlying chronic diseases [16, 39].

In these situations, Tenoten probably exerts its effect through the modification of S100 protein, controlling neuroinflammation processes and reducing damage to the nerve tissue.

In the past 10 years, it has been commonly recognized that inflammation may be a common mechanism in the pathogenesis of neuropsychiatric disorders as well as somatic diseases. In the CNS, this can be manifested in excitotoxicity and glial dysfunction. It has been shown that hyperproduction of the pro-inflammatory protein S100B (micromolar levels) may have a neurotoxic effect and occur in brain lesions as a result of stroke and ischemia [40], or accompany such severe CNS conditions as schizophrenia, bipolar disorder, depression, Alzheimer's disease, Down syndrome [41–44].

The levels of S100B in blood serum strongly correlate with its concentrations in the cerebrospinal fluid, where it mainly enters from astrocytes and oligodendrocytes [45]. S100B is involved in the regulation of glutamate and calcium intake, neuronal plasticity, energy metabolism, and various processes of neural development, especially those associated with the neurotrophic function of serotonin, a neurotransmitter that interacts with dopamine to regulate impulsivity and sensitivity to emotions [46].

With regard to ADHD, there is increasing evidence supporting a role of S100B in the pathogenesis of neuroinflammation, glial injury with function impairment, and subsequent changes in dopaminergic (DA) neurotransmission; however, a few studies of S100B protein in ADHD as a marker of glial dysfunction have shown conflicting results, although some data on an increase in its peripheral levels have been published [47].

The effectiveness of Tenoten for children in conditions of early brain damage and neurodevelopmental disorders is probably due to its effect on neuroplasticity, leading to restoration of impaired CNS functions in children [48].

Tenoten for children was also used in children with anxiety, in whom anxiety disorder proceeded with the development of somatic anxiety masks, i.e. in SAD, when neurotic disorders caused functional disorders in the respiratory, digestive, cardiovascular, endocrine and other body systems [39, 49]. The use of Tenoten for Children is indicated in cases where somatic symptoms are due to the child's anxiety [39, 49].

The efficacy, safety and good tolerance of Tenoten for Children make it possible to use it in combination with other drugs for SAD with anxiety and phobic manifestations [48].

Some studies evaluated the speed of onset of the action of Tenoten. According to the obtained results, the time of onset of its maximum anxiolytic effect ranged from 2 to 12 weeks. However, there are data on the onset of the action within 20 to 30 minutes after administration when Tenoten was used as an anxiolytic for the relief of situational anxiety during a dental appointment in both children and adults [39].

Tenoten has established itself as a daytime anxiolytic that does not cause drowsiness or inhibition, with a minimal likelihood of adverse reactions [37, 50].

The obtained data expand our understanding of the mechanism of action of TPA to S100 and possibilities of their use.

The medicinal product Tenoten contains TPA to S100 protein and has a wide range of psychotropic and neurotropic pharmacological actions, including anxiolytic, antidepressant and neuroprotective effects, and enables patients to maintain performance and concentration throughout the day [36]. Tenoten may be combined with medicinal products of other groups and used as a daytime anxiolytic in socially active populations [51]. Its efficacy in the treatment of anxiety disorders was comparable to that of benzodiazepines.

The obtained data expand our understanding of the mechanism of action of TPA to S100 and possibilities of their use.

The therapeutic efficacy and safety of Tenoten and Tenoten for Children was confirmed in clinical trials and observation program involving 8935 patients.

According to Marketing Authorization Holder's 2020–2022 in-house pharmacovigilance data, more than 1.3 million patients took Tenoten and more than 1 million patients took Tenoten for Children. At present, Tenoten and Tenoten for Children are marketed in 16 countries worldwide. There were no marketing authorization denials, or authorization suspensions for safety reasons, or cases of product recall from the market. During the reporting period, 17 reports of 24 adverse events (AEs) and other safety issues (accidental or intentional overdose) were recorded, all of which were not serious and did not cause health harm. In the company's opinion, in-house data obtained during the reporting period do not constitute safety signals or require a revision of the benefit-risk ratio of Tenoten and Tenoten for Children.

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Conflict of Interest Statement

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Perez M. https://orcid.org/0000-0002-7588-458X
Zavadenko N.N. https://orcid.org/0000-0003-0103-7422
Skipetrova L.A. https://orcid.org/0000000260194981
Smirnov I.I. https://orcid.org/000000020149487X
Nesterovsky Y.E. https://orcid.org/0000-0002-4276-8400