VILNIUS UNIVERSITY

ROBERTAS BADARAS

RAPID OPIOID DETOXIFICATION WITH AN IMPLEMENTATION OF THE NEW METHOD OF GRADUALLY INCREASING DOSAGE OF NALTREXONE INDUCTION

Summary of Doctoral Dissertation

Biomedical Sciences, Medicine (06 B)

Vilnius, 2016

The doctoral dissertation was prepared during the period of 2011–2015 at Vilnius University, in cooperation with Republic Vilnius University Hospital.

Scientific supervisor – prof. habil. dr. Juozas Ivaškevičius (Vilnius University, Biomedical Sciences, Medicine – 06B)

The dissertation will be defended at the Scientific Council of Vilnius University:

Chairman – prof. dr. (HP) Janina Tutkuvienė (Vilnius University, Biomedical Sciences, Medicine – 06B)

Members:

prof. habil. dr. Edmundas Širvinskas (Lithuanian University of Health Sciences, Biomedical Sciences, Medicine – 06B)

prof. dr. Andrius Macas (Lithuanian University of Health Sciences, Biomedical Sciences, Medicine – 06B)

assoc. prof. doc. Audrius Andrijauskas (Vilnius University, Biomedical Sciences, Medicine – 06B)

dr. Osvaldas Pranevicius (Weill Cornell University Medical College (USA), Biomedical Sciences, Medicine – 06B)

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Address: Šiltnamių str. 29, LT – 04130, Vilnius, Lithuania

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VILNIAUS UNIVERSITETAS

ROBERTAS BADARAS

GREITOSIOS OPIOIDINĖS DETOKSIKACIJOS EIGA TAIKANT NAUJĄ PALAIPSNIUI DIDĖJANČIŲ NALTREKSONO DOZIŲ INDUKCIJOS METODĄ

Daktaro disertacija
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Disertacija ginama Vilniaus universiteto Medicinos mokslo krypties taryboje:

Pirmininkė – prof. dr. Janina Tutkuvienė (Vilniaus universitetas, biomedicinos mokslai, medicina – 06B)

Nariai:

prof. habil. dr. Edmundas Širvinskas (Lietuvos sveikatos mokslų universitetas, biomedicinos mokslai, medicina – 06B)

prof. dr. Andrius Macas (Lietuvos sveikatos mokslų universitetas, biomedicinos mokslai, medicina – 06B)

doc. dr. Audrius Andrijauskas (Vilniaus universitetas, biomedicinos mokslai, medicina – 06B)

dr. Osvaldas Pranevicius (Weill Cornell universiteto medicinos koledžas, JAV, biomedicinos mokslai, medicina – 06B)

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LIST OF ABBREVATIONS

ACTH	adrenocorticotropic hormone
ALT	alanine aminotransferase
AST	aspartate aminotransferase
Cl^-	chloride
GSH	glutathione
GST	glutathione S-transferase
Hct	hematocrit
Hgb	hemoglobin
K^+	potassium
MCV	mean corpuscular volume
Mg^{++}	magnesium
Na^+	sodium
OOWS	Objective Opioid Withdrawal Scale
PLT	platelets
SOWS	Subjective Opioid Withdrawal Scale
WBC	white blood cells

Introduction

Over the last decades opioid dependence and complications that go along with it have become a rapidly increasing social burden, as well as a vast problem for the whole healthcare system. Some authors name it as the most important challenge to be solved for the world healthcare and society these days. Meanwhile, epidemiological researches show constantly increasing opioid consumption. Acuteness of the problem and its tendency to expand has been induced not only by illegal opioids (for instance, heroin), but also by a constantly growing number of prescribed opioid consumers. Within the European Union, the number of patients, attending opioid detoxification programs, in different age categories increased from 450 000 participants in 2003 up to approximately 700 000 in 2010. It is presumed that prescribed opioid users have made the main impact to this change. According to official data alone, in 2012 in Europe leastwise 1.3 million people were treated from illegal opioid dependence. Opioid addicts make 0.4% of worldwide population among people from 15 to 64 years old. This is a working-age group, with the biggest potential of benefit to the society as well as with potentially highest ability to create the gross domestic product. Unfortunately, 15.5 million people in this group, due to opioid dependence, are not able to function as an efficient social unit. According to Global Burden of Disease Study 2010, this burden estimates 9.2 million and, according to the World Health Organisation, 11.2 million of disability-adjusted life years. In Europe 10 000-20 000 (1-2%) of 15-64 years old opioid addicts die each year. The independent analysis of RAND Europe calculated an approximate financial burden per capita: in various European countries it mediates from 2 627 to 60 665 Euro per year. For instance, there were 2.3 opioid addicts for 1 000 people in Lithuania in 2012. According to the annual report Trends and Developments 2014 of the European Monitoring Centre for Drugs and Drug Addiction, Lithuania had 66% of psychoactive substances (except alcohol) users, treated for the first time, who were heroin addicts (100% intravenous route), while the total rate in the European Union was only 25% (31,8% intravenous route). In Europe in 2012 people, who admitted opioids (mostly heroin) as the main psychoactive substance used, made 46% (18 000) of the population, treated for the drug abuse. For 26% of this group it was their first detoxification. Lithuania is the 5th in range of the European countries, where opioid addicts form 66% of all abusers of psychoactive substances, claiming for treatment for the first time. Unfortunately,

Lithuania also takes the leading position in taking the intravenous route (100%) of psychoactive substances users among people, claiming for treatment for the first time. Obviously comparing with the values of other European Union countries, great demand for programs of qualified opioid addiction treatment remains.

According to nowadays conception of diseases of abuse, dependence from psychoactive substances is a chronic illness with relapses, which has some characteristic features: 1) an uncontrolled will of seeking and using psychoactive substances - craving; 2) loss of control of consumption; 3) a sudden uprise of negative, dysphoric state, including anxiety, irritability, reflecting withdrawal syndrome, when psychoactive substance becomes inaccessible. Precisely an abstinence fear frequently is the first but insurmountable barrier for opioid addicts to determine the consumption of psychoactive substances. Patients, who know the link between dependence and central nervous system, have an advantage because they understand a biological nature of their illness and do not see themselves as "bad people".

Symptoms of opioid withdrawal can be divided into two conditional groups: objective and subjective. The subjective features are determined by the experience of past withdrawals, attitude, expectations and personal peculiarities. While objective symptoms do not depend from emotional state of the patient. This is the reason why patients the absence of opioids often experience as a much more severe state than it can be seen only by external (objective) signs. Opioid withdrawal is a subjectively severe, but frequently underestimated state, if only its objective data is monitored. The Subjective and Objective Opioid Withdrawal Scales enable an accurate evaluation of both – subjective and objective symptoms and signs that occur during an opioid withdrawal. As the main quantitative indicators of opioid withdrawal, the Subjective Opioid Withdrawal Scale (SOWS) and the Objective Opioid Withdrawal Scale (OOWS) were chosen for this study.

The amount of dose and the speed of elimination from organism are directly linked to the severity of withdrawal, which occurs after determination of opioid consumption. However, neither duration of the usage, nor the amount of a dose consumed, are the criteria that can predict an accurate severity of opioid withdrawal which an individual person has to cope with. It is proven that opioid dependence is responsible for pathophysiological changes in central nervous system.

Two main directions – an absolute abstinence and replacement therapies when opioid agonists are used, remain a gold standard in treating opioid withdrawal. However,

their effectiveness is contentious. It is statistically proven that as many as 20–80% of patients fail conventional opioid detoxification programs. The primary motive is duration of the process: programs can last from 1 week till 6 months and this term is often too long for opioid addicts to cope with. Unpleasant feelings related to abstinence lead to unfinished detoxification programs and failure. The need for a more effective method of decreasing the duration and discomfort of opiate detoxification, despite many attempts and studies, remains to be a problem. Opioid detoxification has a special niche in the treatment of opioid addiction. Over the last decades two new programs as a combination of standard methods and time saving techniques are introduced into a clinical practice: “rapid opioid detoxification”, performed under a deep or conscious sedation, and “ultra rapid opioid detoxification”, a method when general anaesthesia is used. The procedures have at least 4 advantages comparing them to standard methods: minimal duration – detoxification program can be finished over a few days; analgesia – detoxification, performed under sedation or under general anaesthesia, causes no or a minimal discomfort to a patient; irreversibility – from the moment an opioid antagonist is given, the detoxification process becomes irreversible. Even if a patient starts using opioids during the first 24 hours after naltrexone has been taken, their effect is blocked and the detoxification process continues; easier way to give naltrexone to a patient – a rapid opioid detoxification is usually finished with naltrexone consumption. Like every other treatment, rapid and ultra rapid opioid detoxification programs both have their negative issues. A higher risk and cost of the procedures remain the main disadvantages. General anaesthesia and opioid antagonists, used as component parts of the ultra rapid opioid detoxification, create a more complicate procedure, with a potentially higher rate of side effects and a larger outlay cost. The rapid opioid detoxification, using sedation as a substitution method for general anaesthesia, on the other hand, is stated as a less dangerous and cheaper method of treatment, making a hypothesis to suspend the clinical practice of ultra rapid opioid detoxification and replace it in the future. In a review article Gowing L et al. state the opinion that the deep (unconscious) sedation has no significant advantages over the light (conscious) sedation, and general anaesthesia, used during the procedure, only induces the rate of side effects. Safety and price are the main issues, and for this reason the rapid opioid detoxification has an advantage over the ultra rapid opioid detoxification program, making a hypothesis to gain the lead in future.

It is already scientifically proven that rapid opioid detoxification under anaesthesia or sedation are significantly more effective methods for achieving short-term abstinence compared to conventional detoxification and detoxification using buprenorphine. However, the techniques cannot function independently. Opioid detoxification is an initial stage of the complex scheme, in which a further therapy of opioid addiction is needed: a supporting post-detoxification treatment, in order to avoid relapse later in the future, is obligatory.

Dosing regimens of naltrexone induction used in clinical trials range from a single dose of 50 mg naltrexone daily to a graduated increase of 12.5 mg naltrexone daily. Clinical practice also notes cases of inducing significantly small doses of naltrexone: the performed study, during which patients were induced with very small (0.125 mg) doses of naltrexone, increasing them gradually, showed that the treatment course witnessed a significant decrease in the necessity of supplementary drugs, while the patients noticed no discomfort and no complications or incidents were noted.

To date, no comparison of stress response when using opioid detoxification under a counscious sedation was carried on. There are also no researches made, which could be able to show a quantitative evaluation of changes in stress hormones concentrations during the opioid detoxification. Some surveys indicate the increasing of plasma ACTH and cortisol 15- and 13-fold levels, respectively during the anaesthesia phase of ultra rapid opioid detoxification.

The present study was performed to compare stress response using different techniques of naltrexone induction during detoxification under light sedation and to test the hypothesis that stress can be avoidable during opioid detoxification.

Aim of the research:

To identify which of the two naltrexone induction techniques during the rapid opioid detoxification procedure – starting from an initially small 50 μg dose and increasing it gradually to a total dose of 12.5 mg, or giving a single 12.5 mg dose of naltrexone - evokes a higher stress response and has higher influence on the acute, antagonist-induced opioid withdrawal and its expression of subjective and objective symptoms.

Goals of the research:

1. To make a quantitative analysis of stress response differences, which occur during an opioid detoxification procedure, by comparing two different naltrexone induction techniques – a gradual increase of naltrexone dosage (starting from an initially small 50 μg dose and increasing it gradually to a total dose of 12.5 mg) and a single dose (12.5 mg) of naltrexone prescription. Evaluation of objective quantitative stress values:

1.1. Usual hormonal indicators of stress response - cortisol and ACTH;

1.2. Indicators of oxidative stress response – GSH and GST.

2. Evaluate quantitative and qualitative changes in haemodynamics, respiratory and gastrointestinal system by comparing two techniques of naltrexone induction: gradual increase (starting from an initially small 50 μg dose and increasing it gradually to a total dose of 12.5 mg) and a single dose (12.5 mg) of naltrexone prescription.

3. Evaluate changes in clinical and biochemical analysis results, which occur during opioid detoxification procedure, by comparing two different techniques of naltrexone induction: gradual increase of naltrexone dosage (starting from an initially small 50 μg dose and increasing it gradually to a total dose of 12.5 mg) and a single dose (12.5 mg) of naltrexone prescription. The biochemical markers to be evaluated are as follows:

3.1. Glucose;

3.2. Electrolytes: K^+, Na^+, Cl^-, Mg^{++};

3.3. C – reactive protein;

3.4. Liver enzymes: AST, ALT;

3.5. Common blood test: Hgb, Hct, MCV, WBC, PLT.

4. To make a qualitative evaluation of symptoms of opioid withdrawal, which occur during a rapid opioid detoxification procedure, by comparing two different techniques of naltrexone induction: a gradual increase of naltrexone dosage (starting from an initially small 50 μg dose and increasing it gradually to a total dose of 12.5 mg) and a single dose (12.5 mg) of naltrexone prescription. The evaluation of objective and subjective symptoms is performed by:

4.1. OOWS values;

4.2. SOWS values.

Statements of defence:

1. Acute antagonist-induced opioid withdrawal and stress response, by using gradual increase of naltrexone dosage (starting from an initially small 50 μg dose and increasing it gradually to a total dose of 12.5 mg), is smaller than a single dose (12.5 mg) of naltrexone administration
2. Rapid opioid detoxification under a conscious sedation technique, implementing it along with a gradual increase of naltrexone dosage, does not induce any changes in biochemical stress response markers.

Innovation of the research:

According to the data bases of Cochrane, PubMed and Web of Science there are no published surveys which could produce any information about the quantitative analysis of stress response, occurring during opioid detoxification under a conscious sedation procedure, by comparing changes in biochemical markers – cortisol, adrenocorticotropic hormone, – and oxidative stress-markers – GSH and GST – by using a common single dose of naltrexone induction or a gradual increase of naltrexone dosage.

Practical adaptation of the research:

- ***Benefits for patients:***

This is an additional possibility for the patients to start rapid opioid detoxification procedure, which leads to a further ambulatory or hospital rehabilitation. By participating in the research, patients are able to start a complex treatment of opioid addiction.

- Scientific benefits:

A proof of the hypothesis that acute antagonist-induced opioid withdrawal and stress response, which occur while using a gradual increase of naltrexone (opioid antagonist) dosage, are significantly smaller comparing them to a single dose of naltrexone

administration scheme. Confirmation of a proposition that rapid opioid detoxification under a conscious sedation procedure, by using a method of a gradual naltrexone increase, does not induce changes in the concentrations of biochemical stress markers.

- Practical benefits:

Positive research results provide new possibilities in treating opioid addiction, simplify the initial stage of the treatment – the opioid detoxification procedure, as well as deny the prevailing statement that every treatment scheme of opioid withdrawal necessarily evokes an expressed stress response. The rapid opioid detoxification procedure would become less precarious and expensive. This would induce adaptability of a rapid opioid detoxification as a routine procedure implemented in clinical practice, not only in problem-oriented departments but also in non-specialized medical institutions. Such change could ease an access to opioid addiction treatment for motivated patients. Further research must focus on the effectiveness of antagonist-induced opioid treatment methods and their influence on severity of the withdrawal, formation of occurring complications, choice of the most effective antagonist-induced method and long-term succession.

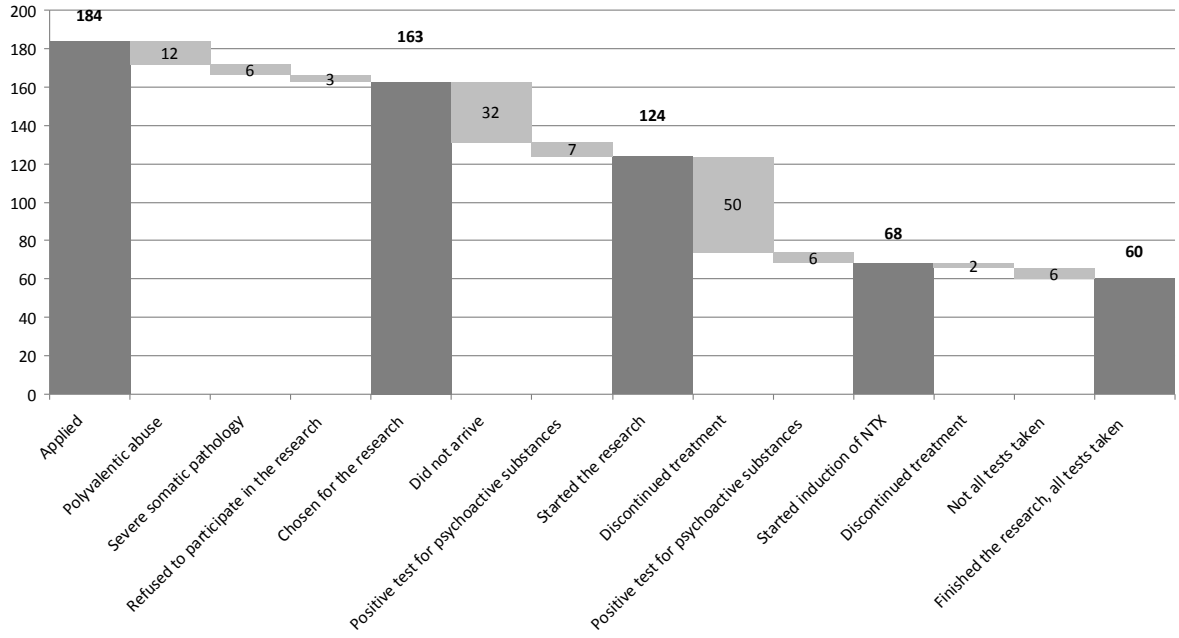
Methods:

Referring to the material from these researches a randomized, double-blind, prospective study was held. The aim of this survey was to identify which method of the two opioid detoxification programs for naltrexone induction – starting from very small doses of naltrexone and increasing them gradually, or prescribing an accustomed 12.5 mg initial dose – could be qualified as a better option while evoking a more extensive stress response, and having a better influence on the acute antagonist-induced opioid abstinence response.

The study was approved by the Lithuanian Bioethics Committee (license No. 158200-01-443-124), registered in ClinicalTrials.gov (Identifier: NCT02362256) and provided in the Toxicology Centre of the Republic Vilnius University Hospital from 2011 till 2015. A written informed consent was obtained prior to participation; confidentiality was strictly maintained. Volunteers were recruited from a local community by a word of mouth and by advertising. All the subjects were evaluated by medical doctors, specializing in medicine of addiction. Evaluation for inclusion and exclusion criteria was made by a clinical toxicologist, using a clinical interview, physical examination

and a review of laboratory and corroborative data. The evaluation included histories of general medicine and substance abuse, physical examination, electrocardiogram, echocardiography and laboratory testing, including a complete blood cell count, serum electrolytes, liver function tests, serological hepatitis B and C testing. The participants afterwards gave a written informed consent for HIV testing. The study population consisted of adult (over 18 years) heroin addicts with an IDC 10 diagnosis of opiate dependence, without ongoing drug or alcohol abuse, or with a dependence history of an opiate addiction for more than 1 year. Exclusion criteria – pregnancy and breast-feeding, complicated heart, lung, kidney diseases, bacterial infections, any psychosis which had occurred during lifetime, diabetes, altered mental status (Glasgow Coma Scale <15 points), surgery over the last month (Picture No. 1):

Picture No. 1. The exclusive criteria of the participants



The subjects were enrolled into the research and allowed to remain in it with the condition of negative urine toxicology results for 10 most popular drugs in Lithuania: opioids, methadone, cocaine, cannabinoids, barbiturates, MDMA (extasy), amphetamine, methamphetamine, tricyclic antidepressants, benzodiazepines (except opioids found on the arrival day and benzodiazepines prescribed during the treatment). A patient, matching the inclusion criteria, was committed not to use any psychoactive substances for at least 12 hours before the hospitalization and was able to terminate his/her participation in the research at any stage of the treatment. The study included

60 participants (41 men and 19 women), who were randomly divided into two groups of 30 persons each – an experimental group and a control group. After arrival at 8^{00} am for the 1st and 2nd days, the patients in both groups underwent an identical treatment. They were administered basic medications of the rapid opioid detoxification treatment – clonidine, lorazepam and haloperidol, each medication in its fixed dose, as well as intravenous crystalloid infusion therapy (1000 ml/day). The extent of the opioid abstinence was evaluated and adjusted referring to Objective Opioid Withdrawal Scale – OOWS and Subjective Opioid Withdrawal Scale – SOWS (Handlesman, 1987). If the marginal thresholds were exceeded (≥5 points OOWS or ≥15 points SOWS) and no contraindications (heart rate ≤50 beats/min, arterial pressure ≤90/60 mmHg) were observed, the patient was given an additional doses of 150.0 μg clonidine and 5.0 mg lorazepam orally. An additional haloperidol prescription was used only in specific situations – in a presence of intense agitation (Table No. 1):

Table No. 1. Scheme of medicine prescription for the 1st ir 2nd days

Day	1st				2nd			
Hour	8^{00}	12^{00}	16^{00}	20^{00}	8^{00}	12^{00}	16^{00}	20^{00}
CLO (μg)	150	150	150	150	150	150	150	150
LOR (mg)	5	5	5	5	5	5	5	5
HAL (mg)	5	wh	wn	wn	5	wn	wn	wn

CLO - clonidine; LOR – lorazepam, HAL – haloperidol, wn – when needed

In this phase no other preparations, affecting central nervous system were given to the participants. No intravenous glucose was infused either as not to influence the blood glucose concentration levels. Starting with the 3rd day of the research, changes in the treatment scheme over the two groups were made: the control group was administered a naltrexone induction – starting from a customary dose of 12.5 mg and continuing by giving only an intravenous physiological saline infusion. Whereas the experimental group patients, according to the scheme, were given very small initial naltrexone doses, increasing them gradually up to the total dose of 12.5 mg (Table No. 2):

Table No. 2. Natrexone induction scheme for the groups

Time (hours)	9^{00}	9^{30}	10^{00}	10^{30}	11^{00}	11^{30}	12^{00}	12^{30}	13^{00}	13^{30}
EG (μg)	50	50	100	100	200	400	800	1600	3200	6000
CG (μg)	12 500	0	0	0	0	0	0	0	0	0

EG – experimental group; CG – control group

On the 4th day of the research, both the experimental group and the control group were given 25.0 mg of naltrexone orally. In those rare cases when clinical symptoms of the opioid abstinence did not manage to regress (SOWS did not reach ≤5 points and OOWS ≤3 points), on the 4th day of the treatment the patient was hospitalized for observation without administering any other medications, except 50.0 mg of naltrexone orally. The patient was afterwards discharged from the hospital and further complex treatment of opioid dependence in specialized healthcare centres was recommended. If the marginal thresholds were exceeded (≥5 points OOWS or ≥15 points SOWS), the patient was given an additional doses of 150.0 μg clonidine and 5.0 mg lorazepam orally and an additional haloperidol prescription was used only in presence of intense agitation - as for the 1st and 2nd days of the research (Table No. 3). All complications that occurred during the survey were recorded in the patient's research protocol.

Table No. 3. Scheme of medicine prescription for the 3rd and 4th days

	3rd				4th			
Hour	8^{00}	12^{00}	16^{00}	20^{00}	8^{00}	12^{00}	16^{00}	20^{00}
CLO (μg)	150	150	wn	wn	wn	wn	wn	wn
LOR (mg)	5	5	wn	wn	wn	wn	wn	wn
HAL (mg)	5	wn	wn	wn	-	-	-	-

CLO - clonidine; LOR – lorazepam, HAL – haloperidol, wn – when needed

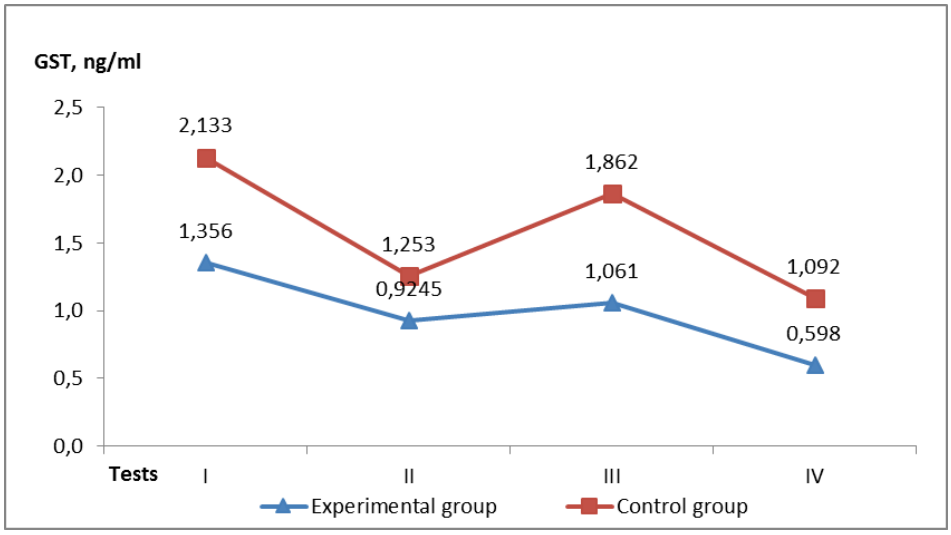
Results:

The statistical analysis of the data was performed by using the *Open Source R Project for Statistical Computing* program, version 3.2.2. For the comparison of two dependable samples *Wilcoxon criteria* was used, and for the independent samples comparison - *Mann-Whitney-Wilcoxon* rank sum test was performed. The *Friedman*

analysis of variance by ranks was used for the three dependable samples and *Kruskal–Wallis* one-way analysis of variance was performed for the independent samples. *Pearson* (r_p) and *Spearman* (r_s) correlation coefficients for a measurement of the linear correlation between two variables, giving a value between +1 and −1 inclusive, were calculated. The difference was verified as statistically significant, if the p-value was <0.05.

Given the spread of the tested parameter values, data was divided into two ranges: GST concentration formed the range of the data values from 0.160 to 8.768 ng/ml (Picture No. 2), and from 8.769 to 23.863 ng/ml (Picture No. 3); GSH formed the range of the data values from 1.749 mg/ml to 4.888 µg/ml, and from 4.889 µg/ml to 10.079 µg/ml. GST concentration in the experimental group at the range of data values from 0.160 to 8.768 ng/ml showed statistically significant reduction after 23 hours compared to GST concentration after 5 hours of naltrexone induction. In the control group, lower levels of GST concentration were observed 1 hour and 23 hours after naltrexone induction. GSH concentration was significantly lower only in the control group 1 hour after naltrexone induction and remained lower compared to the starting level.

Picture No. 2. Glutathion S-transferase concentration changes in values in the interval from 0.160 till 8.768 ng/ml



Picture No. 3. Glutathion S-transferase concentration changes in values in the interval from 8.769 till 23.863 ng/ml

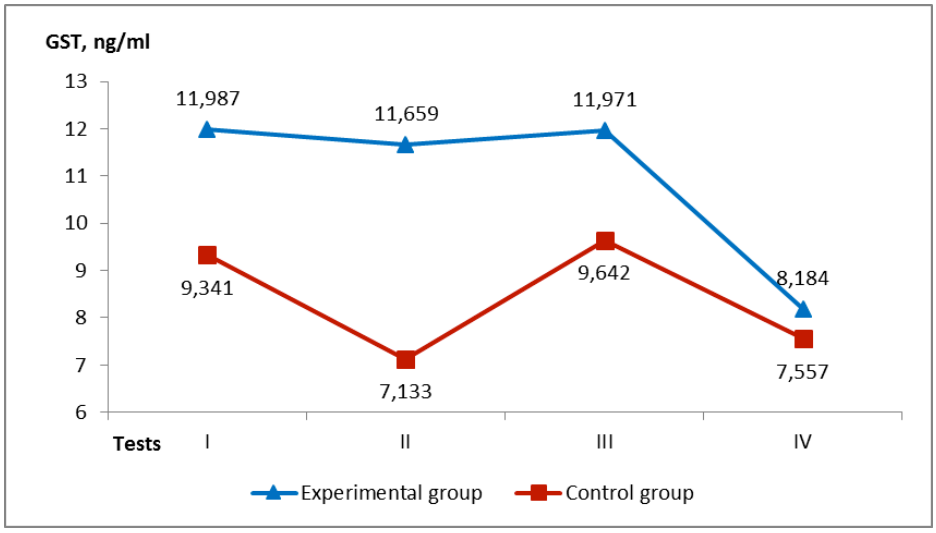


Table No. 4. GST values deviation in the experimental group:

GST / Research	[0.16; 8.768]		[8.769; 23.863]	
	$\bar{x} \pm sd$ *	Md**	$\bar{x} \pm sd$ *	Md**
I	1.71 ± 1.60	1.36	12.62 ± 5.30	11.99
II	1.74 ± 2.15	0.92	11.18 ±5.07	11.66
II	2.11 ± 2.40	1.06	12.58 ± 4.86	11.97
IV	1.58 ± 1.98	0.60	9.63 ± 5.73	8.18

*Values are shown as aritmetic means ± standart deviation; ** – median of the values

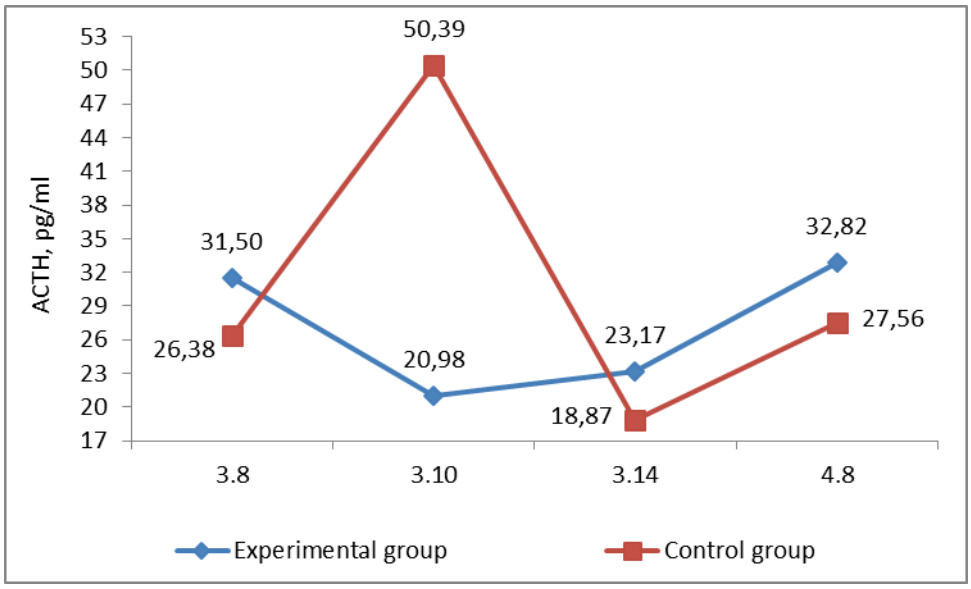
Table No. 5. GST values deviation in the control group:

GST / Research	[0.16; 8.768]		[8.769; 23.863]	
	$\bar{x} \pm sd$ *	Md**	$\bar{x} \pm sd$ *	Md**
I	3.34 ± 2.96	2.13	11.32 ± 4.60	9.34
II	2.71 ± 3.02	1.25	6.57 ± 4.77	7.13
II	3.58 ± +3.71	1.86	10.55 ± 4.86	9.64
IV	2.23 ± 2.91	1.09	6.79 ± 4.64	7.56

*Values are shown as aritmetic means ± standart deviation; ** – median of the values

Comparing ACTH values, the medians and changes of the values were calculated. The values in the experimental and control groups were compared separately and also among the groups (Picture No. 4):

Picture No. 4. Comparison of ACTH concentrations among the groups



ACTH values in the experimental group after naltrexone induction were significantly reduced: the concentration 1 hour before the induction (3.8[1]) and 1 hour after the start of naltrexone induction (3.10) decreased from 31.5 pg/ml till 20.98 pg/ml (p=0.007); and comparing 3.8 and the concentration at the end of naltrexone induction (3.14), the values decreased from 31.5 pg/ml till 23.17 pg/ml (p=0.011) (Table No. 6):

Table No. 6. Comparison of ACTH concentrations medians in the experimental group

Analysis	3.8	3.10	3.14	4.8
3.8	1	***0,007***	***0,011***	0,855
3.10	***0,007***	1	0,687	***0,008***
3.14	***0,011***	0,687	1	***0,019***
4.8	0,855	***0,008***	***0,019***	1

In the control group an opposite dynamics was fixated: ACTH concentrations increased after the naltrexone induction: by comparing the concentration 1 hour before naltrexone induction (3.8) and 1 hour after the start of naltrexone induction (3.10), the values increased from 26.38 pg/ml till 50.39 pg/ml (p=0.027) (Table No. 7):

[1] First number (3) – day of the research; second number (8) – hour

Table No. 7. Comparison of ACTH concentrations medians in the control group

Analysis	3.8	3.10	3.14	4.8
3.8	1	***0,027***	0,258	0,684
3.10	***0,027***	1	***0,009***	***0,016***
3.14	0,258	***0,009***	1	0,525
4.8	0,684	***0,016***	0,525	1

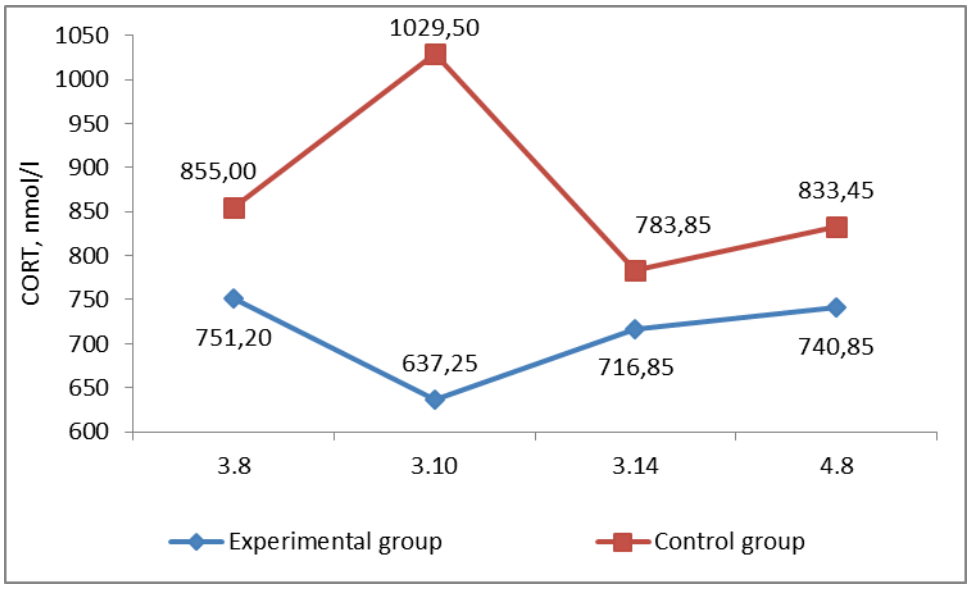
By comparing ACTH concentrations among the groups, it is obvious that ACTH concentration in the experimental group had a tendency to reduce, while in the control group it was continuously increasing: a significant difference among the experimental and control groups in 1 hour after naltrexone induction was detected (p=0.002) (Table No. 8):

Table No. 8. Comparison of medians of ACTH concentrations among the groups

Analysis	3.8	3.10	3.14	4.8
3.8	0.1761			
3.10		0.002107		
3.14			0.4581	
4.8				0.1433

Evaluating cortisol concentrations, medians of the values and changes of the values were calculated. The values in the experimental and control groups were compared separately and also among the groups (Picture No. 5):

Picture No. 5. Comparison of cortisol concentrations among the groups



Values of cortisol concentrations in the experimental group after naltrexone induction significantly decreased: by comparing the concentration 1 hour before naltrexone induction (3.8) and 1 hour after the start of naltrexone induction (3.10), the values decreased from 751.2 nmol/l till 637.25 nmol/l (p=0.004) (Table No. 9):

Table No. 9. Comparison of corticol concentrations medians in the experimental group

Analysis	3.8	3.10	3.14	4.8
3.8	1	***0,040***	0,281	0,924
3.10	***0,040***	1	0,390	***0,031***
3.14	0,281	0,390	1	0,254
4.8	0,924	***0,031***	0,254	1

In the control group an opposite dynamics was fixated: cortisol concentrations increased after the naltrexone induction: by comparing the concentration 1 hour before naltrexone induction (3.8) and 1 hour after the start of naltrexone induction (3.10), the values increased from 855 nmol/l till 1029.5 nmol/l (p=0.011) (Table No. 10):

Table No. 10. Comparison of cortisol concentrations medians in the control group

Research	3.8	3.10	3.14	4.8
3.8	1	***0,011***	0,843	0,859
3.10	***0,011***	1	0,077	***0,021***
3.14	0,843	0,077	1	0,708
4.8	0,859	***0,021***	0,708	1

By comparing cortisol concentrations among the groups, it is obvious that cortisol concentration in the experimental group had a tendency to reduce, while in the control group it was continuously increasing: a significant difference among the experimental and control groups in 1 hour after naltrexone induction was detected (p=2.233e-05) (Table No. 11):

Table No. 11. Comparison of medians of cortisol concentrations among the groups

Analysis	3.8	3.10	3.14	4.8
3.8	0.3504			
3.10		2.233e-05		
3.14			0.1159	
4.8				0.3898

Changes in haemodynamics:

ABP changes have been valued according to the changes in derivative values of the mean arterial pressure ABP (MEAN), which was calculated by using a formula:
ABP (MEAN)=2/3×ABP (DIA)+1/3×ABP (SIS). (Tables No. 12, 13, 14):

Table No. 12. ABP (MEAN) values dispersion on the 1st day of the research among the groups

Day. Hour	Experimental Group		Control Group		p-value
	$\bar{x} \pm sd$ *	Md**	$\bar{x} \pm sd$ *	Md**	
1.8	92.84 ± 12.98	95.83	94.26 ± 8.59	93.00	0.622
1.12	89.92 ± 10.94	87.50	92.44 ± 9.39	91.83	0.342
1.16	86.21 ± 9.80	86.50	88.52 ± 12.14	87.67	0.421
1.20	92.46 ± 11.43	89.33	89.19 ± 9.12	89.50	0.56

*Values are shown as aritmetic means ± standart deviation; ** – median of the values

Table No. 13. ABP (MEAN) values dispersion on the 2nd day of the research among the groups

Day. Hour	Experimental Group		Control Group		p-value
	$\bar{x} \pm sd$ *	Md**	$\bar{x} \pm sd$ *	Md**	
2.8	92.19 ± 10.84	92.67	90.36 ± 13.15	91.00	0.280
2.12	92.22 ± 11.77	91.00	92.36 ± 10.18	91.5	0.963
2.16	90.09 ± 11.71	87.50	93.83 ± 11.70	93.83	0.220
2.20	92.16 ± 10.42	90.33	92.36 ± 12.14	93.17	0.807

*Values are shown as aritmetic means ± standart deviation; ** – median of the values

Table No. 14. ABP (MEAN) values dispersion on the 3rd and 4th days of the research among the groups

Day. Hour	Experimental Group		Control Group		p-value
	$\bar{x} \pm sd$ *	Md**	$\bar{x} \pm sd$ *	Md**	
3.8	88.41 ± 10.83	87.00	93.73 ± 11.14	92.83	**0.031**
3.10	88.66 ± 9.51	87.33	91.93 ± 11.86	93.33	0.243
3.12	90.19 ± 11.72	87.00	96.99 ± 11.79	95.50	**0.016**
3.16	91.47 ± 8.17	91.50	95.18 ± 9.80	93.50	0.186
3.20	91.64 ± 11.15	91.83	94.04 ± 9.49	93.67	0.373
4.8	90.37 ± 6.80	89.33	89.77 ± 9.29	88.83	0.777
4.12	88.74 ± 4.40	88.67	89.91 ± 7.39	89.83	0.461

*Values are shown as aritmetic means ± standart deviation; ** – median of the values

Glucose concentration:

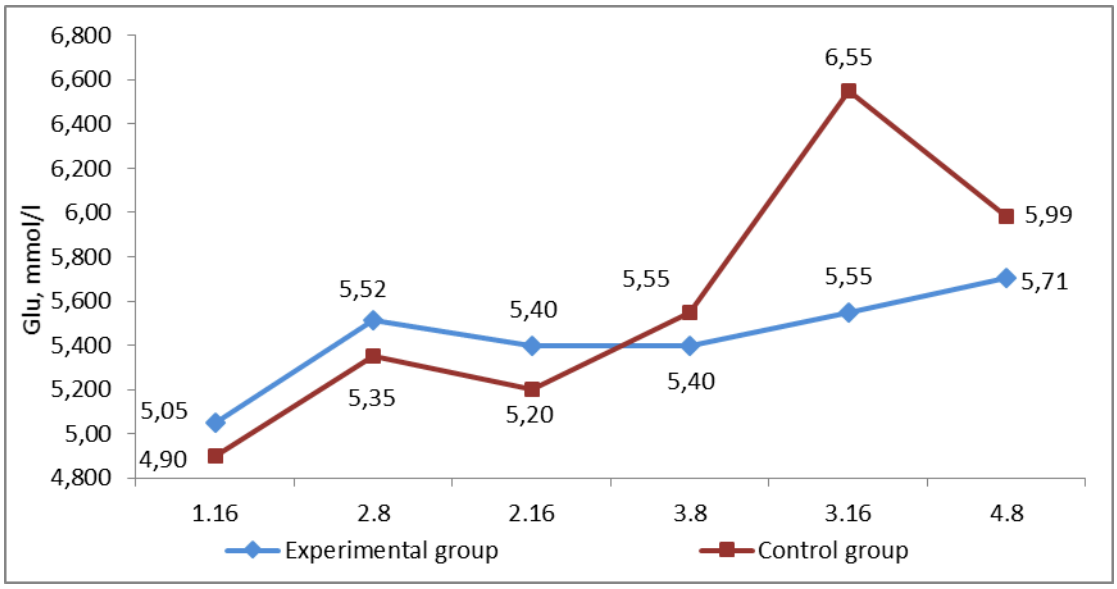
By comparing glucose concentrations among the groups, on the 3rd day of the research a significant difference between the means of the experimental (5.55 mmol/l) and control (6.55 mmol/l) groups after 7 hours of naltrexone induction was detected (3.16) (p=0.01269) (Table No. 15) (Picture No. 6):

Table No. 15. Glucose concentration values dispersion among the groups

Day. Hour	Experimental group		Control group		p-value
	$\bar{x} \pm sd$ *	Md**	$\bar{x} \pm sd$ *	Md**	
1.16	4.90 ± 0.72	5.05	4.95 ± 0.92	4.90	0.812
2.8	5.56 ± 0.91	5.52	5.69 ± 0.76	5.54	0.912
2.16	5.34 ± 0.64	5.40	5.32 ± 0.88	5.20	0.382
3.8	5.65 ± 1.08	5.40	5.99 ± 1.27	5.55	0.379
3.16	5.72 ± 1.41	5.55	6.35 ± 1.40	6.55	**0.013**
4.8	5.76 ± 1.17	5.71	5.91 ± 1.14	5.41	0.584

**Values are shown as aritmetic means ± standart deviation; ** – median of the values

Picture No. 6. Comparison of glucose concentrations among the groups



C-reactive protein:

By comparing CRP concentrations among the groups, on the 4rd day of the research a significant difference between the means of the experimental (1.00 mg/l) and control (3.10 mg/l) groups was detected (3.16) (p=***0.040***).

Table No.16. CRP values dispersion among the groups

CRP / Day	Experimental group		Control group		p-value
	$\bar{x} \pm sd$ *	Md**	$\bar{x} \pm sd$ *	Md**	
2	3.64 ± 4.62	2.50	6.84 ± 8.90	4.85	0.071
3	1.49 ± 2.14	1.00	2.43 ± 2.90	1.40	0.224
4	2.04 ± 3.16	1.00	5.09 ± 7.81	3.10	***0.040***

*Values are shown as aritmetic means ± standart deviation; ** – median of the values

Table No. 17. Comparison of CRP concentration means among the groups

Criteria	p-value	Test
2CRB	0.071	Wilcoxon rank sum
3CRB	0.224	Wilcoxon rank sum
4CRB	***0.040***	Wilcoxon rank sum

Electrolytes:

There was no significant difference among the experimental and control groups by comparing serum electrolytes concentrations (Tables No. 18, 19, 20, 21):

Table No. 18. Potassium (K^+) serum concentration values among the groups

K / Day	Experimental group		Control group		p-value
	$\bar{x} \pm sd$ *	Md**	$\bar{x} \pm sd$ *	Md**	
2	4.14 ± 0.26	4.20	4.20 ± 0.23	4.20	0.288
3	3.83 ± 0.26	3.87	3.92 ± 0.26	3.97	0.105
4	3.92 ± 0.37	3.90	3.98 ± 0.35	3.90	0.645

*Values are shown as aritmetic means ± standart deviation; ** – median of the values

Table No. 19. Sodium (Na^+) serum concentration values among the groups

Na / Day	Experimental group		Control group		p-value
	$\bar{x} \pm sd$ *	Md**	$\bar{x} \pm sd$ *	Md**	
2	138.70 ± 2.59	139	138.17 ± 2.80	138	0.210
3	140.80 ± 3.39	141	140.13 ± 4.55	140	0.344
4	139.73 ± 2.46	140	138.87 ± 3.00	139	0.227

*Values are shown as aritmetic means ± standart deviation; ** – median of the values

Table No. 20. Chloride (Cl^-) serum concentration values among the groups

Cl / Day	Experimental group		Control group		p-value
	$\bar{x} \pm sd$ *	Md**	$\bar{x} \pm sd$ *	Md**	
2	104.85 ± 2.87	104.00	104.26 ± 2.92	104.00	0.633
3	102.58 ± 3.20	101.80	102.95 ± 3.47	102.70	0.669
4	105.60 ± 3.56	106.00	104.71 ± 3.74	105.50	0.573

*Values are shown as aritmetic means ± standart deviation; ** – median of the values

Table No. 21. Magnesium (Mg^{++}) serum concentration values among the groups

Mg / Day	Experimental group		Control group		p-value
	$\bar{x} \pm sd$ *	Md**	$\bar{x} \pm sd$ *	Md**	
2	0.82 ± 0.09	0.80	0.89 ± 0.28	0.83	0.157
3	0.88 ± 0.19	0.91	0.95 ± 0.26	0.94	0.214
4	0.76 ± 0.06	0.77	0.80 ±0.08	0.79	0.041

*Values are shown as aritmetic means ± standart deviation; ** – median of the values

Liver enzymes: AST, ALT

There was no significant difference among the experimental and control groups by comparing serum liver enzymes (AST and ALT) concentrations (Tables No. 22, 23):

Table No. 22. AST serum concentration values among the groups

AST / Day	Experimental group		Control group		p-value
	$\bar{x} \pm sd$ *	Md**	$\bar{x} \pm sd$ *	Md**	
2	31,83 ± 19,99	24,0	49,07 ± 77,37	30,0	0,270
3	28,03 ± 17,34	23,0	43,07 ± 37,19	31,0	0,108
4	29,76 ± 14,53	24,0	43,04 ± 32,60	32,5	0,160

*Values are shown as aritmetic means ± standart deviation; ** – median of the values

Table No. 23. ALT serum concentration values among the groups

ALT / Day	Experimental group		Control group		p-value
	$\bar{x} \pm sd$ *	Md**	$\bar{x} \pm sd$ *	Md**	
2	33,72 ± 23,90	24,0	49,68 ± 44,46	31,5	0,090
3	33,34 ± 23,39	24,0	53,96 ± 49,32	35,0	0,089
4	30,90 ± 18,74	22,0	48,71 ± 38,09	37,5	0,078

*Values are shown as aritmetic means ± standart deviation; ** – median of the values

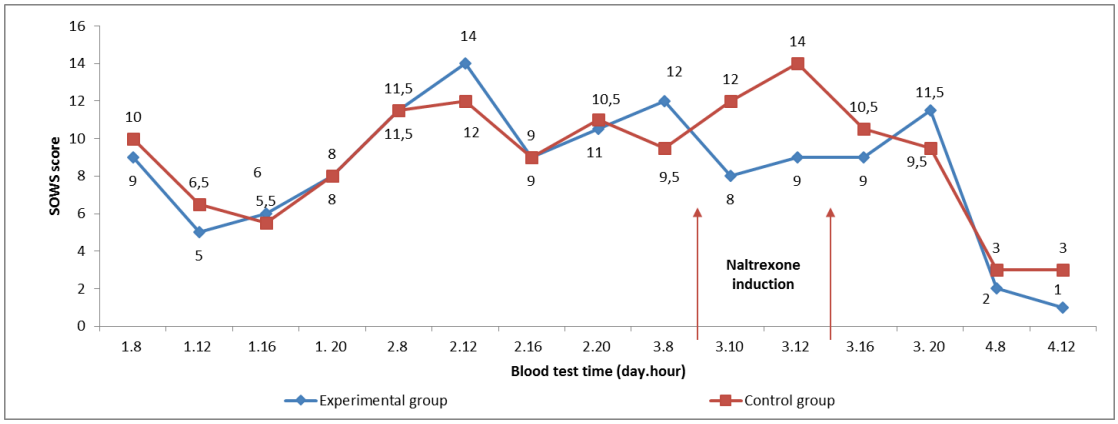
Common blood test:

There was no significant difference among the experimental and control groups by comparing common blood test: Hgb, Hct, MCV, WBC, PLT.

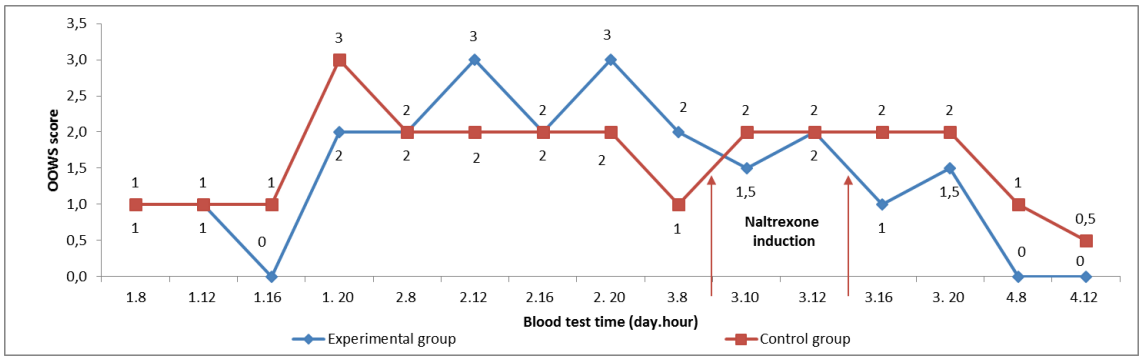
SOWS and OOWS values:

There was no significant difference among the groups in quantities of medications used during the rapid opioid detoxification procedure; that is why the results of SOWS and OOWS were not influenced by the variety of doses of medicine prescribed. The survey showed no statistically significant difference when comparing the results of the scales among the control and experimental groups either, until the naltrexone induction started (morning of the 3rd day of the research). After the beginning of naltrexone induction, significant improvement in opioid withdrawal treatment in the experimental group was registered: the values of SOWS and OOWS were significantly lower as compared to the ones before the induction (Picture No. 7 and Picture No. 8):

Picture No. 7. Changes of SOWS values in the groups



Picture No. 8. Changes of OOWS values in the groups



Meanwhile, the control group had opposite results: the subjective and objective values of the scales showed an exacerbation of opioid withdrawal after naltrexone induction. In the evening of the 3rd day, when the stress impact, evoked by the naltrexone induction, ended, both subjective and objective withdrawal expressions regressed into normal ranges and managed to match the values before the naltrexone induction in both groups. However, the experimental group showed less acutely expressed opioid withdrawal comparing to the control group. On the 4th day of the research (1 day after naltrexone induction), the values in both subjective and objective opioid withdrawal scales in the experimental group were significantly lower comparing to the values in the control group, giving the notion the participants in the experimental group felt objectively and subjectively better than the participants in the control group.

Conclusions:

1. Rapid opioid detoxification under a conscious sedation technique, by using a method of a gradual increase in naltrexone dosage (starting from an initially small dose of 50 µg and increasing it gradually till a total dose of 12.5 mg) induces neither significant increase in concentrations of usual stress markers – cortisol and ACTH, nor oxidative stress markers – GSH and GST, and in some cases even induces a significant reduction in concentrations of stress markers. By comparing the two methods of naltrexone induction – a gradual increase of naltrexone (starting from an initially small dose of 50 µg and increasing it gradually till a total dose of 12.5 mg) and giving a single (12.5 mg) dose of naltrexone, - a gradual increase in naltrexone dosage has been considered as a

method, causing significantly smaller stress respond than the one of a single naltrexone dosage.

2. There was no significant difference in quantitative and qualitative changes of haemodynamics, respiratory system, gastrointestinal tract function while using the two methods of naltrexone induction – a gradual increase of naltrexone (starting from an initially small dose of 50 μg and increasing it gradually till a total dose of 12.5 mg) or giving a single (12.5 mg) dose of naltrexone.
3. By comparing the two methods of naltrexone induction – a gradual increase of naltrexone (starting from an initially small dose of 50 μg and increasing it gradually till a total dose of 12.5 mg) or giving a single (12.5 mg) dose of naltrexone, has been proven that:
   3.1. Glucose concentration, while using a single dose (12.5 mg) method of naltrexone induction, was constantly increasing from the beginning till the end of the research, and its concentration after single dose naltrexone induction was significantly higher than using a gradual increase of naltrexone (starting from an initially small dose of 50 μg and increasing it gradually till a total dose of 12.5 mg).
   3.2. There were no significant changes in concentrations of K^+, Na^+, Cl^-, Mg^{++} ions while comparing the methods;
   3.3. There were no significant changes in concentrations of C-reactive protein while comparing the methods;
   3.4. There were no significant changes in concentrations of AST, ALT while comparing the methods;
   3.5. There were no significant changes in the count of WBC, PLT and in concentrations of Hgb, Hct while comparing the methods.
4. By comparing the expression of opioid withdrawal after start of naltrexone induction and after the end of induction, while using a gradual increase of naltrexone (starting from an initially small dose of 50 μg and increasing it gradually till a total dose of 12.5 mg) and giving a single (12.5 mg) dose of naltrexone, has been proven that:
   4.1. Objective opioid withdrawal symptoms, according to the OOWS values, were significantly higher while using method of a single dose (12.5 mg) naltrexone induction;

4.2. Subjective opioid withdrawal symptoms, according to the SOWS values, were significantly higher while using method of a single dose (12.5 mg) naltrexone induction.

Discussion:

Introducing opioid antagonists to clinical practice as a special method for treating opioid withdrawal has been a method known for 40 years (Blachley P, Casey D, Marcel L, 1975). However, special dosage considerations have not been solved. Our research, as well as some other investigations (Spanagel R, Lancet 1999; Gowing L, Ali R, et al., Cochrane 2000) justifies benefits of rapid opioid detoxification by using low-dose naltrexone induction. The technique is innovative and new, that is why not much information, concerning the method, can be found, but literature shows beneficial side of this treatment. There have been some published articles describing enhanced analgesic effects of opiates by using very low doses of opioid antagonists: Crain SM, Shen KF in their research 2001 with acute hyperalgesic effects on mice, treated with opioids, show the benefit of co-treatment with ultra-low-dose of naltrexone (1–100 pg/kg). According to the research, by using very small amounts of naltrexone, is possible to "block opioid-induced hyperalgesia and unmask potent opioid analgesia". Moreover, an increase of opioid analgesic effect after administering a low dose (0.25 μg x kg-1) of naltrexone has been registered in postoperative patients after an abdominal hysterectomy operation (Gan TJ, Ginsberg B, 1997). A greater degree of pupillary miosis, as a proof of synergistic effect of opioids and their antagonists co-acting, has been registered in Praitner M, Loimer N. research in 1990. The survey shows a physiological (objective) respond, not only a subjective feeling of analgesia, which can be interpreted by a patient himself. In our research subjective and objective data was also collected separately in order to achieve more reliable results. Literature also gives some information concerning the treatment of opioid withdrawal by using higher doses of naltrexone. Mannelli P, De Risio S, et al. (1999) introduced a case report in which an accidental ingestion of naltrexone (50.0 mg) in a patient, who had been taking methadone, was made. The amount of naltrexone, which was used, induced symptoms of acute withdrawal and the patient, in order to ease his state, had been sedated for 47 hours. After the sedation he did not have any symptoms of opioid withdrawal. The method was similar to a rapid opioid detoxification procedure, which

was used in our survey, and helped to support the beneficial effect of antagonist induced opioid detoxification. However, a single dose of naltrexone (50.0 mg) was not described as an appropriate dose for opioid detoxification due to severe withdrawal symptoms, which occurred. Later in 2013 Mannelli P, Gottheil E, et al. maintained an idea that using low doses of naltrexone (0.125-0.250 mg) did not induce opioid withdrawal. Our survey also supports the opinion that a gradual increase of low doses of naltrexone is a better choice than using a single dose of naltrexone induction.

Practical recommendations:

According to the results of the research, Rapid opioid detoxification under a conscious sedation technique, while using a gradual increase of naltrexone induction, starting from an initially small dose of 50 μg and increasing it gradually till a total dose of 12.5 mg on the 3rd day of the detoxification, induces neither subjective, nor objective increase in symptoms of opioid withdrawal or other dangerous complications. Opposite, while using this method of naltrexone induction, a reduction in classic stress markers and oxidative stress markers has been showed. The complex consisting of rapid opioid detoxification, based on basic pharmaceutical requirements, and the method of a gradual dosage of naltrexone induction, described in the research, enables to accomplish an opioid detoxification procedure during a very short period of time and with a low expenditure. This procedure could be especially effective for motivated patients who show their will to continue a complex opioid dependency treatment in specialized health care centres. The practical use of this method does not require hospitalization in specialized centres. That is why the procedure can be safely used in non-specialized hospitals or dependency centres. This change would simplify and increase the efficiency of the opioid detoxification procedure, as well as enable to decrease a non motivated fear of detoxification for opioid addicts. The method of opioid detoxification, which does not induce a stress response, may decrease the risk of the detoxification procedure, especially for patients who have cardiovascular illnesses, diabetes mellitus or other severe somatic disease, because an acute stress response may induce a severe deterioration of their health condition. No special training or special medical equipment and medicine are needed for the practical use of the method. That is why the procedure can be introduced into clinical practice in the

every 2nd or 3rd level health care institution, which allows hospitalization of the patient.

PUBLICATIONS AND PRESENTATIONS BY THE AUTHOR IN RELATION TO THE TOPIC OF THE THESIS

Publications

1. **Badaras R**, Dragelytė G, Vaitekonytė I, Ivaškevičius J, Šipylaitė J. The Stress Respond, Related To the Opioid Abstinence And Detoxification: literature review [Article in Lithuanian]. Medicinos teorija ir praktika. 2015;21(1):86–90.
2. **Badaras R**, Kazbarienė B, Zdanavičius L, Vaitekonytė I, Dragelytė G, Molytė A, Ivaškevičius J, Didžiapetrienė J. Changes in reduced Glutathione and Glutathione S-transferase concentration during rapid opioid detoxification [Article in Lithuanian]. Laboratorinė medicina. 2015;17(4):147–52.
3. **Badaras R**, Vaitekonytė I, Molytė A, Zdanavičius L, Dragelytė G, Mikulevičienė G, Garšva J, Barkovski M, Didžiapetrienė J, Ivaškevičius J. The influence of Naltrexone induction method on changes of opioid addiction scores during rapid opioid detoxification [Article in Lithuanian]. Acta Medica Lituanica. 2015;22(4):223–35.

Presentations

1. **Badaras R.** Stress can be avoidable in opioid detoxification. Conference "Evolutionary medicine: perspectives in understanding health and disease", May 27-30, 2014, Vilnius. (Oral presentation).
2. **Badaras R**, Dragelyte G, Zdanavicius L, Jovaisa T, Dirzys D, Ivaskevicius J. Stress can be avoidable in opioid detoxification. 16th World Congress of International Society of Addiction Medicine (ISAM), October 2-6, 2014, Yokohama, Japan. (Oral presentation).
3. **Badaras R**, Dragelyte G, Zdanavicius L, Jovaisa T, Ivaskevicius J. Influence of Naltrexone induction regime on the concentration of stress hormones during rapid opioid detoxification. J Tox Clin Tox. 2015;53(1): 354-5. 35th International Congress of European Association of Poisons Centres and Clinical Toxicologists (EAPCCT), May 26-29, 2015, Malta.

(Oral presentation has been short-listed for the Congress prize for best scientific presentation).

ABOUT THE AUTHOR OF THE THESIS

First name, surname	Robertas Badaras
Date of birth	18 August 1965
Nationality	Lithuanian
Investigational site address	Republic Vilnius University Hospital Siltnamiu 29 Vilnius, LT-04130

Education

1983-1989	Pre-medicine and medicine studies, Medical Faculty, Kaunas Medical Academy
1989-1990	Fellow of Internal Medicine, Vilnius University Medical Faculty
1991-1993	Residency in Clinical Toxicology, Vilnius University Medical Faculty
2007-2009	Residency in Anesthesiology and Reanimatology, Vilnius University Medical Faculty

Working experience

1991 – 2010	Clinical toxicologist in Vilnius University Emergency Hospital
2003 – present	Assistant in Vilnius University Clinic of Anaesthesiology and Intensive Care
2003 – present	Manager of specialized fellowship in Clinical Toxicology in Vilnius University Medical Faculty
2010 – present	Head of the Toxicology Centre in Vilnius University Emergency Hospital

Other publications

1. Co-author of handbook „Klinikinė toksikologija“, Kaunas 2002.
2. Co-author of handbook „Medicinos toksikologija - ūminių apsinuodijimų diagnostika ir gydymas“, Kaunas 2010.
3. Co-author of handbook „Greitieji opioidinės priklausomybės detoksikacijos būdai“, Vilnius University 2009.
4. Co-author of handbook „Dug abuse treatment and prevention: Study manual for medical students and young doctors“, Leonardo da Vinci Programme Pilot Project: BG/04/B/F/PP-166016.
5. Ivaskevicius J, Jovaisa T, Laurinenas G, Vosylius S, Sipylaite J, **Badaras R**. Safety and effectiveness of opiate antagonist detoxification under general anesthesia [Article in Lithuanian]. Medicina. 2005;41(12):1011-8.

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8. Dragelyte G, **Badaras R**, Zdanavicius L. The Serotonin Syndrome – difficult to recognize, easy to treat [Article in Lithuanian]. Medicinos teorija ir praktika (Medical theory and practice). 2013;19(2),153–160.