The Treatment of Anxiety in Patients with Somatoform Dysfunction, Reaction to Severe Stress and other Neurotic Disorders: A Multicenter Double-blind Placebo-controlled Randomized Trial

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The treatment of anxiety in patients with somatoform dysfunction, reaction to severe stress and other neurotic disorders: a multicenter double-blind placebo-controlled randomized trial

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Abstract

Background

The existing treatment of somatoform dysfunction (SD), reaction to severe stress (RSS) and adjustment disorders (AjD) is insufficiently effective and safe. Anxiolytic drug Tenoten (NPF Materia Medica Holding) is shown to be effective in clinical trials (CT).

Objectives

The aim of multicenter double-blind placebo-controlled randomized CT was to investigate the safety and efficacy of Tenoten in the anxiety treatment of adults with SD, RSS, AjD and other neurotic disorders (oNDs).

Methods

390 adults with SD, RSS and AjD or oNDs with the Hospital Anxiety and Depression scale-anxiety (HADS-A) score ≥11 were randomized into 4 groups (Tenoten group 14 tablets/day n=127; Tenoten group 3 8 tablets/day n=131, combined Placebo group 2+4 n= 132). The changes from baseline in the mean Hamilton Anxiety Rating Scale (HAM-A) score in groups 1 and 3 after 12 weeks was the primary outcome.

Results

The decrease in the HAM-A score from 18.81±5.81 to 7.26±4.63 (group 1) and from 18.38±4.3 to 6.40±4.02 (group 3) was observed post-treatment ($p_{group\ 1/placebo}$=0.0055, p_{group}

$_{3/placebo}$<0.0001). The mean changes in the scores in the groups 1, 3 and the Placebo were 11.25, 11.91 and 9.71, respectively.

In total, 46 AEs (28 AEs in the Tenoten groups, 18 in the Placebo) were registered in 37 patients (20 in the Tenoten groups, and 17 in the Placebo). No differences in frequency of AEs between groups were found.

Conclusions

Tenoten was shown to be significantly more effective than placebo in the anxiety treatment of adults with SD, RSS, AjD and oNDs (clinicaltrials.gov NCT03036293).

Introduction

Somatoform dysfunction (SD) is a group of medically unexplained symptoms (MUSs) unrelated to pathology of an organ, classified in ICD-10 under F40-F48. The prevalence rate of SD is 20-25% [1, 2]. SD is often underdiagnosed and only 33-60% of patients undergo treatments [3].

Post-traumatic stress disorder (PTSD) is another neurotic disorder (ND) from section F43 Reaction to severe stress and adjustment disorder (RSS). Around 1.3–8.1% of people were diagnosed with PTSD once in their life [4].

Comorbidity with anxiety or depression occurs in about 60% of PTSD patients and in 20-67% with SD [5]. MUSs are often co-occur with anxiety [6]. In a study, 7-48% of primary care patients with anxiety reported somatic symptoms [7].

Pathological mechanisms of NDs remain unclear. Authors associate symptoms with the alterations in the hypothalamic-pituitary-adrenal axis, immune-to-brain dysregulation and cytokine imbalance [8, 9]. Given the similarity of pathogenesis between SD and anxiety and their increased co-incidence in patients, the presence of MUS can be considered as a predictor of a risk of limited social functioning and somatic diseases development [10].

Antidepressant efficacy in SD is low and their use is complicated with a high rate of adverse events (AEs) [11]. There is controversial data on the psychotherapy efficacy [12, 13]. The same is true for the PTSD: meta-analysis showed the small effect size of selective serotonin reuptake inhibitors [14]. The search for safe and successful strategies for treatment is relevant.

Tenoten (NPF Materia Medica Holding, Russian Federation (RF)) is an anxiolytic drug containing highly diluted antibodies to S100 protein (HD Abs to S100). High dilutions of substances obtained using a technological process, namely by a repeated dilution of the original substance in combination with an external physical impact, have the ability to modify the activity of the original substance [15]. The mechanism of action of HD is based on their ability to induce conformational changes of the original substance/target molecule [16]. The modifying effect of HD Abs to S100 has been demonstrated in experimental studies [17-27].

Tenoten is manufactured under GMP condition and has been registered as a conventional drug in the European Economic Community (marketing authorization number ЛП-N(000029)-(РГ-RU)) [28]. Though Tenoten is not registered in USA, FDA experts concluded that drugs based on HD Abs should be studied and proceeded for registration using a standard regulatory approach [29]. Clinical trials (CTs) have demonstrated the efficacy and safety of HD Abs to S100 in patients with anxiety [30].

The aim of CT was to investigate the safety and efficacy of Tenoten in the treatment of anxiety in adults with SD, RSS, AjD and other NDs.

The trial has been registered at clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT03036293) in 30/01/2017.

Materials and Methods

Trial design

This multicenter double-blind placebo-controlled randomized CT was conducted according to GCP at 23 sites in the RF and Kazakhstan between February 2017 and March 2019. The CT was approved by the regulatory agencies: the Ministry of Health of the RF (approval #549

August 03, 2016) and Kazakhstan (#30 February 15, 2017). The study was approved by the National Ethics Committee of the Ministry of Health of the RF (#129 July 26, 2016).

Participants

Inclusion and exclusion criteria

Outpatients (18-45 years old) with anxiety and SD (F45.0, F45.1, F45.2, F45.4, F45.8, F45.9), RSS and AjD (F43.0, F43.1, F43.2, F43.8, F43.9) or other NDs (F48.8, F48.9) diagnosed prior to the study were enrolled in four groups stratified by type and dosage of treatment. Inclusion criteria were an anxiety (Hospital Anxiety and Depression scale-anxiety (HADS-A) scores ≥11) and a signed informed consent form.

Exclusion criteria are listed at clinicaltrials.gov NCT03036293.

Study procedures and treatment

All methods were carried out in accordance with relevant guidelines and regulations. After signing the informed consent form, the neurologist examined a patient, recorded demographic data and concomitant medications, administered a pregnancy test and filled the HAM-A scale. Patients filled the HADS and EQ-$_5$D-$_3$L.

The treatment period was 12 weeks. During Visit 1 participants were randomized in 4 groups. Patients in the group 1 and 3 were administered Tenoten 2 tablets 2 times a day or 2 tablets 4 times a day, respectively. The Placebo groups 2 and 4 were administered placebo in dosages similar to Tenoten.

Every 4 weeks the investigator examined patients, filled the HAM-A scale, recorded concomitant medication and assessed the safety and compliance. The evaluation of the Clinical Global Impression-Efficacy Index (CGI-EI) and the filling of EQ-$_5$D-$_3$L were performed during the last visit.

Psycholeptics, psychoanaleptics, antiepileptics, anticholinergic and dopaminergic agents, antioxidants, hormones, psychotherapy were not allowed 4 months prior and during the study.

Outcomes

The changes from baseline in the mean HAM-A score in groups 1 and 3 after 12 weeks was the primary outcome.

The exploratory outcomes were: changes from baseline in the mean HAM-A score after 4 and 8 weeks, the percentage of patients with response (≥50% reduction on HAM-A) and the percentage of patients without anxiety (HAM-A<14) after 4, 8, 12 weeks, the changes from baseline in the EQ-$_5$D-$_3$L scores after 12 weeks, the CGI score.

In the post-hoc analysis the affection of the type of diagnosis on the mean HAM-A scores, subscores for each separate question, and somatic component subscores of HAM-A scale (questions 7-13) were assessed. The interaction between placebo effect and diagnosis was also evaluated.

Sample size determination and randomization

Sample size of the study was set in order to have desired control of type I and II errors during investigation of the primary outcome. Overall error levels were 0.05 and 0.2, respectively. There were three independent formal hypotheses: inequality of each treatment with placebo (1 hypothesis for each Tenoten group) and equivalence of treatments. Type I error level was evenly distributed and fixed across mentioned hypotheses. It was assumed that the difference in the HAM-A score decrease between each Tenoten and Placebo groups would be greater than 4 points, and the difference in the HAM-A score decrease between Tenoten groups would be <3 points. The variance of the change in the HAM-A score was a priory estimated as 44. The dropout rate during the screening was planned to be <20%. The recruitment expectation was set at 390 patients. The ratio of patients, between Tenoten and Placebo groups, was 1:1:0.5:0.5. Placebo groups 2 and 4 were combined.

Eligible patients were randomized into four groups via interactive system based on a random number generator.

Statistics

Two-tailed statistical criteria were used. Changes from baseline were analyzed with ANCOVA, normality assumptions were controlled with the Kolmogorov-Smirnov test and Q-Q plot; Yeo-Johnson normalizing transformation was applied if necessary. Count data analysis was performed with Fisher test (FT) and/or conditional logistic regression. Non-gaussian data were analyzed with the Kruscall-Wallis test. Statistical inference results are presented as p-value and appropriate central tendency with confidence limits, type I error for primary outcome was controlled, for exploratory data, unadjusted p-values and 95% confidence intervals are presented. The post-hoc analysis was held using multinomial or mixed ANOVA. For analysis of HAM-A questions 7-13 data were normalized using Yeo-Johnson transformation. Analyses were performed using SAS v9.4.

Results

Study group characteristics

A total of 390 patients were enrolled in CT, with 258 participants in Tenoten groups (group 1 n=127; group 3 n=131) and 132 patients in the Placebo group (group 2+4). The patients were stratified into general groups by the type of diagnosis: F43, F45, F48. No differences between groups in baseline data were found (Table 1).

	Tenoten group 1	**Tenoten group 3**	**Placebo**	**Total**	**Statistics**		
					Tenoten group 1 vs group 3	**Tenoten group 1 vs Placebo**	**Tenoten group 3 vs Placebo**
ITT-set	**n=126**	**n=130**	**n=128**	**n=384**			
Age, years					Kruskal-Wallis test:		
Mean±SD	32.7±7.1	32.9±7.6	34.3±7.7	33.3±7.5	p=0.6177	p=0.8022	p=0.0819
Sex, n (%)					χ^2 criterion:		
Men	27 (21.4)	28 (21.5)	29 (22.7)	84 (21.9)	p=0.9829	p=0.8135	p=0.8287
Women	99 (78.6)	102 (78.5)	99 (77.3)	300 (78.1)			
Diagnostic categories					ANOVA (multinomial)		
Patients with F43, n (%)	27 (21.4)	19 (14.6)	31 (24.2)*	77(20.0)*	p= 0.82		
Patients with F45, n (%)	56 (44.4)	67 (51.5)	62 (48.4)	185(48.2)			
Patients with F48, n (%)	43 (34.1)	44 (33.8)	36 (28.1)	123(32.0)			
HAM-A, score					Kruskal-Wallis test:		
Mean±SD	18.81±5.81	18.38±4.3	17.88±5.42		p=0.49		
EQ-$_5$D-$_3$L, score					Kruskal-Wallis test:		
Mean±SD	7.44±1.44	7.42±1.05	7.48±1.28		p=0.99		
PP-set	**n=114**	**n=119**	**n=111**	**n=344**			
Age, years					Kruskal-Wallis test:		
Mean±SD	32.6±7.0	33.0±7.5	34.5±7.5	33.3±7.4			
Sex, n (%)					χ^2 criterion:		
Men	26 (22.8)	26 (21.8)	24 (21.6)	76 (22.1)	p=0.8606	p=0.8307	p=0.9667
Women	88 (77.2)	93 (78.2)	87 (78.4)	268 (77.9)			

	Tenoten group 1	Tenoten group 3	Placebo	Total	Statistics		
					Tenoten group 1 vs group 3	Tenoten group 1 vs Placebo	Tenoten group 3 vs Placebo
Diagnostic categories					ANOVA (multinomial)		
Patients with F43, n (%)	25 (21.9)	18 (15.1)	28 (25.2)	71 (20.6)	p=0.48		
Patients with F45,n (%)	48 (42.1)	62 (52.1)	55 (49.5)	165 (47.9)			
Patients with F48,n (%)	41 (35.9)	39 (32.8)	28 (25.2)	108 (31.4)			
HAM-A, score					Kruskal-Wallis test:		
Mean±SD	18.49±5.44	18.50±4.38	18.05±5.01		p=0.52		
EQ-$_5$D-$_3$L, score					Kruskal-Wallis test:		
Mean±SD	7.41±1.25	7.42±1.08	7.5±1.26		p=0.93		

Table 1. Baseline characteristics of patients

Note: PP data are placed in square brackets. *1 patient in Placebo group had mixed F43+F45 disorder. HAM-A - Hospital Anxiety and Depression scale-anxiety, SD - Standard Deviation.

All 390 patients formed a safety population set. The monitoring revealed that 6 patients fulfilled exclusion criteria, so 384 participants with HADS-A ≥11 continued with the treatment and were included in the Intention-to-treat (ITT) set. Finally, 344 participants formed the PP set (fig. 1). All results are presented for ITT and PP (showed in square brackets) sets.

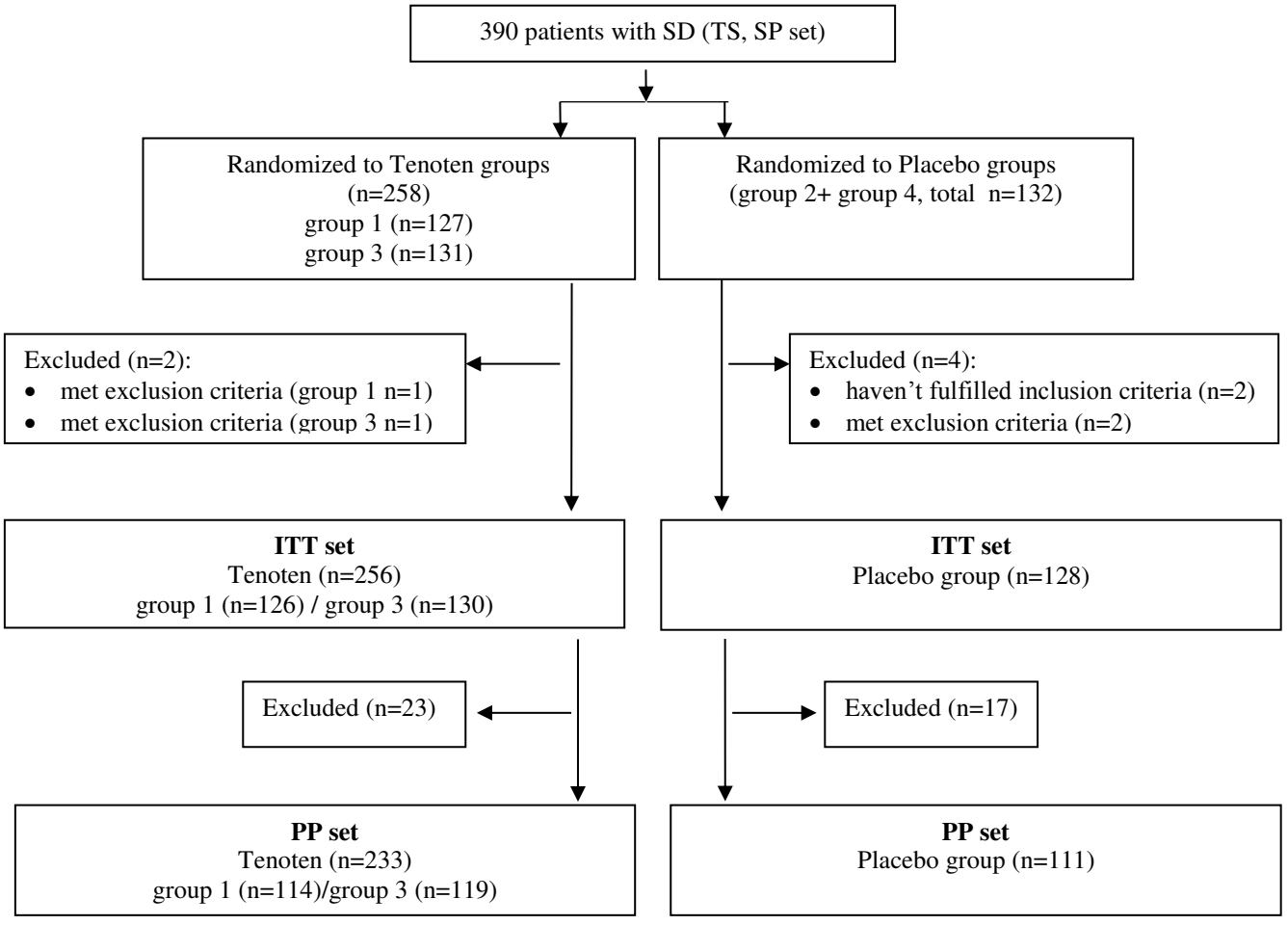

Figure 1. Patient flow diagram
Note: TS–total set, SP–Safety population set.

8-12% of patients were administered permitted medications: analgesics, non-steroidal anti-inflammatory drugs and antimicrobials. FT did not reveal differences between groups.

Compliance assessment demonstrated a high level of adherence to therapy without differences between groups at 12 weeks (Kruskal-Wallis test, $p_{group\ 1/placebo}$=0.4362 [0.2506], $p_{group\ 3/placebo}$=0.1936 [0.3229], $p_{group\ 1/group\ 3}$=0.0598 [0.0519]). The mean compliance index was close to 100% (Total set: $p_{group\ 1/placebo}$=0.63; $p_{group\ 3/placebo}$=0.13; $p_{group\ 1/group\ 3}$=0.07).

Efficacy analysis

Primary outcome

The decrease in the mean HAM-A score to 7.26±4.63 [7.12±4.65] in group 1 and 6.40±4.02 [6.08±3.78] in group 3 was observed after 12 weeks (vs 8.48±5.13 [8.31±4.51] in the Placebo group; ANCOVA $p_{group\ 1/placebo}$=0.0055 [0.0155], $p_{group\ 3/placebo}$<0.0001[0.0001]) (fig. 2c).

The mean changes in the scores in group 1, group 3 and Placebo group were 11.25 [11.23], 11.91 [12.36] and 9.71 [9.94], respectively. The efficacy of two dosage regimens of Tenoten was superior to placebo.

Equivalence analysis showed no differences between Tenoten groups with different dosage regimens (ANCOVA p=0.008 [0.008]).

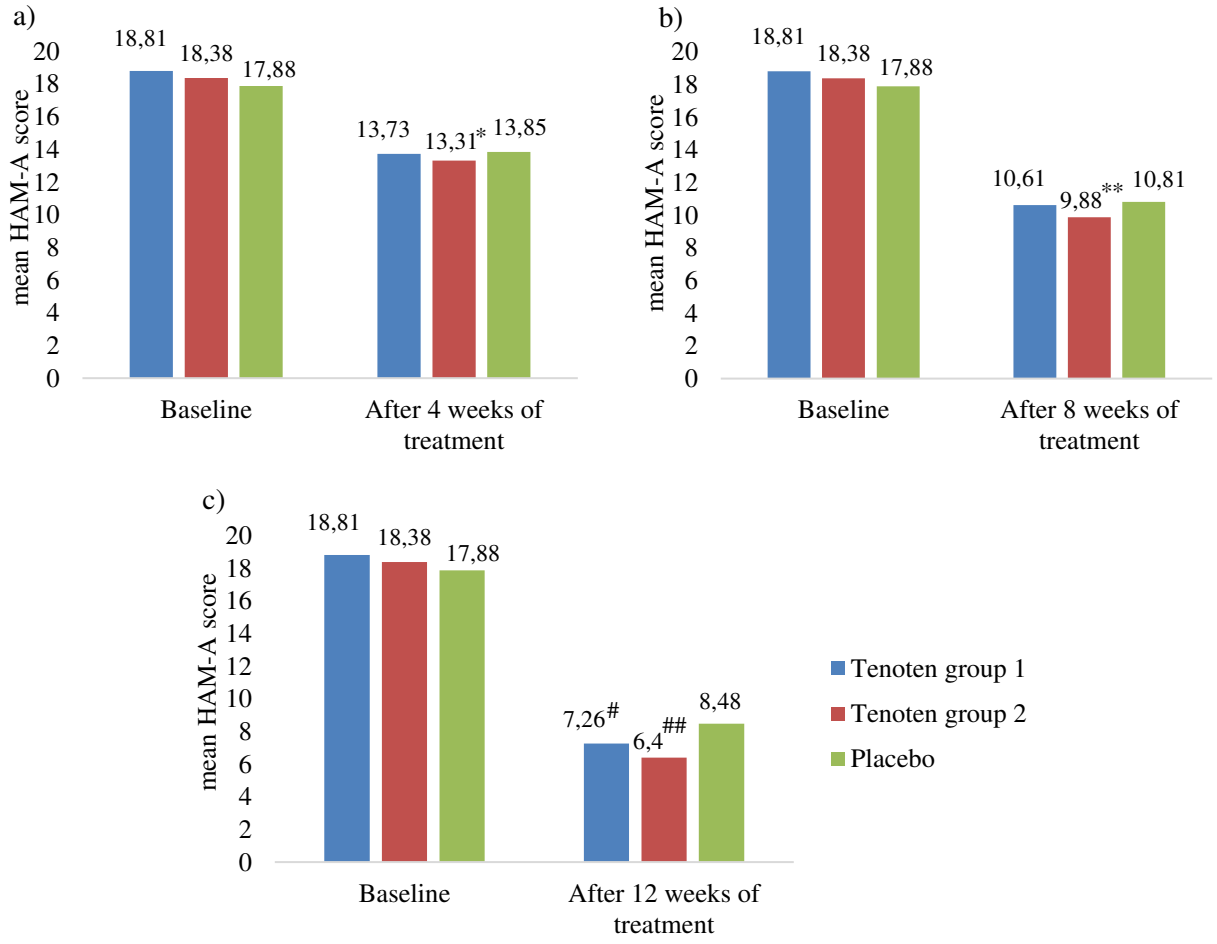

Figure 2. The change in the mean HAM-A score after 4 (a), 8 (b), 12 (c) weeks
Note: ITT-set. **p=0.027 vs Placebo; *p=0.044 vs Placebo; $^{\#}$p=0.0155 vs Placebo, t-test; $^{\#\#}$p<0.0001 vs Placebo, t-test.

Exploratory outcomes

The remission of anxiety (HAM-A<14) was found in 46% of patients in group 1 and in 48.5% of patients in group 3 after 4 weeks. The percentage of patients in remission increased to

88.1% and 96.2% after 12 weeks in group 1 and 3, respectively. The efficacy of Tenoten in dosage of 8 tablets a day was superior to placebo (FT $p_{group\ 3/placebo}$=0.007) (fig. 3).

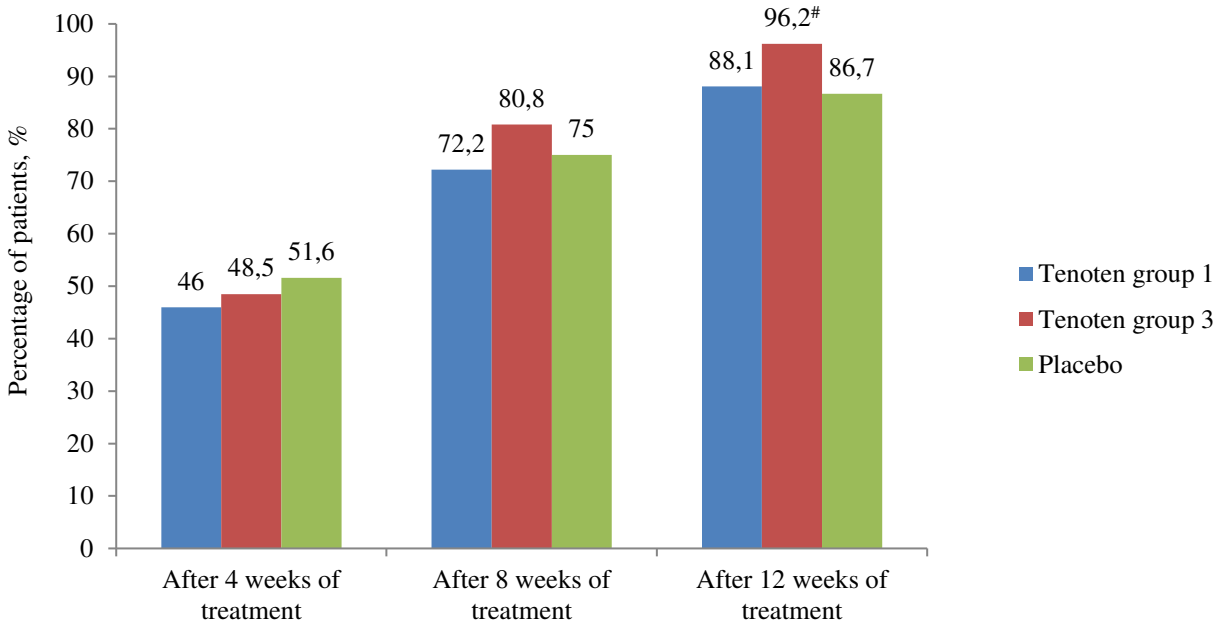

Figure 3. The percentage of patients with remission of anxiety symptoms after 4, 8, 12 weeks

Note: ITT-set. #p=0.007 vs Placebo.

Dynamics of the mean HAM-A score after 4 weeks of treatment

The mean HAM-A score decreased from baseline to 13.31±4.7 [13.33±4.8] in group 3 (vs 13.85±5.34 [13.99±4.91] in Placebo group; ANCOVA t-test p=0.044 [0.047]) (fig.2a). The change in mean HAM-A was 4.37 [4.35] and 3.29 [3.64] points in the Tenoten 1 and Placebo groups, respectively.

The analysis found no differences between group 1 and the Placebo group (ANCOVA t-test p=0.08 [0.14]).

Dynamics of the mean HAM-A score after 8 weeks of treatment

Tenoten administration led to positive dynamics in severity of anxiety in group 3. The decrease in mean HAM-A score to 9.88±4.93 [9.82±4.97] in these patients was 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]) (fig. 2b).

The percentage of patients with response (≥50% reduction on HAM-A scale)

There were 12.7%, 34.9% and 69.8% of responders in group 1 after 4, 8 and 12 weeks, respectively. Group 3 response rates were 13.8% at week 4, 42.3% at week 8 and 73.8% at week 12. Differences between Tenoten and Placebo groups were significant only after 12 weeks (FT $p_{group\ 1/placebo}$=0.01, $p_{group\ 3/placebo}$=0.001).

Quality of life

The mean EQ-$_5$D-$_3$L scores increased to 5.84 ± 1.05 in the group 1, 5.71 ± 0.82 in group 3, 6.05 ± 1.07 in the Placebo group. Wilcoxon-Mann-Whitney test showed the superiority of Tenoten at a dosage of 8 tablets per day over Placebo (p=0.031).

CGI-EI score

The mean CGI-EI index was high for both Tenoten groups and differed from that in the Placebo group (Wilcoxon-Mann-Whitney test $p_{group\ 1/placebo}$=0.0021, $p_{group\ 3/placebo}$=0.0056). Thus, the efficacy of Tenoten in both doses was high.

Post-hoc analysis

Type of diagnosis did not affect mean HAM-A score dynamics in groups (mixed ANOVA $p_{\text{treatment x visit x diagnosis}}=0.23$).

Pairwise comparison showed the mean HAM-A score significantly differed between F43 and F45 patients diagnoses regardless of the group and visit (mixed ANOVA p=0.03). The mean score during the study was higher in patients with SD than in those with RSS and AjD (13.3±0.3 vs 11.9±0.5).

The dynamics of the mean HAM-A subscores for questions 1-4 didn't depend on the diagnosis. The mean subscore changes differed between treatment groups for questions 1 and 2 (mixed ANOVA $_{\text{treatment x visit}}$ p question 1=0.0008 and p question 2<0.0001).

The analysis of questions 5 and 6 showed the diagnosis affected the mean subscores (mixed ANOVA $_{\text{treatment x visit x diagnosis}}$ p question 5=0.002 and p question 6<0.0001). Scores in F43 patients in group 1 differed significantly from F45 ones in group 3 for question 5 and from F45 and F48 participants in group 3 for question 6 (mixed ANOVA $p_{\text{F43-F45}}$ question 5=0.0003 and $p_{\text{F43-F45}}$ question 6=0.00013, $p_{\text{F43-F48}}$ question 6=0.025).

The analysis of the relationship between diagnosis and somatic component subscores of HAM-A scale (questions 7-13) showed that the dynamics of somatic complaints was significantly different in groups regardless of ND type (ANOVA $p_{\text{treatment x visit}}=0.019$, $p_{\text{treatment x visit x diagnosis}}=0.92$). Nevertheless, the mean HAM-A somatic subscores in F43 patients differed significantly from other patients' scores in pairwise comparison ($p_{\text{F43-F45}}=0.0002$; $p_{\text{F43-F48}}=0.045$). The mean HAM-A 7-13 questions subscore in patients with RSS and AjD during the study was 2.84±0.13 and was lower than those in F45 and F48 groups (3.46±0.08 and 3.23±0.1, respectively). Patients with SD performed the highest mean HAM-A subscores in questions 8 (0.94±0.04; mixed ANOVA $p_{\text{F43-F45}}=0.0006$; $p_{\text{F45-F48}}=0.019$) and 10 (0.78±0.04; mixed ANOVA $p_{\text{F43-F45}}=0.0004$; $p_{\text{F45-F48}}=0.008$).

Patients' diagnosis didn't affect the placebo effect degree in combined Placebo group and mean HAM-A score dynamics in all diagnostic groups was similar (ANOVA $p_{\text{diagnosis x visit}}=0.87$).

3.2.4 Safety analysis

Investigators registered 46 AEs (10 in group 1, 18 in group 3, 18 in the Placebo group) in 37 patients (8 patients (6.3%) in group 1, 12 (9.2%) in group 3 and 17 (12.9%) in the Placebo group.

There were 6 (60%) and 14 (77.8%) mild AEs in group 1 and 3, respectively. There were 4 (40%) and 4 (22.2%) AEs of moderate severity in group 1 and 3, respectively. There were 12 (66.7%) and 6 (33.3%) AEs of mild and moderate severity registered in the Placebo group, respectively. No serious AEs were registered. The frequency of AEs did not differ between the groups (FT $p_{\text{group 1/placebo}}=0.092$; $p_{\text{group 3/placebo}}=0.432$; $p_{\text{group 1/group 3}}=0.487$).

The relationship of AEs with Tenoten was absent in 70% cases in group 1 and in 100% cases in group 3. The relationship was unlikely in 1 case and possible in 1 case in group 1. There were no AEs unlikely or possibly related with Tenoten in group 3. One AE had a probable association with the study drug in group 1. No AEs with a definite relationship with Tenoten administration were registered. The distribution of AEs by cause was significantly different between group 3 and Placebo group: the number of AEs related to placebo was higher than those related to the study drug in group 3.

Discussion

In this multicenter double-blind randomized CT, the efficacy of two dosage regimens of Tenoten in treatment of anxiety was shown. According to post-hoc data, the changes in anxious mood and feeling of tension depended on type of therapy and were not related to patients' diagnosis.

After 12 weeks response was found in 69.8% and 73.8% of patients administered Tenoten 4 and 8 tablets a day, respectively, and only in 53.9% in the Placebo group ($p_{\text{group1/placebo}}$ and $p_{\text{group3/placebo}}<0.05$). More than 95% of patients receiving 8 tablets of Tenoten per day presented with the anxiety symptoms remission after 12 weeks (p=0.007 vs Placebo). The quality of life improved in group 3 after 12 weeks.

The improvement of intellectual functions due to Tenoten treatment in dosage regimen 8 tablets per day was more pronounced in patients with RSS and AjD than in F45 patients and the reduction of depressive complaints was the greatest in F43 participants.

Tenoten administration led to more significant improvement in somatic complaints in F45 and F48 patients than in F43. Decrease of sensory and respiratory symptoms was the most prominent in patients with SD. The mean HAM-A somatic subscores were the lowest in F43 patients during the study.

We can assume that anxiety plays an important role in SD manifestation. The influence of therapy on anxiety pathological mechanisms leads to improvement of mental state in patients with SD and other NDs.

A comparatively high placebo effect was probably due to pre-treatment conversation with an investigator regarding the cause of underlying symptoms. We can assume the conversation partially affected the results by reducing the fear of somatic disease. These assumptions arose from the findings of the role of an interview and the therapeutic relationship between physician and patient during the treatment described in [31-32]. The high frequency of substance administration could have contributed to the placebo effect degree, and we made an effort to lower it by combining Placebo groups 2+4. It is worth noticing the placebo effect decreasing over time, while the effect of Tenoten increased at the end of the treatment.

Tenoten was well tolerated: only 20 patients in groups 1 and 3 experienced AEs. There was no difference in AEs frequency between groups. No AEs were serious and definitely related to Tenoten. Thus, the administration of Tenoten resulted in an anxiolytic effect with minimal AEs. This conclusion was in agreement with a preferable safety to efficacy ratio according to investigators' assessments.

The key trends for the anxiolytic therapy development were discussed [33]. First, a drug should influence several pathways of anxiety pathogenesis to avoid polypharmacy and second, it should demonstrate both high efficacy and tolerability. Possible drug interactions resulting in AEs that may occur with the antidepressants or benzodiazepines administration in patients receiving other medications was emphasized [13]. In accordance with these considerations, Tenoten seems to be a promising drug with anxiolytic properties. It was shown that almost 35% of all-time CTs of Tenoten were of high evidence level. No interaction between Tenoten and concomitant therapy was found [34]. In general, the safety profile of drug is consistent with the results of study.

Inclusion of patients with several psychiatric diseases and the absence of dose-frequency adjustment during the therapy are the main limitations. The study was mostly held in neurological centers. No special psychiatric interview methods were used to establish a diagnosis. In addition, we observed relatively high placebo effect, the possible cause of which was discussed above.

The study had some advantages contributing to bias control: multicenter double-blind randomized design, a sufficient number of participants, and 4-month washout period before the onset of study treatment. A training session was held to master the investigators on CT procedures. Trial protocol was posted at clinicaltrials.gov prior to the beginning of study and results were added immediately after the analysis was submitted to regulatory authorities. Altogether, these facts provide evidence of the CT data reliability without the risk of biases.

Further long-term studies with the follow-up period should be performed to apply these results to a broader population.

Other information

The trial has been registered at clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT03036293) in 30/01/2017.

Trial protocol can be assessed at clinicaltrials.gov NCT03036293.

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Figures

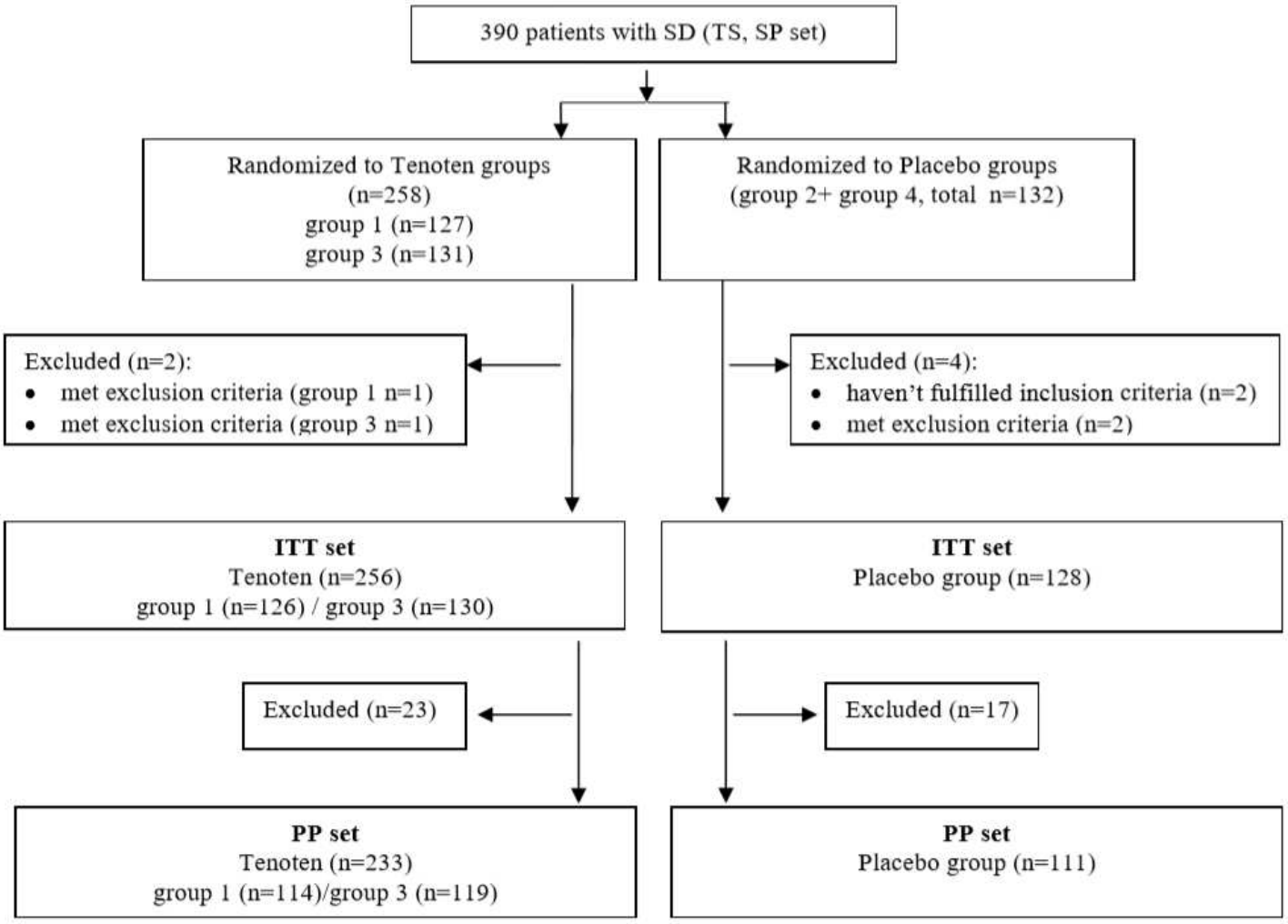

Figure 1

Patient flow diagram Note: TS–total set, SP–Safety population set.

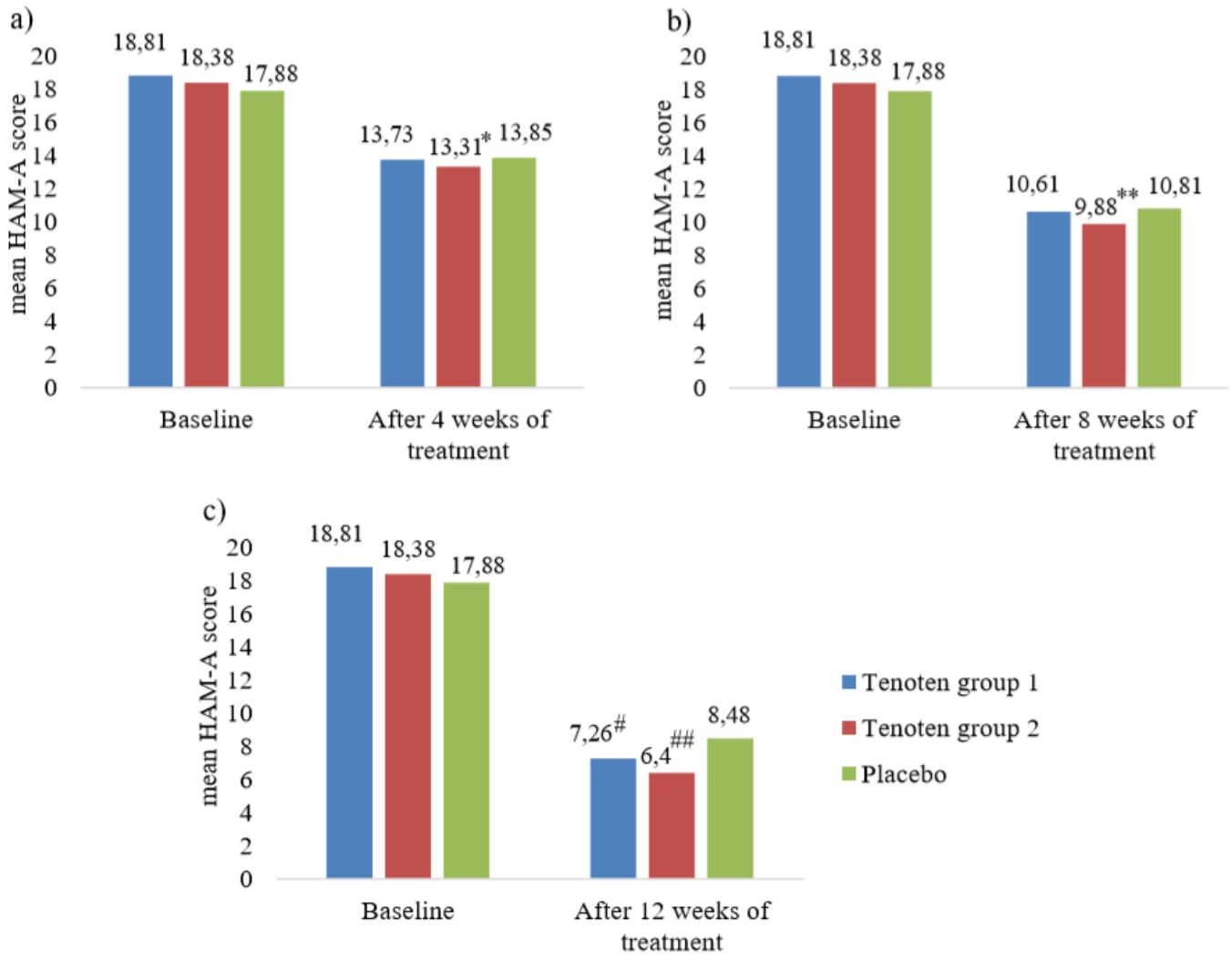

Figure 2

The change in the mean HAM-A score after 4 (a), 8 (b), 12 (c) weeks Note: ITT-set. **p=0.027 vs Placebo; *p=0.044 vs Placebo; #p=0.0155 vs Placebo, t-test; ##p<0.0001 vs Placebo, t-test.

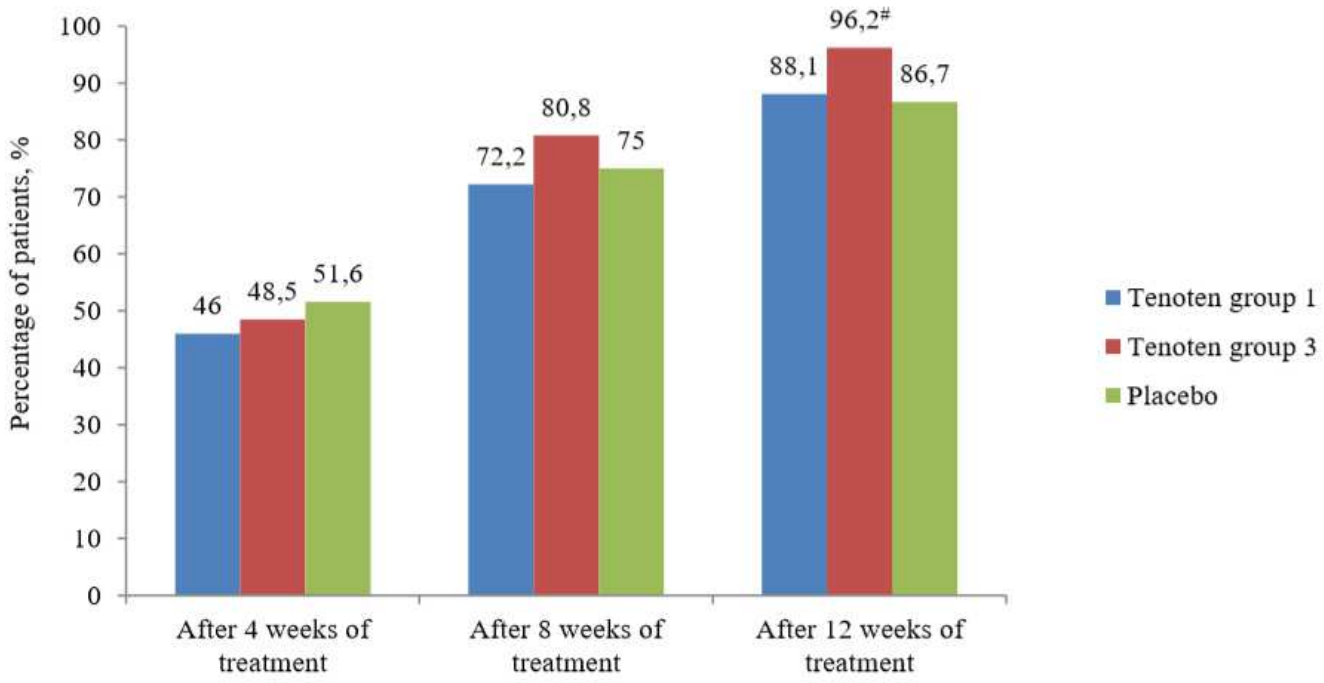

Figure 3

The percentage of patients with remission of anxiety symptoms after 4, 8, 12 weeks Note: ITT-set. #p=0.007 vs Placebo.