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UNIVERSITĀTE

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**POSTTRAUMATIC STRESS DISORDER
AND OXIDATIVE STRESS PARAMETERS
ASSESSMENT AND CORRECTION
BY MEANS OF ANTIOXIDANTS
IN CONTINGENT OF
INTERNATIONAL OPERATIONS**

Summary of the dissertation
Scientific discipline – Health Care

Rīga, 2012

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ABBREVIATIONS USED IN THE WORK

AO	- Antioxidants;
AOS	- Antioxidative system;
BL	- Baseline;
CIO	- The Contingent of International Operations;
CNS	- Central Nervous System;
DSM	- The Diagnostic and Statistical Manual of Mental Disorders, IV ed;
ET	- Excitotoxicity;
GLU	- Glutamate;
GPx	- Glutathione peroxidase;
IR	- Incidence Rate;
LP	- Lipid peroxidation;
MDA	- Malondialdehyde;
NADPH	- Nicotinamide Adenine Dinucleotide Phosphate;
NADP+	- Oxidized NADPH;
NMDA	- <i>N</i> -methyl <i>D</i> -aspartate;
OS	- Oxidative stress;
PI	- Placebo;
PCL	- Posttraumatic Stress Disorder Checklist;
PCL-M	- Posttraumatic Stress Disorder Checklist, Military version;
PR	- Prevalence Rate;
PSM	- Peace Support Mission;
PTSD	- Posttraumatic Stress Disorder;
RR	- Response Rate;
RSU	- Riga Stradins university;
Se	- Selenium;
SOD	- Superoxide Dismutase;
UK	- The United Kingdom;
USA	- The United States of America.

INTRODUCTION

It is known that combats - The Contingent of International Operations (CIO) is a subject for several severe factors, that can lead to acute stress. In some cases it can also cause Post-traumatic stress syndrome (PTSD).

After deploying from missions a complex rehabilitation is necessary to help CIO to return to „civil“ life conditions. In the case of PTSS development warrior practically becomes a disabled person. PTSS changes the quality of life to a significantly lower level, worsens forecast and progress of a comorbid condition (vegetative pain, emotional disorder and chronic pain). Asocial behaviour, problem gambling, alcoholism and drug abuse are often observed. Family, children and relatives are also involved in the problem. This problem is of a medically social kind and is up to date in all the countries whose armed forces take part Peace Support Mission (PSM).

The basis of PTSD pathogenesis is hyperactivation of neurones under stress factors influence, so-called excitotoxicity (ET).

ET develops in response to stressors; it is currently followed by oxidative stress (OS) because of accumulation of free radicals. Neuronal membrane phospholipids are particularly vulnerable to oxidative damage that results in signal transmission mechanism alteration and PTSD development. One can find literature data on this problem, but these are incomplete to explain PTSD origin.

1. ACTUALITY OF THE STUDY

Traditionally stress is defined as body homeostasis changes because of various internal and external factors. In the last few years a new definition has appeared, in contrary to the classic doctrine of H. Selye [1] that talks about different stressors influence over body and it's neurohumoral reaction particularities [2, 3].

It is known that The Contingent of the International Operations can be a subject to various extreme factors, which may cause Posttraumatic Stress Disorder (PTSD). According to the International Classification of Diseases IDC -10 PTSD is defined as "neurotic, associated with stress disorder, which can develop after one or more traumatic events, threats or major physical damage, can cause diffuse severe emotional troubles it is a set of symptoms that is faced by traumatic stress survivors [4, 5].

Common PTSD symptoms are found in compound psychophysiological hypertrophic reactions: intrusive exposures to a traumatic event, mirages, hallucinations, constant avoidance of stimuli related with trauma, and general emotional senselessness, which occur throughout no less than a month. Specified by the diagnostic standard DSM-IV, PTSD clinical identification is done utilizing clinical question sheet PCL-M. PCL-M question sheet numbers 17 components, it is advised for work as a verifiable diagnostic implement for inspection of patients with PTSD and patients of PTSD risk group [6-10].

In accordance with present data PTSD level before Peace Support Mission is 2.4-9.3% in the American Contingent of the International Operations [11-12] and 2.4% in the British Contingent of the International Operations [13]. PTSD level subsequently Peace Support Mission is 11.2% in the American

Contingent of the International Operations 11,2% [12] and 4.0-9.5% in the British Contingent of the International Operations [13, 14]. There is no medical data about PTSD level in the Latvian Contingent of the International Operations available.

PTSD pathophysiology and pathogenesis is linked with excitotoxicity. Excitotoxicity is the pathological process by means of which neurons are harmed caused by the excitatory neurotransmitter glutamate hyper activations [15]. Glial cells, as well as harmed neurons, turn into the starting point of the exceedingly high glutamate quantity, as glutamate releases by way of exocytosis [16]. Atypically risen glutamate amount constrains *N*-methyl *D*-aspartate (NMDA) receptors: enormous calcium ions amount [Ca²⁺] goes into the cell. Intracellular [Ca²⁺] influx sets going several enzymes, incorporating phospholipases, endonucleases, proteases and triggers oxidation processes [17]. Excitotoxicity-operated microglia cells create cytokines that are possibly neurotoxic, protease, tumour necrosis elements, superoxide anions and ligands for NMDA-glutamate system. Those are the origins of chronic oxidative processes that cause Oxidative stress. [18]

Oxidative stress is a balance shift in the direction of the prooxidants in between the pro- and antioxidants (AO). State which usually leads to cell damage, individual organ and organism itself, impairment. Antioxidative system of organism is the one, which can both regulate and protect cells and organs against oxidative damage. Normally, AOS is able to ensure both cell entirety and organs and their systems normal physiological functioning. In the mean time, there are some conditions in the organism or in the environment around it, in which AOS is not able to fully fulfil proper protection measures. This improper for organism pro-/antioxidant balance situation change is called oxidative stress (OS). OS can combine all possible kinds of stress, e.g.: physical and chemical (temperature changes, ultraviolet radiation, radiation, chemical agents, noise, vibration, electromagnetic radiation etc.) as well as

psycho-emotional (pain, fear, emotional stress, etc.).

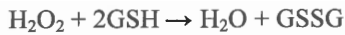
Phospholipids of neuronal membrane are especially vulnerable to oxidative damage by changing signal transduction mechanism and, moreover, information processing disorders. Effects of hyperoxidation, oxidative and carbonyl stresses influence on the cerebral suppression and its relation to brain degeneration with respect of neuronal functions researches are of considerable interest and significance.

Oxidative stress intensity is mostly evaluated marking the level of Malondialdehyde (MDA) plasma. One of the most regularly used lipid peroxidation direct indicators is unsaturated carbonyl MDA [19, 20, 21].

MDA is a normally present metabolic polyunsaturated fat degradation (lipid peroxidation) and prostaglandin biosynthesis by-product and is mutagenic and carcinogenic. In the result of free radical damage to lipids, MDA in reaction with DNA turns into deoxyguanosine and deoxyadenosine and sets free as transitional product of formaldehyde [21]. At low concentrations formaldehyde induces misfolding of proteins with a high cytotoxic aggregation. Breaking the homeostasis that links excitatory and inhibitory neurons, MDA can weaken cerebral function working as a metabolic product in the course of oxidative stress. MDA has a rather longer half-life since it is less active than other free radical; consequently, it has an ability to spread from the generation spots to other locations, producing following oxidative stress.

The GPx main biological function is protecting body from oxidative damage. GPx biochemical function is reducing hydrogen peroxide in alcohol, as well as reducing free hydrogen in water [22]. GPx links very active hydroxyl metabolite radical without forming unwanted toxic products. In cells GPx is present in high concentrations and it has defining role in ensuring the reduced state.

GPx kills H_2O_2 , by means of glutathione (tripeptide):



GPx catalyzes fatty acids hydroperoxides splitting:



As antioxidant GPx is particularly important for the brain, as it is very sensitive to free radicals presence [23]. The insufficient GPx amount and/or activity complicate oxidative stress [24].

At the same time, a lot of studies do not provide an exhaustive response to the questions connected with stress during SOK missions.

Researches in this area are complicated by the fact that AO has to be used as part of the treatment, not to mention in the field conditions, thus considerably complicating the analysis of the obtained data.

Body AO protection disorders are fundamental features in different critical nature states. It is known that AO therapy positively influences results of the treatment, reduces the length of the hospital treatment [25]. The fact that AO efficiency effect reveals after a certain period of time, possibly is identified with development of the complications and expressed blood vessel functional disorder. Many authors note that additional AO entering is indicated for the treatment of the patients in intensive care units. The duration of the treatment needed to achieve the effect has to be no less than 3 weeks [26, 27].

Out of many AO used, until now, only Selenium (Se) has shown to have positive effect on patients in critical conditions. High Se doses can reduce lethality for patients with sepsis [28]. According to AO status indicators the course of the disease and possible outcome can be predicted [29].

Heterogeneity of earlier researches of gender, race, age, nutrition, different deployment factors and stressors creates problems in analysing those processes [30, 31].

Mostly PTSD studies are retrospective or prospective “*ex post facto*”.

Most study results are only theoretical and do not offer real solutions to prevent/reduce the likelihood of developing PTSD in the risk group.

There is no scientific data available on presence of PTSS in Latvian SOK.

It is problematic to use different medications to prevent PTSD in mission conditions. Taking into account specific way of using medication in such conditions, it has to respond to the following requirements:

1. It must be uttermost physiological, thus identical to processes on-going in the body. Non-physiological medication can provoke unpredictable behaviour results, which will suspend natural characteristics of body functioning.
2. There should not be any reactions to intellectual, vegetative and motoric sphere that can sufficiently interrupt the accomplishment of SOK professional obligations.
3. Medication has to be pill-shaped, thus ensuring possibility of SOK using it independently.
4. Package and storage conditions of the medication must be at appropriate temperature, light and moisture modes in relevant mission.

2. DESCRIPTION OF THE STUDY

2.1. Aim of the study

To study Incidence and Prevalence of PTSD, some of the laboratory determinable OS parameters changes of patients with the risk of PTSD developing, as well as possibility to make corrections with using AO on the background.

2.2. Objectives of the study

1. At different stages of PSM to determine some pro- and antioxidative indexes that feature PTSD incidence.
2. Find out if (and to what extent) there is intercorrelation between OS and PTSD.
3. Investigate, whether AO supplementation influences PTSD and OS parameters.

2.3. Hypothesis

1. There is reliable intercorrelation between OS parameters, PTSD incidence and PTSD prevalence.
2. The use of AO during PSM allows to reduce OS and consequently to minimize PTSD incidence in SOK.

2.4. The scientific novelty

The first prospective PTSD induced by war factors study in statistically

homogeneous PTSD risk group.

The first OS and PTSD parameters correlation assessment.

The first study of Se advances to reduce PTSD incidence in a risk group.

The first wide-scaled research in Latvian Military medicine and Psychosomatic medicine branches.

2.5. Work structure and volume

Structure of the dissertation corresponds to the above formulated research objectives. Work is written in Latvian on 113 pages. It has 13 parts: Abstract in Latvian and English, Introduction, Actuality of the Study, Literature review, Study planning, Methodology, Study results, Discussion, Conclusions, Acknowledgements, References, List of the authors' publications, Study approbation, Supplementations. Text also includes 13 tables, 18 pictures and 5 supplementations. Literature list consists of 277 literature references.

3. MATERIALS AND METHODS

Prospective placebo-controlled randomized study has been successfully completed in Riga Stradins University (RSU) Psychosomatic Medicine and Psychotherapy department (Riga, Latvia) in close cooperation with RSU Biochemical laboratory (Riga, Latvia), RSU Internal Diseases department (Riga, Latvia) and National Armed Forces Medical Support Centre (Riga, Latvia).

The protocol of study, the protocol of agreement, and the protocol of participation corresponded to the Helsinki declaration on principles of humanity in medicine and approved by RSU Ethics committee – E-9 (2), 17.12.2009.

3.1. Target population, grouping of the population

We took for our research the participants - PTSD risk group, group with highest possible level of homogeneity to avoid difficulties in results rating and interpreting. Totally 143 participants — Latvian CIO, regular military personnel, males, Europeans, average age of 27.4, before and after the same Peace Support Mission in Afghanistan (6 months), with the same duty tasks during the mission were examined. For grouping of the population see Table 3.1.

“Se” group received 200 mcg (2 tablets) of organic Se per day during mission, “PI” group received (2 tablets) of PI per day during mission.

Table 3.1.

Grouping of the population:

Group	Number of CIO	2 months before PSM	PSM	After PSM
BL	143*	Biochemistry, surveys	-	-
Se	67	Biochemistry, surveys	Se	Biochemistry, surveys
PI	37	Biochemistry, surveys	PI	Biochemistry, surveys

*including Se and PI group participants

3.2. Data collection methods

3.2.1. Clinical examination – PTSD diagnostics:

PTSD examination was done according to the following schedule:

1. 2 months before PSM outgo;
2. Immediately after PSM comeback;

Clinical examination was made according to the diagnostic pattern DSM-IV [6]. The following diagnostic criteria were assessed:

Criterion A: stressor - The person has been exposed to a traumatic event in which both of the following have been present:

- 1.The person has experienced, witnessed, or been confronted with an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others;
- 2.The person's response involved intense fear, helplessness, or horror.

Criterion B: intrusive recollection - The traumatic event is persistently re-experienced in at least one of the following ways:

- 1.Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions;

2.Recurrent distressing dreams of the event;

3.Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur upon awakening or when intoxicated);

4.Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

5.Physiologic reactivity upon exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

Criterion C: avoidant/numbing - Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by at least three of the following:

1.Efforts to avoid thoughts, feelings, or conversations associated with the trauma;

2.Efforts to avoid activities, places, or people that arouse recollections of the trauma;

3.Inability to recall an important aspect of the trauma;

4.Markedly diminished interest or participation in significant activities;

5.Feeling of detachment or estrangement from others;

6.Restricted range of affect (e.g., unable to have loving feelings);

7.Sense of foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span).

Criterion D: hyper-arousal - Persistent symptoms of increasing arousal (not present before the trauma), indicated by at least two of the following:

1.Difficulty falling or staying asleep;

2.Irritability or outbursts of anger;

3.Difficulty concentrating;

4.Hyper-vigilance;

5.Exaggerated startle response;

Criterion E: duration - Duration of the disturbance (symptoms in B, C, and D) is more than one month.

Criterion F: functional significance - The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Worldwide-recognized questionnaire PCL-M was used for objective PTSD evaluation [7]. The PTSD Checklist (PCL) is a 17-item self-report measure of PTSD symptoms corresponding to DSM-IV. Respondents are asked about certain troubles during last month; the answers are evaluated by 5-point scale. PCL questionnaire was worked out at PTSD National Centre, USA in 1993. The PCL questionnaire has a variety of purposes, including screening individuals for PTSD, diagnosing PTSD, monitoring symptom change during and after treatment. There are three versions of the PCL questionnaire: PCL-C (civilian), PCL-M (military) and PCL-S (specific). PCL-M questionnaire asks about symptoms in response to "stressful military experiences" and used for active service members and veterans. Participants of a research study can complete the PCL-M questionnaire in approximately 5-10 minutes. PCL-M questionnaire's interpretation should be completed by a clinician [8, 9, 10]. We used the valid Latvian language PCL-M questionnaire [32].

Diagnostics procedure:

1. Determining whether an individual meets DSM-IV symptom criteria, i.e., at least 1 B item (questions 1-5), 3 C items (questions 6-12), and at least 2 D items (questions 13-17). Symptoms rated as "Moderately" or above (responses 3 through 5) are counted as present.
2. Determining whether the total severity score exceeds a given cut point.

Combining methods (1) and (2) to ensure that an individual has sufficient severity as well as the necessary pattern of symptoms required by the

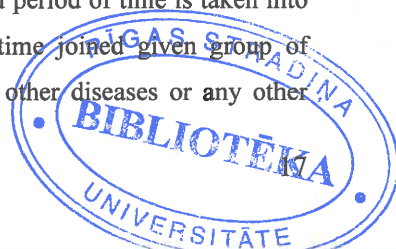
DSM. A higher cutoff should be considered when attempting to make a definitive diagnosis or to minimize false positives, score of 50 is considered to be positive PTSD in military populations [8].

Based on the acquired data the main epidemiological case frequency indexes were acquired [33]:

1) Morbidity, which is measured by Prevalence Rate (PR). PR is number of participants that suffer from the disease in the specific moment / quantity of members in the given group in the mean time. PR – such part of members, that suffers from the given disease at the current point of time. As any proportion it is without any size scale and cannot be less than 0 or greater than 1.

2) Incidence Rate (IR) – number of cases of the disease in the group of participants at some specific point of time / each person's sum of the duration of a disease risk in the given participants group. The sum of the duration of a disease risk denominator is often measured in years and called human-years, human-time or risk time. For each person in the given group of participants the risk of disease is time, during which this person belongs to the studies group and does not suffer given disease, thus there is a health risk getting the disease. These periods of risk are being summed for each given group of participants member.

In fact, the total quantity that goes from healthy condition to disease condition in a given period of time consists of three factor derivatives: size of the given group of participants, time duration and “level of morbidity”, that is typical for the given group members. Exactly with this “level of morbidity” IR is being measured. Thus, IR is obtained by dividing the number of cases with derivation of amount of group participants and length of the time period, which equals with every group member amount of the time period. Dividing the number of disease cases with risk time, the studied period of time is taken into account. Individuals, that in a given period of time joined given group of participants or left because of migration, deaths, other diseases or any other



reason are also taken into account. In that way, including disease risk time factor in the formula, we take into account the main mistakes that appear from the calculation of the cumulative incidence of indicators. Infected were excluded from the study, because their disease risk exists no longer. Approach to the overall amount of risk time is usually considered as satisfactory result, that can be obtained by multiplying the average number of group participants during the study with it's duration. Such approximation can be also used for the given group number of participants in the middle of the study. IR is not a proportion, because the counter shows the number of diseased cases, but denominator – human-time number of units. Size of IR under any circumstances can not be less than 0 and it has no upper limit [34].

3.2.2. Clinical examination – blood tests:

Blood samples for biochemistry tests were taken following the schedule:

1. Two months before the mission;
2. Immediately after the return from the mission.

In all groups (following the schedule) it was obtained:

1. The amount of Se in blood plasma (fluometric method);
2. Activity of antioxidative enzymes (Cu,Zn-SOD, GPx) (Radox diagnostic kits RanSOD, RanSEL; spectrofotometric methods);
3. Intensity of lipid peroxidation is measured after metabolism interproducts (MDA) content in the blood by ELISA method.

Activity of antioxidant enzymes - Glutathione peroxidase (GPx) and intensity of lipid peroxidation - Malondialdehyde (MDA) as Oxidative stress indicators in blood were determined. Blood samples were taken from all individuals in the morning at 8.00 (before meal). Venous blood was collected into a vacutainer (Venoject II BD) containing lithium/heparin as anticoagulant. The reaction of selenium (VI) with 2,3-diaminonaphthalene (DAN) to form a

fluorescent Se-DAN heterocyclic compound is the basic of the fluorimetric method for Se determination. Fluorescence degree is measured at 369 nm and emission of 518 nm at maximal level of 515-518 [35].

Antioxidant enzymes (GPx and SOD) activity was measured to assess blood AO defence as well as MDA was measured to assess intensity of LP. Activity of GPx was determined in heparinized whole blood by the method of Paglia and Valentine [36] using commercial tests manufactured by Randox Laboratories (UK, Antrium) in a RX Daytona analyzer. GPx catalyzes the oxidation of Glutathione (GSH) by Cumene Hydroperoxide. In the presence of Glutathione Reductase and Nicotinamide Adenine Dinucleotide Phosphate (NADPH) the Oxidized Glutathione (GSSG) is immediately converted to the reduced form with a concomitant oxidation of NADPH to the Oxidized NADPH (NADP⁺). The decrease in absorbance at 340 nm is measured. In the presence of Hydroperoxide GPx catalyzes oxidation of GSH to GSSG. The latter (GSSG) undergoes NADPH-dependent reduction to GSH catalyzed by Glutathione Reductase. This reaction is accompanied by NADPH oxidation to NADP⁺. Thus, activity of GPx corresponds to the decrease in absorbance at 340 nm induced by NADPH oxidation and one unit of enzyme activity is defined as the enzyme content required for oxidation of 1.0 μmol of NADPH per 1 min at 340 nm and 37°C.

SOD activity is measured in heparanized whole blood, after *Suttle and McMurray*, using diagnostical kits ar diagnostikas Randox Laboratories Ltd. (UK, Antrium), and RX Daytona analyzer. The method employs xanthine and xanthine oxidase to generate superoxide radicals which react with 2-(4-iodophenyl)-3-(4-nitrophenol)-5-phenyltetrazolium chloride, to form a red formazan dye. The SOD activity is measured by the degree of inhibition of this reaction [37, 38, 39, 40].

Plasma was prepared by centrifugation and used to measure MDA by the colorimetric method of Esterbauer and Cheesman [41] using Lipids

peroxidation microplate based assay kit (Oxford biomedical research, #FR22). The principle mechanism of the assay is based on the reaction of a chromogenic reagent, N-methyl-2-phenylindole (R1), with MDA at 45°C. One molecule of MDA reacts with 2 molecules of reagent R1 to yield a stable chromophore with maximal absorbance at 586 nm.

3.3. Study design

Prospective study:

5 months	Fulfilled observe of the literature and data collection
20 months	Clinical studies
5 months	Data summarizing
18 months	Analysis of the results and presentation

3.4. Statistical analysis

Personal computer application SPSS 20.0 was used to obtain qualitative and quantitative processing of data statistics.

Statistical significance of mean values was evaluated by means of the Paired-samples T-test. Interrelationship between parameters was evaluated by the Wilcoxon correlation coefficient; as well as regressive and correlation analysis by Spearman un Pearson were made. Comparing the variational series differences were considered as statistically significant at $p < 0.05$.

3.5. Material-technical support

Promotional work was done with financial support of European Social Fund “Support for doctorates in acquiring study programme and obtaining scientific degree in Riga Stradins University” (Project agreement Nr.

2009/0147/ 1DP/1.1.2.1.2/09/IPIA/VIAA/009).

Study was done with support of Latvian National Armed Forces Medical Support Centre.

Se medication *SelenoPrecise*[®] from Denmark company *Pharma Nord ApS* was received in the form of humanitarian aid, it contains high-quality organic Se and year 1999 was registered as a food supplement in Latvian Food Centre (Resolution N.141).

Biochemical analysis was completed in certified RSU Biochemistry laboratory.

4. RESULTS

1. On the various PSM stages pro- and AO describing indicators in SOK blood and PTSD describing indicators were defined. After supplementation with organic selenium, 2 tablets (200 mcg) *per os* daily, regardless of meals during the whole mission time (PSM, 6 months), the following results have been obtained (see Tables 4.1-4.6).

1. Se plasma level in Se group (103.24 $\mu\text{g/L}$) has increased after mission for 21.10% compared with BL rate (85.25 $\mu\text{g/L}$) and increased for 4.15% - in Pl group (88.79 $\mu\text{g/L}$);
2. GPx activity in Se group (8440.30 U/L) has increased for 4.69% compared with BL rate (8061.98 U/L) and reduced for 9.35 % - in Pl group (7308.31 U/L);
3. MDA level in Se group (2.4119 μM) has reduced for 5.72% compared with rate in BL group (2.5582 μM) and increased for 24.19% - in Pl group (3.1815 μM);
4. SOD activity in Se group (1424.88 U/gHB) has reduced for 1.68% compared with BL rate (1449.20 U/gHB) and increased for 2.89% - in Pl group (1491.03 U/gHB);
5. PTSD symptomatic severity rate - PTSD symptoms ranking rate in Se group (21.56 PCL-M questionnaire points) has reduced for 5.85% compared with rate in BL group (22.90 points) and increased for 14.45% - in Pl group (26.21 points), see Table 4.1.;
6. PTSD PR rate after PSM – in Se group 0.0476 has reduced to 46.03% compared with rate 0.0882 (Pl group) and to 49.89...57.50% compared with available literature data 0.095 – 0.112 (UK and USA CIO) [12, 13,14], see Table 4.2..

Table 4.1.

One-Sample Kolmogorov-Smirnov Test

Parameters	N ¹	Normal Parameters ^{a,b}		Most Extreme Differences			K-S Z ²	AS ³
		Mean	Std. Deviation	Abs.	Pos.	Neg.		
GPx, BL, U/L	106	8061.98	1369.116	.061	.061	-.048	.623	.832
GPx, Se, U/L	33	8440.30	1839.952	.102	.102	-.062	.583	.886
GPx, Pl, U/L	29	7308.31	1129.871	.123	.092	-.123	.661	.775
SOD, BL, U/gHB	106	1449.20	137.173	.049	.039	-.049	.503	.962
SOD, Se, U/gHB	33	1424.88	103.449	.098	.098	-.044	.563	.909
SOD, Pl, U/gHB	29	1491.03	121.739	.219	.219	-.116	1.181	.123
MDA, BL, μ M	49	2.5582	.63475	.067	.067	-.057	.467	.981
MDA, Se, μ M	32	2.4119	.60997	.122	.122	-.080	.690	.728
MDA, Pl, μ M	13	3.1815	.68560	.125	.125	-.092	.450	.987
Se, BL, μ g/L	106	85.25	14.419	.073	.073	-.053	.750	.628
Se, Se, μ g/L	33	103.24	14.324	.105	.105	-.063	.601	.862
Se, Pl, μ g/L	29	88.79	11.047	.099	.099	-.062	.532	.939
PCL, BL, points	140	22.90	6.734	.190	.149	-.190	2.254	.000
PCL, Se, points	63	21.56	6.428	.239	.234	-.239	1.899	.001
PCL, Pl, points	34	26.21	9.247	.201	.201	-.160	1.172	.128
PTSD, BL, PR+1	140	1.04	.186	.540	.540	-.424	6.393	.000
PTSD, Se, PR+1	63	1.05	.215	.540	.540	-.412	4.287	.000
PTSD, Pl, PR+1	34	1.09	.288	.532	.532	-.380	3.103	.000

a. Test distribution is Normal.

b. Calculated from data.

¹No. of CIO

²Kolmogorov-Smirnov Z

³Asymp. Sig. (2-tailed)

Table 4.2.

PTSD prevalence in CIO

CIO group	No. of CIO	Mean age	RR ¹	PR ²	IR ³
PTSD, BL gr.	143	27.36	97.90	0.0357	-
PTSD, Se gr.	63	26.60	94.03	0.0476	0.0952
PTSD, Pl gr.	34	26.20	91.89	0.0882	0.1765

¹ Response rate² Prevalence rate³ Incidence rate

Table 4.3

OS and PTSD rates after PSM

Parameters	Se group	Pl group	Se gr. / Pl gr., %
MDA, μM	2.4119	3.1815	75.81
Se, $\mu\text{g/L}$	103.24	88.79	116.27
PTSD, PR ¹	0.0476	0.0882	53.97

¹ Prevalence rate

Table 4.4.

Descriptive statistics in BL group

PTSD, BL gr., cases		N	Min.	Max.	Average	Std. deviation
Neg	GPx, BL, U/L	101	4587	11324	8029.64	1349.184
	SOD, BL, U/gHB	101	1102	1742	1448.92	138.787
	MDA, BL, μM	44	1.25	3.72	2.5475	.63131
	Se, BL, $\mu\text{g/L}$	101	57	135	85.52	14.513
	PCL, BL, points	135	17	39	21.97	4.692
	Valid results	44				
Pos	GPx, BL, U/L	5	6820	11218	8715.20	1771.396
	SOD, BL, U/gHB	5	1349	1612	1454.89	111.125
	MDA, BL, μM	5	1.86	3.79	2.6520	.73367
	Se, BL, $\mu\text{g/L}$	5	66	94	79.60	12.260
	PCL, BL, points	5	42	52	48.00	4.637
	Valid results	5				

Table 4.5

Descriptive statistics in Se group

PTSD, Se gr., cases		N	Min.	Max.	Average	Std. deviation
Neg	GPx, Se, U/L	30	4606	13105	8227.10	1758.766
	SOD, Se, U/gHB	30	1248	1678	1428.03	107.434
	MDA, Se, μ M	29	1.48	4.49	2.3524	.58621
	Se, Se, μ g/L	30	79	139	104.87	13.925
	PCL, Se, points	60	17	36	20.48	4.316
	Valid results	29				
Pos	GPx, Se, U/L	3	9049	11606	10572.33	1346.994
	SOD, Se, U/gHB	3	1339	1424	1393.33	47.184
	MDA, Se, μ M	3	2.44	3.69	2.9867	.63956
	Se, Se, μ g/L	3	81	93	87.00	6.000
	PCL, Se, points	3	41	46	43.00	2.646
	Valid results	3				

Table 4.6

Descriptive statistics in Pl group

PTSD, Pl gr., cases		N	Min.	Max.	Average	Std. deviation
Neg	GPx, Pl, U/L	26	4874	9503	7411.69	1065.002
	SOD, Pl, U/gHB	26	1315	1821	1479.54	118.677
	MDA, Pl, μ M	10	2.14	3.83	3.0540	.54443
	Se, Pl, μ g/L	26	75	116	90.42	10.152
	PCL, Pl, points	31	17	36	23.90	5.262
	Valid results	10				
Pos	GPx, Pl, U/L	3	4799	7851	6412.33	1533.479
	SOD, Pl, U/gHB	3	1456	1693	1590.67	121.763
	MDA, Pl, μ M	3	2.41	4.45	3.6067	1.06491
	Se, Pl, μ g/L	3	67	85	74.67	9.292
	PCL, Pl, points	3	42	58	50.00	8.000
	Valid results	3				

5. DISCUSSION

Oxidation processes prevalence accompanied by antioxidant defence system failure leads to the development of oxidative stress that is one of the universal mechanisms of tissue damage. Enzymatic activity of antioxidant systems (catalase, glutathione peroxidase) in the brain is significantly lower than in other tissues. A free radical is a particle of the molecule containing unpaired electron at an orbit. Oxygen radicals (having oxygen with an unpaired electron) are superoxide anion and hydroxyl radical. These are extremely aggressive. Glutamate is a substrate that is able to support maximal H_2O_2 production rates by means of $[Ca^{2+}]$ mediated excitotoxicity. Full reduction of the oxygen molecule to water requires four electrons: first during the transfer of superoxide radical is formed, when moving the second - hydrogen peroxide, the most toxic and reactive hydroxyl radical is the result of third transfer and fourth transfer due to which a water molecule is formed. Scavengers of free radicals are located in the cytoplasm or on cell membranes, these are mainly substances with low molecular weight: superoxide dismutase, glutathione, glutathione peroxidase, catalase, ceruloplasmin, vitamin A, vitamin E, vitamin C, vitamin K, flavonoids, coumarins.

Lipid peroxidation plays a crucial role in brain injury. The brain contains a large amount of lipids (50% in a dry matter), most of them appear to be unsaturated becoming substrates for lipid peroxidation. Phospholipids make up over half of all lipids of nervous tissue. Fatty acid and phospholipids determine structural features and function of cell membranes, contribute to its better penetration, and provide the density. Lipid peroxidation of any intensity leads to functional brain disorder [42, 43]. Moreover, it could become a cause of structural and morphological alterations, and degeneration processes. PTSD is a severe anxiety disorder that develops beyond experiencing or witnessing a traumatic event [1]. The PTSD patients also note problems in cognition

(memory, attention), somatic concerns (headache), and affective dysregulation (impulsivity, irritability, anxiety), particularly in the time period shortly after the traumatic event (whether psychological, biomechanical, or both) [6].

Biochemical mechanism with elevated levels of Oxidative stress parameters has been proposed to explain the etiology of PTSD (common etiology of posttraumatic stress disorder, fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity) [44, 45, 46].

Alterations of glutamatergic and NMDA receptor functions play a role in the etiology of PTSD in humans [47]. Glutamate plays a crucial role in anxiety-related behaviour. Some clinical studies have observed a marked increasing of cerebral neurotransmitter glutamate in PTSD [48, 49, 50]. Stress increases glutamate release, which is recognized as an important mediator of excitotoxicity. Since a prominent role of glutamate –related excitotoxicity followed by neuronal damage, glutamatergic pathways may have an important role in stress-related hippocampal degenerative pathology and cognitive deficits seen in patients with PTSD [51]. Brain imaging studies revealed a marked reduction in hippocampal volume [52]. Such morphological alterations appear to become positively correlated with the degree of cognitive deficit noted in these patients. PTSD-induced Oxidative stress has been proposed in this apparent atrophy. Recent clinical studies confirmed the involvement of neurodegenerative pathology in the PTSD pathogenesis. Particularly neurochemically-mediated damage could conceivably interact with neurohumoral dysregulation.

Pathophysiology and pathogenesis of PTSD is associated with the overstimulation processes predominance. GLU seems to be the most significant neurotransmitter; small GLU amounts stimulate spinal, cortical, cerebellar neurons, other CNS structures. Prolonged stress results in continued impact of stressful neurons stimulation; the level of glutamate is not being reduced, so that a pathological overactivation of N-methyl-D-aspartate (NMDA) receptors is present. Exceed glutamate release is followed by postsynaptic receptors

overstimulation and leads to its dysfunction. Glutamate is released in the synaptic structures and interacts in the postsynaptic membrane with the glutamate-sensitive N-methyl-D-aspartate (NMDA) post-synaptic membrane receptors. Experimental GLU injection into some cerebral regions (including amygdala, striatum) resulted in cramps and depression even then, when GLU amount was apparently the same like normal one [53].

Of special consideration is fact, that these structures are responsible for memory and cognition, also sensory function, which need particular synaptic plasticity [54]. These structures represent low epileptic level, high excitation. NMDA receptors overactivation leads to its dysfunction, so that high blood glutamate can cause injury and even neuronal death. Excessive stimulation NMDA-receptors due to high glutamate level is called "toxicity of excitatory amino acids," or ET.

Exciting amino acids (GLU, aspartate) stimulate neuronal NMDA-receptors, that control calcium channels. NMDA receptors overactivation results in calcium ions $[Ca^{2+}]$ massive influx into the cells. Severe increase in $[Ca^{2+}]$ ions contents leads to a number of intracellular enzyme systems (proteases, endonucleases, lipases, phospholipases) overactivation, initiating a cascade of catabolic and cytodenerative processes and lysis of cells [2]. Not only neurons but also glial cells possess a mechanism of glutamate release by exocytosis (discharge of the intracellular content). As a result of exocytosis, a sharp increase in extracellular glutamate, further overactivation of glutamate receptors and the subsequent series of neurodegenerative cell reactions are initiated. Phospholipase influences phospholipid damage within mitochondrial membranes (A2 Phospholipase), organelles (lysosomes), and also cellular membrane. Lipid peroxidation (LP) increases. LP end products include MDA, non-saturated fatty acids (arachidonic), free oxygen radicals. Arachidonic acid destruction end products include: thromboxane A₂, other hydro peroxides, and leukotriene. Thromboxane A₂ induces cerebral spasms; intensify platelets

aggregation, alterations of coagulation homeostasis. Leukotriene demonstrates vasoactive effects. LP activation decrease amount of AO as these are responsible for peroxides, free radicals inactivation/inhibition.

Since microglia is hyper activated, its cells produce potentially neurotoxic factors: pro-inflammatory cytokines (interleukins 1,6,8), tumor necrosis factor, glutamate-receptors ligands, proteases, superoxide anions, etc. NMDA-receptors stimulation activates NO-synthetize, which participate in NO transformation from arginine. NO and superoxide anion combination delays neurotrophins production. Neurotrophins – these are proteins, which regulate neuronal cells; these develop within neurons and microglia and have local influence on dendrites branching and axons development. These are nerve growth factor, cerebral growth factor, Neurotrophins -3, etc. Anti-inflammatory factors (interleukins 4,10) and neurotrophins cease neurotoxic damage of LP concerning neurons and glial cells. But phospholipid damage within neurons results in antibody formation. Anti-inflammatory and vasoactive release results in neurospecific proteins in blood, autoimmune reaction against neurons develops. Mostly glial cells are involved into the pathological processes; cerebral neurons are of less significance. NMDA-receptors activation additional results in intracellular active oxygen forms development, mostly superoxide-anion and hydroxide-radical. In case of needy arginine and nitroxide synthetase superoxide-anion is also developed. When increased development of different free radicals is present, possible interaction with one more messenger – nitrogen oxide and superoxide transform into peroxynitrite of extremely high oxidation potential.

ET clinical manifestation include stress reactions, vegetative disorders, neurological disorders [55, 56], these are diagnosed by clinical examination (neurological state, psychical state, pathological reflexes, psycho- and cognitive disorders).

An increasing amount of experimental evidence has clarified that glutamate level is significantly increased in blood in different types of depression, stress, in pain, PTSD, stroke, etc. [55, 57, 58]. Pathophysiology and pathogenesis of PTSD is associated with the overstimulation processes predominance.

The best approach to protect from excitotoxicity is to use preparation that correct pathological disorder. Such preparation should reduce excitotoxicity that result from NMDA pathological stimulation.

Since excitotoxicity develops due to glutamate-sensitive NMDA receptors overactivation; the NMDA receptors antagonists were studied considering probable NMDA receptors block to normalize neurotransmission [59]. In experimental models in rats showed that clinical use of antagonists of NMDA receptors is not possible, since these drugs completely block neurotransmission, causing severe side effects (confusion, hallucinations, and seizure activity) [60]. One can find data about the possibility of using different groups of antidepressants for the correction of pathological symptoms caused by increased levels of glutamate in the blood. An experimental model in rats demonstrated that the tricyclic antidepressant amitriptyline suitable for treatment of symptoms of overstimulation (anxiety, fear, painful memories, illusions) influences glutamatergic neurotransmission by increasing transport protein EAAT3 [61]. An experimental model in rats demonstrated that serotonin reuptake inhibitor (tianeptine) is able to block glutamatergic neurotransmission changes in hippocampus, caused by stress [62].

In the process of stimulation realization GLU includes transport, uptake, release linked with receptors. In these GLU metabolism transport and uptake stages Se cooperates in [63, 64]. The amount of Se in cerebral cells is higher than in other tissues [65, 66]. Low Se rate is linked with pathology of delay processes, probably some kinds of seizure attacks may be cured with Se. Se deficit is noted in neurodegenerative diseases [67, 68]. Se is directly

involved in GLU metabolic processes [68]. Se part in GLU capturing suppression on the background of excessive excitement processes is proven, as well as Se participation as selenoprotein P in functioning of glutamate-sensitive receptors [69]. There is data about Se as AO appliance to cure neurodegenerative diseases (Parkinson, Alzheimer) [70, 71].

To study the preventive effect of Se on PTSD development by blocking GLU-mediated over irritation on persons, that are undergoing stress and are found in PTSD development risk group, both organic and non-organic Se are used.

Organic selenium is registered in Latvia as a dietary supplement and is recommended for widespread use as an antioxidant. Human supplementation with selenium may take the form of an organic compound composed of amino acids (selenmethionine, selencysteine, etc.), as well as inorganic salts (sodium selenite or selenate). Both organic and inorganic selenium is easily absorbed in the gastrointestinal tract.

Both organic and inorganic forms of selenium were studied to understand which form and method of use are preferable for OS prevention treatment within PSM. Inorganic Se (selenite and selenite) is available through pharmacological supplement; these possess lower biological availability and result in the different physiological response than organic ones.

In *vivo* studies demonstrated different availability for organic and inorganic Se. Nutritional Se consists of selenmethionine (plants, animal), which accounts half of dietary Se; its bioavailability is more than 90%; selencysteine (animal), also of high bioavailability; Se inorganic forms (selenite, selenite) of lower bioavailability about 50%. Physiological Se intake (with food) (0,1–0,3 ppm), since methionine supplementation is normal, Se-Met, selenite and selenite are equally efficient. But in case of insufficient methionine, inorganic Se becomes more effective. Nevertheless Se-Met (organic Se) is much less toxic than inorganic, over dosage risk therefore is low. Organic Se retention is

higher than inorganic. This is because mostly organic Se is recommended as preferable for supplementation, treatment, and prophylaxis [72, 73, 74, 75, 76].

Se-dependent GPx activity is measured to clarify Se dosage. According to WHO recommendations, the necessary and sufficient selenium intake dosage is such when GPX demonstrates 66% (2/3) of its maximum activity [78]. When organic selenium was administered in a dosage 50-100 mcg per day no selenium-dependent glutathione peroxidase activity increase. One can find data about Se-Met supplementation in healthy volunteers and/or patients in dosage 400–700 mcg/day for a long time with no adverse effects [72]. But increasing Se dosage above 200 mcg, Se-dependent GPx activity does not increase. So Se dosage 200 mcg appears to be the most effective and optimal. Inorganic Se (Na selenite) pharmacological form (solution) is difficult and less suitable for PSM. Indeed Se 200 mcg per day results in Se-dependent GPx activity increasing. Reaching a peak, GPx showed a plateau phase.

6. CONCLUSIONS

There is reliable correlation between PTSD prevalence and OS parameters.

There is reliable correlation between PTSD symptomatic severity and OS parameters.

Selenium as antioxidant supplementation during mission can reduce OS parameters.

Selenium as antioxidant supplementation during mission can minimise PTSD prevalence.

Selenium as antioxidant supplementation during mission can reduce PTSD symptomatic severity.

6.1. Practical significance

1. Ownership of the intellectual property of the invention was obtained, international patent "*Preparation that effectively reduces high glutamate level in blood*" (Claim PCT/LV2012/000001) do results from the research.
2. Validated *PCL-M* questionnaire in Latvian language can be recommended for use as an effective instrument for PTSD military contingent diagnostics and screening.
3. Developed practical method of PTSD risk groups morbidity diminishing (field conditions included): it is recommended to orally intake organic medication Se (2 pills) 200 mcg per day regardless of mealtimes during all stressor exposure time period. Taking Se long-term (more than 6 months) it is recommended to control Se and GPx blood rate.

6.2. Practical recommendations

1. PTSD in military staff and their family members appears to become a medically-social problem, additional studies in this field are needed to be done.
2. It is necessary to create military stress and military medicine permanently running institution (scientific-medical-education centre) for particular professionals work coordination (psychosomatic medicine doctors, military doctors, psychologists, social workers) to make and bring in special complex medical and rehabilitation programme.

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7.1. Conflict of interest

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The present study protects the rights and welfare of participants in the spirit of ethical guidelines outlined under the Declaration of Helsinki. The study further respects the ethical principles of the RSU and Latvian National Armed Forces, NBS Medical Guarantee Centre recommendations, the Law on personal data protection rules.

Confidence can be assured in the ethics, safety, scientific rigor, and reliability of the research. Personal information obtained in the course of the research will be strictly secured to avoid external leaks.

The protocol of study, the protocol of agreement, and the protocol of participation corresponded to the Helsinki declaration on principles of humanity in medicine and approved by Ethics committee of Riga Stradins university (Riga, Latvia) – E-9 (2), 17.12.2009.

Informative seminars took place and informative sheets were distributed to inform study participants about the nature of the study.

Opinions expressed in the work belong to the author and do not reflect Latvian government, Latvian National Armed Forces and RSU position or politics.

Conflict of interest is absent.

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Proceedings, Books of abstracts:

1. Войцеховскис В.В., Войцеховска Ю.Г., Шкестерс А., Анцане Г., Силова А., Ивашенко Т., Мичанс Я., Вайвадс Н. К вопросу о нейропротективном действии селена при риске развития посттравматического стрессового расстройства. *Donozologija-2012, 8th International Scientific Conferences Proceedings, St. Petersburg, Russia 2012 Dec 13-14: accepted.*
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26. Войцеховскис ВВ, Анцанс А, Анцане Г, Бернхофс В, Войцеховска ЮГ, Курьяне Н, Лусе А, Мичанс Я, Островска И, Тарасова Э, Трачевска Т, Шкестерс А. Опыт создания Междисциплинарной рабочей группы изучения, разработки методов профилактики и реабилитации ПТСС у Контингента Международных Операций. 2nd Eastern European Psychiatric Congress Materials, Moscow, Russia 2009 Oct 27-30: 75-6.
27. Voicehovskis V, Ancane G, Skesters A. Oxidative stress as indicator of post-traumaic stress disorder in a contingent of international operations. 20th World Congress on Psychosomatic Medicine, Torino, Italy 2009 Sep 24-26, *Panminerva Medica*, Italy 2009 Sep; 51(3-1): 122.
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29. Voicehovskis VV, Ancāne G, Šķesters A. Oksidatīvā stresa indikatori posttraumatiskā stresa sindroma gadījumā straprtautisko opēraciju kontingenta latvijas dalībniekiem. 6. Latvijas Ārstu kongress, Tēzes, Rīga,

Latvija 2009 Jun 19-21: 102.

30. Voicehovskis VV, Ancane G, Skesters A. Correction of Indicators of Oxidative Stress in Posttraumatic Stress Disorder at the Missions Contingent. XII. International Congress of IFPE, Book of abstracts, Vienna, Austria 2009 Apr 16-19: 140.
31. Voicehovskis VV, Ancāne G, Šķesters A. Oksidatīvā stresa rādītāju noteikšana posttraumatiskā stresa sindroma diagnosticēšanai starptautisko operāciju kontingenta dalībniekiem un to korekcija izmantojot antioksidantus. RSU 2009.g. 8. zinātniskā konference, Tēzes, Rīga, Latvija 2009 Apr 8-9: 76.
32. Войцеховский ВВ, Анцане Г, Шкестерс А. Коррекция показателей оксидативного стресса как проявления ПТСС у контингента международных операций. Donozologija-2008, 4th Int Scient Conf Proceedings, St. Petersburg, Russia 2008 Dec 18-19: 291-2.

10. STUDY APPROBATION

10.1. PhD theses approbation

RSU Psychosomatic medicine and psychotherapy Dept. and Clinic extended conference, RSU Psychosomatic medicine and psychotherapy Clinic, Riga, Latvia, 17.04.2012.

10.2. Oral presentations at conferences

1. Voicehovskis V, Ancane G, Ivascenko T, Skesters A, Voicehovska J, Micans J, Vaivads N. Defense Methods Against Posttraumatic Stress Disorder Development in a Contingent of International Operations. 4th Annual Conference on Coping with Extreme Situations, Prague, Czech Rep 2011 Nov 21-25.
2. Voicehovskis VV, Ancane G, Ivascenko T, Skesters A, Voicehovska JG, Micans J, Vaivads N. Posttraumatic Stress Disorder Prevention in a Contingent of International Operations. V. Baltic Military Psychologists Conference, Riga, Latvia 2011 Oct 6-7.
3. Voicehovskis VV, Ancane G, Ivascenko T. Predisposition to Posttraumatic Stress Disorder in Latvian Contingent of International Operations. The International Applied Military Psychology Symposium - IAMPS 2011, Vienna, Austria 2011 May 23-27.
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5. Voicehovskis VV, Ancane G, Ivascenko T, Skesters A. Epidemiology of Posttraumatic Stress Disorder in Latvian Contingent of International Operations. RSU 2010.g. X. Zinātn. konf., Rīga, Latvija 2011 Apr 14-15.
6. Voicehovskis VV, Ancane G, Ivascenko T, Micans J, Skesters A, Vaivads N. Posttraumatic Stress Disorder Assessment at Latvian Contingent of International Operations. International Conference „Psychosomatic aspects of therapy and recovery”, Warsaw, Poland 2011 Jan 23-23.
7. Voicehovskis VV, Ancane G. The Quality of Life in Psychosomatic patients. Psychosomatic medicine in the health care system: Today and tomorrow, Latvian - German Scient. Seminar, Rīga, Latvija 2010 Nov 27.
8. Voicehovskis VV, Ancāne G, Ancāns A, Draudiņa R, Ivaščenko T, Meistere L, Ostrovska I, Siņicka J, Šķesters A, Švarcs V, Utināns A, Užāns A, Vasiļevska M. Posttraumatiskā stresa sindroma bāzes līmeņa noteikšana Starptautisko Operāciju Kontingenta Latvijas dalībniekiem. RSU 2010.g. 9. zinātniskā konference, Rīga, Latvija 2010 Mar 18-19.
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11. Войцеховский ВВ, Анцане Г, Шкестерс А. О возможности использования показателей оксидативного стресса как индикаторов проявления ПТСС. Donozologija-2008, 4th International Scientific Conference, St. Petersburg, Russia 2008 Dec 18-19.

10.3. Poster presentations at conferences

1. Войцеховскис В.В., Войцеховска Ю.Г., Шкестерс А., Анцане Г., Силова А., Иващенко Т., Мичанс Я., Вайвадс Н. К вопросу о нейропротективном действии селена при риске развития посттравматического стрессового расстройства. Donozologija-2012, 8th International Scientific Conference, St. Petersburg, Russia 2011 Dec 13-14: accepted.
2. Voicehovskis VV, Voicehovska JG, Ancane G, Skesters A, Silova A, Ivascenko T, Micans J, Vaivads N. Stress-induced Neurodegeneration Prevention by Selenium. 8th European Masters in Anti-Aging Medicine Congress Proceedings, Paris, France 2012 Oct 12-14.
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