

Immunological patterns of opioid withdrawal

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Opioid drug abuse and modulation of immune function

- Psychoactive substances lead to dysregulation of brain neurochemical systems (dopamine, serotonin, opioid, GABAergic); activate the HPA axis; change regulation of emotional, motivational processes, causing the development of dependence syndrome.
- endogenous opioid peptides enhance the immune response, exogenous - have immunosuppressive effects through molecular and biochemical mechanisms. The slide shows some of them:
 - opioid receptors (*mu*, *delta*, and *kappa*) - belong to G-protein-coupled receptor (GPCR) superfamily;
 - transcription nuclear factor- κ B (NF- κ B); chemokine receptors CXCR4; amine-associated receptor 1 (TAAR1); glucocorticoid hormones.

(Крыжановский Г. Н. и др., 1998, 2003 ; Анохина И. П., Борисова Е. В., 1999; Давыдова Т. В. и др., 2002; Панченко Л. Ф., Гуревич К.Г., 2001; Mansour A et al, 1995; Friedman H. et al., 2003; Rahim RT et al., 2004; Spanagel R., Heilig M., 2005; Li L. et al., 2005; Williams JP, Lambert DG, 2005; Sharp B. M., 2006; Frolich N et al., 2011; Rogers TJ, 2012; Zhang L et al., 2012; Hwang CK et al., 2012; Mithal DS, Banisadr G, Miller RJ, 2012; Podhaizer EM, 2012).

- Studies supporting a direct role for opioids on immune system modulation emerged with the discovery of opioid receptors and other neuropeptide receptors on immune cells. Because these receptors are expressed in both neural and immune cells and are involved in the regulation of brain-immune axis, they initiate a complex series of signaling events under the influence of drugs, and exert psychoneuroimmunomodulation effect.

(Зозуля А.А., 1990; Девойно Л. В., Ильюченко Р. Ю., 1993; Крыжановский Г. Н. , Магаева С. В. 1998; Корнева Е. А., 1999; Давыдова Т.В., Фомина В. Г., 2006; Идова, Г.В., 2006; Крыжановский и др., 2010; Devoino L., Idova G., Cheido M., 1986; Bhargava H. N., 1990; Roda LG et al., 1996; Friedman H. et al., 2003; Sharp B. M., 2006; Saurer TB et al., 2006; Roy S et al., 2006; 2011; Chang MC et al., 2011; Rogers TJ., 2012; Sacerdote P, Franchi S, Panerai AF, 2012; Nicovic' J, Roy S, 2013)

- The use of opioids and other drugs is associated with significant impact on adaptive and innate immunity, mainly – immunosuppressive:

Impaired function of antigen presenting cells and phagocytic function; modulation of activity of NK cells; changes in the activity of lymphocytes and their number; change in the immune response Th1, Th2; cytokine imbalance.

(Гамалея Н.Б., 1992; Иванец Н.Н., Винникова М.А., 2002; Ветлугина Т.П., Бохан, Н. А., 2005, 2010; Гамалея Н.Б., Ульянова Л.И., 2007; Roy S , 2001 - 2011; Yokota T, Uehara K, Nomoto Y, 2004; Saurer TB et al., 2006; Sacerdote P, 2006; Wang J et al., 2008; Borner C et al., 2009; Rivera-Amill et al., 2010; Clark KH, Wiley CA, Bradberry CW, 2013; Abo-Elnazar S et al., 2014; Loftis JM, Janowsky A, 2014; Sua'rez-Pinilla P et al., 2014; Moaaz M et al., 2014)

- Reduction of protective immune mechanisms in chronic drug abuse contributes to increased host susceptibility to microbial pathogens.
- Epidemiological studies demonstrate that injection drug users (IDU's) are susceptible to sexually transmitted infections caused by a wide range of bacterial, viral, fungal and protozoan pathogens, human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV). Cumulative studies from the past 30 years further establish the correlation between intravenous drug abuse and HIV infection

(Жанков А.И. и др., 1999; Мандель А.И., 2001; Мандель А.И., Бохан Н.А., Редченкова Е.М., 2001; Баранов И.П. и др., 2003; Чуйкова К.И., Скрипник О.Г., Ковалева Т.А., 2004; Alme B et al., 1987; Robinson GM et al., 1987; Wiesli P et al., 2006; Kelschenbach J et al., 2008; Topp L et al., 2008; Cox AL, Thomas DL, 2013; Loftis JM, Janowsky A, 2014; Wiessing L et al., 2014; Salamanca SA et al., 2015).

OPIOID WITHDRAWAL AND IMMUNE MODULATION

- Morphine abuse also leads to development of tolerance and physical dependence, which is well characterized by withdrawal syndromes when morphine is terminated. Morphine withdrawal could be either abrupt (abrupt termination of morphine abuse) (Rahim RT et al., 2002) or precipitated (termination of drug effect by the use of morphine antagonists like Naloxone) (Bhargava HN et al., 1994).
- Morphine withdrawal by itself is considered a stress response where it modulates behavioral, neural and endocrine activity (Houshyar H et al., 2001).
- Morphine withdrawal (both abrupt and precipitated) to have very strong immunosuppressive effects, where the mechanisms mediating immunosuppression are largely unknown and is actively being explored, mainly in experimental models.

(Rahim RT et al., 2002-2005; Feng P et al., 2005; Kelschenbach J et al., 2005; 2008; Eisentein TK et al., 2006; Das S et al., 2011; Nugent AL, Houghtling RA, Bayer BM, 2011; Jamali A et al., 2012; Campbell LA et al., 2013)

Цель исследования:

Study Aim:

Изучить
состояние
системы
иммунитета
при опийной
наркоomanии
на разных этапах
синдрома
отмены

**To examine the
state of the
immune system
in opioid
addiction at
different stages
of opioid
withdrawal**

Methods

- **Cells with receptors:**

CD3, CD4, CD8, CD16, CD72, HLADR, D-RFC (dopamine positive Cells), C-RFC (serotonine positive Cells)

- **Parameters of of humoral immunity:**

IgM, IgG, IgA, IC (immune complexes)

- **cortisol level**

- **Clinical and biochemical blood parameters**

The group examined

Обследованы больные опийной наркоманей со сформировавшейся физической зависимостью, принимающие наркотический препарат, полученный при кустарной химической обработке опия-сырца различными органическими растворителями; одна торговая доза (т. д.) препарата содержит около 0,02 г хлорида морфина

Intravenous drug users with formed physical dependence were examined; used the drug obtained at handicraft chemical treatment of a raw opium; one trade dose (t.d.) contains about 0,02 g of morphine chloride

Characteristics of patients with opioid addiction by sex and age

Men		Women		All patients	
абс.	%	абс.	%	абс.	%
107	79	29	21	136	100
Age at the time of the study ($M \pm \sigma$)					
23,18 \pm 4,35		21,82 \pm 3,34		22,88\pm4,16 (from 15 to 35 years)	

Clinical characteristics of patients studied ($M \pm \sigma$)

Parameters	Patients (n=136)
Средний возраст начала употребления наркотика Age at onset of opioid use	$17,57 \pm 2,88$ (from 12 to 27 years)
Длительность употребления опиатов на момент исследования The duration of drug use at the time of the study	$5,06 \pm 2,69$ (from 1 to 14 years)
Максимальная толерантность Maximum tolerance	$17,64 \pm 9,45$ (from 2 to 40 T.D.)
Срок достижения максимальной толерантности The term of maximum tolerance	$1,93 \pm 1,50$ (from 1,5 months to 8 years)
Продолжительность абстинентного синдрома The duration of withdrawal symptoms	$5,94 \pm 0,90$ (from 4 to 9 days)
Длительность постабстинентного состояния The duration of postabstinent state	$13,56 \pm 6,80$ (from 7 to 35 days)
Количество ремиссий Number of remissions	$2,38 \pm 1,64$ (от 0 до 8)

Этапы иммунологического исследования. Stages of immunological study

- 1 этап – острый абстинентный синдром (ОАС) – больные обследованы в первые сутки поступления в стационар при отнятия наркотика (58 чел.)
Stage 1 - acute withdrawal syndrome (AWS) - patients were examined on the first day of admission to hospital with drug withdrawal (58 persons).
- 2 этап - постабстинентное состояние (ПАС) - больные обследованы на 7-е сутки интенсивной терапии абстинентного синдрома (78 чел.)
Stage 2 – post-abstinence state (PAS) - patients were examined on the 7th day of intensive therapy of withdrawal symptoms (78 persons).
- 3 этап - становление терапевтической ремиссии (ТР) - больные обследованы на 28—35-й день со дня поступления в стационар (69 чел.)
Stage 3 - formation of therapeutic remission (TR) - patients were examined on 28-35 th day after admission to the hospital (69 persons).
- Группы 2 и 3 этапа составили одни и те же пациенты, часть из которых к концу исследования выбыли самостоятельно или по решению лечащего врача.
Groups of stages 2 and 3 included the same patients, some of them by the end of the study dropped out on their own or at the decision of the attending physician.

Pharmacotherapeutic regimens

- **Detoxification** (up to 3 days)
- Differentiated administration of the main groups of drugs to correct disorders:
 - **affective** (Amitriptyline - up to 100 mg / day;
 - **dissonic** (Chlorprothixene up to 100 mg / day);
 - **behavioural** (Neuleptil - up to 30 mg / day, Sonapax up to 50 mg / day);
 - **neurovegetative** (Pyrroxanum - up to 60 mg / day, Grandaxin - up to 100 mg / day);
 - **nootropics** (Piracetam - up to 800 mg / day).

Clinical characteristics of Opioid withdrawal

- Ведущими в структуре ОАС являлись алгический симптомокомплекс, аффективные нарушения (дисфорические, тревожно-депрессивные), диссомнические, нейровегетативные расстройства.

Pain syndrome, affective disturbances (dysphoric, anxiety-depressive), dissomnic, neurovegetative disorders were the leading ones in the structure of the AWS.

- На этапе ПАС алгические, гастроинтестинальные расстройства были слабо выражены у большинства больных. Ведущими симптомокомплексами при ПАС выступали астенические, аффективные и диссомнические расстройства.

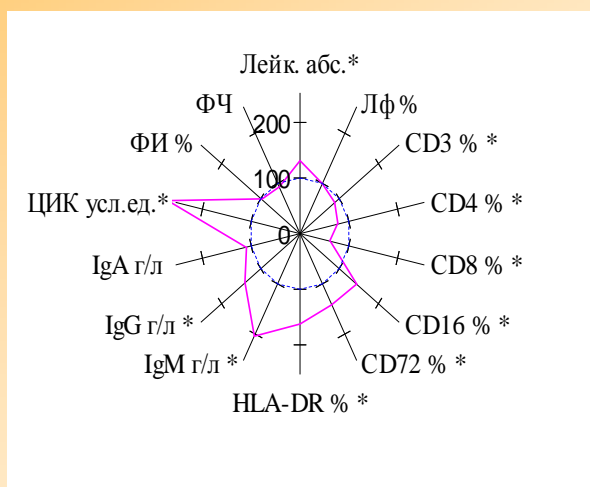
At the stage of PAS, pain, gastrointestinal disorders were mild in most patients. The leading symptoms during PAS were asthenic, affective and dissomnic disorders.

- На этапе формирования терапевтической ремиссии (ТР) аффективные расстройства отмечались в единичных случаях и были представлены тревожно-ипохондрической, резидуальной астенодепрессивной симптоматикой с пониженным настроением, ощущением психического дискомфорта.

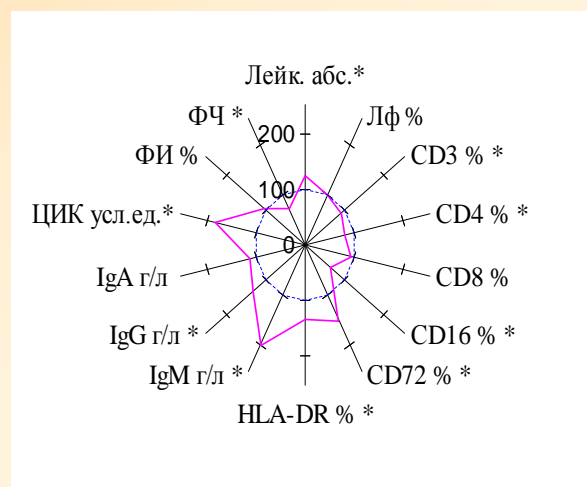
At the stage of formation of therapeutic remission (TP) affective disorders were observed in some cases and were represented by anxiety-hypochondriac, residual asthenodepressive symptoms with low mood, sense of mental discomfort.

Состояние системы иммунитета у больных опийной наркоманией на этапах синдрома отмены

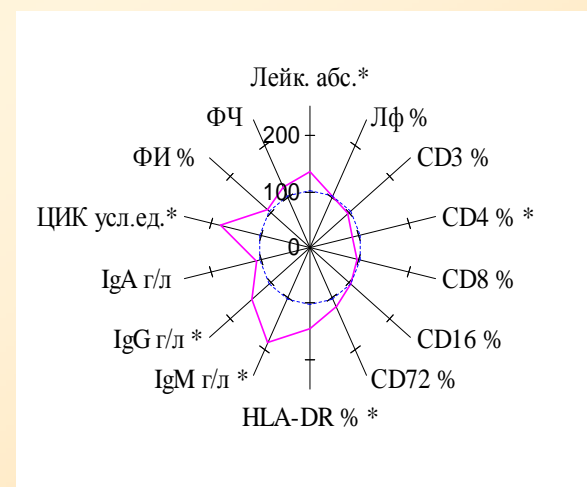
The state of the immune system in patients with opioid addiction at the stages of withdrawal



A



B



C

A – опийный абстинентный синдром (ОАС); **B** – постабстинентное состояние (ПАС); **C** – формирования терапевтической ремиссии (ТР)

A - acute withdrawal syndrome (AWS) ; B - post-abstinence state (PAS);

C - formation of therapeutic remission (TR)

The state of the immune system in patients with opioid addiction at the stages of withdrawal

- **AWS** - in patients compared with controls: leukocytosis, increased numbers of HLADR⁺, CD72⁺, CD16⁺, depletion of the pool of immunocompetent cells by mature CD3⁺ lymphocytes, helpers/inducers CD4⁺, cytotoxic T-lymphocytes CD8⁺, activation of factors of the humoral immunity with increasing concentration of immunoglobulins and circulating immune complexes were found.
- **PAS** - the basic character of immune disturbances remains, there is an increase in cytotoxic T-lymphocytes up to normal values, however, the number of natural killer cells (CD16⁺), both in relation to the first point of the study, and to the values of norm decreases.
- **TR** - the clinical effect of treatment is accompanied by positive dynamics of some parameters of cellular immunity: normal number of CD16⁺, CD8⁺ - lymphocytes, there was a trend to the values of the norm of lymphocytes CD3⁺, CD 72⁺. However, there remain quantitative deficiency of CD4⁺, increased number of HLADR⁺- lymphocytes and level of IgG, IgM; the level of circulating immune complexes is twice as high than in the healthy group.

Immune complexes in the organism of patients with opioid addiction

- The accumulation of immune complexes in the organism of patients with opioid addiction may be linked to permanent antigenic load (toxic factors, chronic viral infection), as well as - to impaired elimination of circulating immune complexes from the body.
- In order to reveal possible causes of accumulation of circulating in the blood of patients complexes "antigen-antibody", a comparative study of the functional activity of neutrophils of patients with opioid addiction and healthy persons in relation to the immune complexes in experiments in vitro has been conducted .
- Neutrophils isolated from the blood of patients and healthy persons were incubated with the standard serum with known concentration of immune complexes at 37 ° C. The percentage of immune complexes bound by neutrophils from serum was measured after 30, 60 and 90 minutes

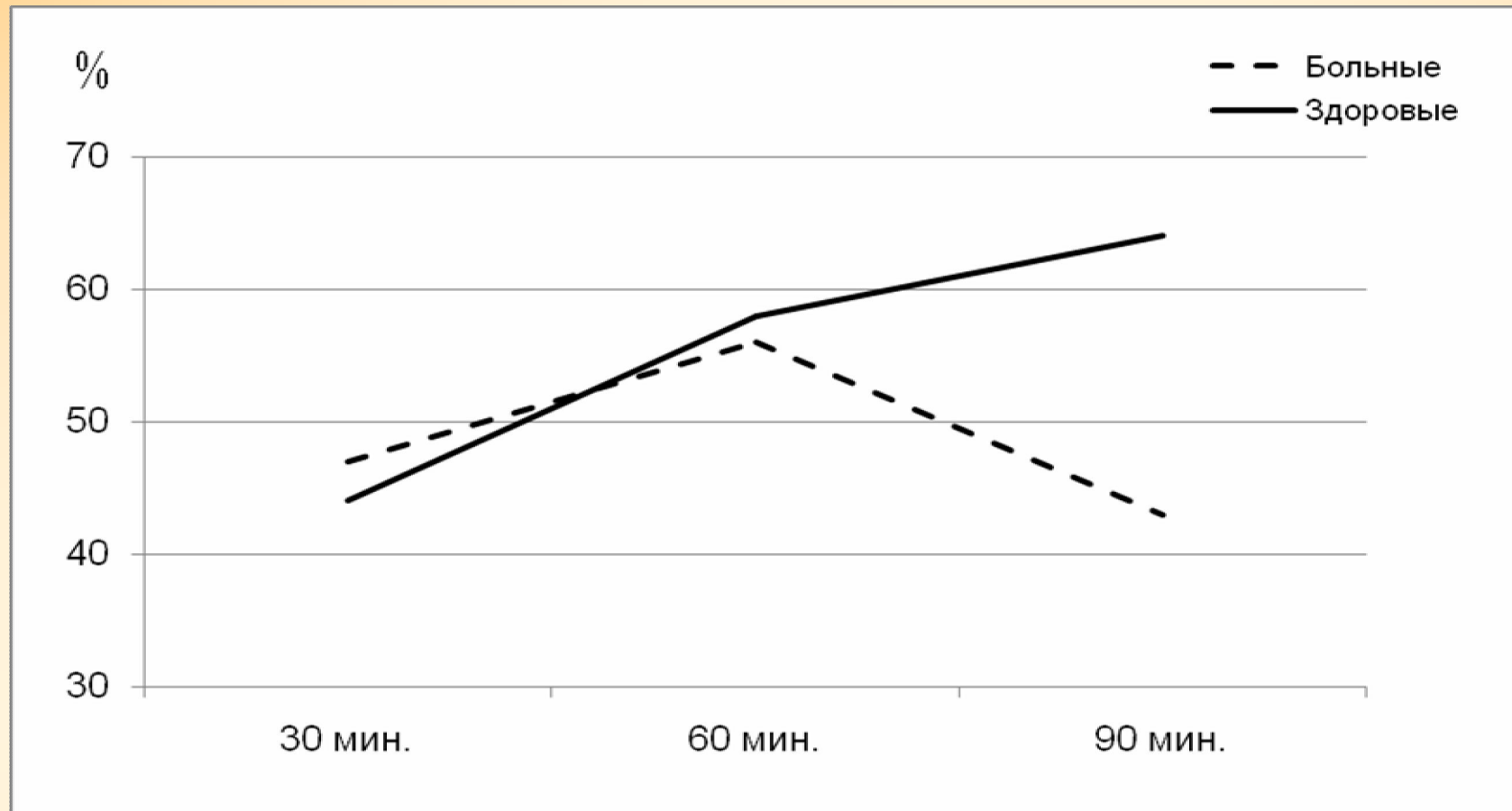
Dynamics of immune complexes in vitro experiments

- - - opioid adiction (IDU's); _____ healthy persons

After 30 minutes of incubation, neutrophils of healthy persons and addicts bound $44,38 \pm 3,10$ and $47,33 \pm 3,70\%$ of immune complexes.

After 60 minutes - $57,88 \pm 3,51$ and $55,67 \pm 2,53\%$, respectively.

After 90 minutes of incubation, part of the patients' neutrophils-bound immune complexes was eluted again in the incubation mixture and the percentage of bound immune complexes decreased abruptly, while in the experiments with neutrophils of healthy persons - increased ($42,50 \pm 2,22\%$ in patients and $64,00 \pm 3,60\%$ in controls).

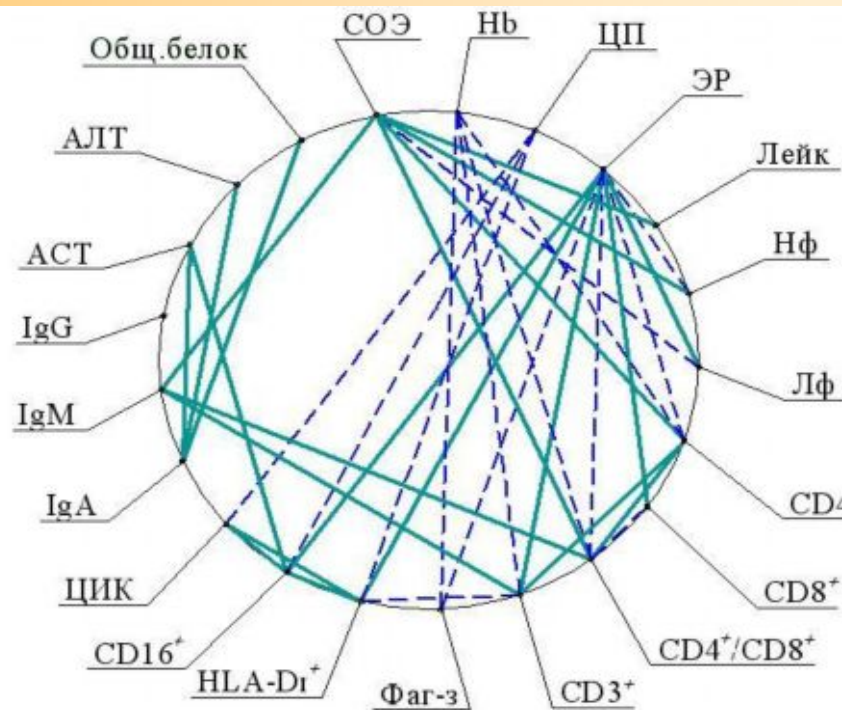


Psychoneuroimmunomodulation in opioid withdrawal

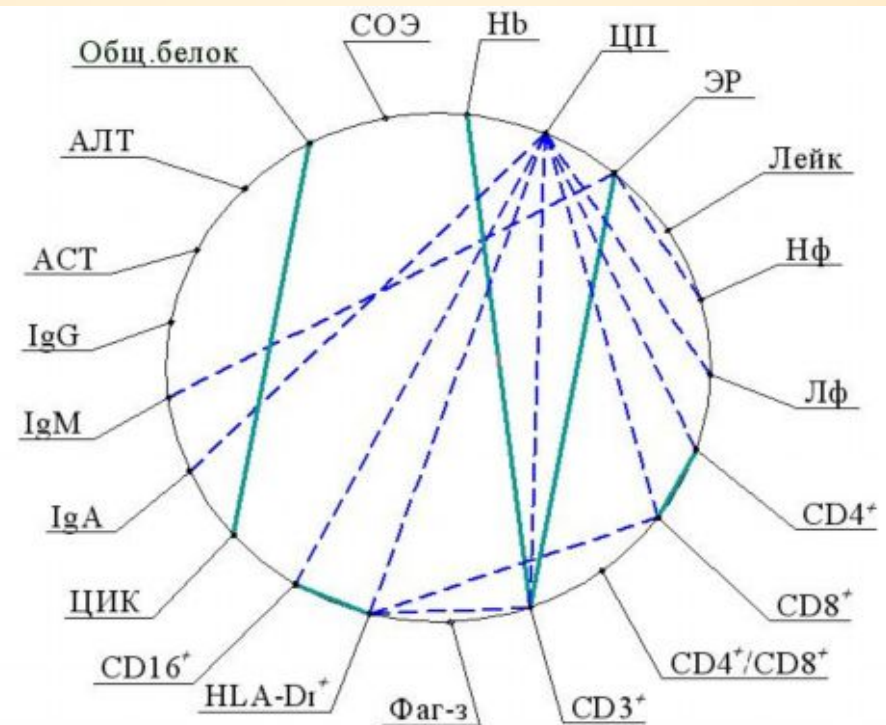
- Psychoneuroimmunomodulation - to change the parameters of immunity, depending on the clinical features of the pathological process.
- In this study, the following clinical characteristics were taken into account: the stages of withdrawal; duration of drug use, tolerance in trade doses (t.d.).
- At the stage of acute withdrawal syndrome (AWS) in the first day of admission to hospital patients interrelation between the parameters of immunity and clinical characteristics were not found. This is probably due to the predominance in the clinical picture of AWS somatic component, the toxic effect of narcotic substances on immunocompetent cells, systems and organs.
This is probably due to the predominance in the clinical picture of AWS of somatic component, a toxic effect of narcotic substance on immunocompetent cells, systems and organs. The high correlation among parameters of the immunity, biochemical parameters and indicators of red blood cells confirms this , and testifies to the tensions of functions of homeostatic body systems.
- These data on the next slide shows.

Structure of reliable correlations between parameters of immunity with biochemical parameters and parameters of red blood cells

AWS



PAS



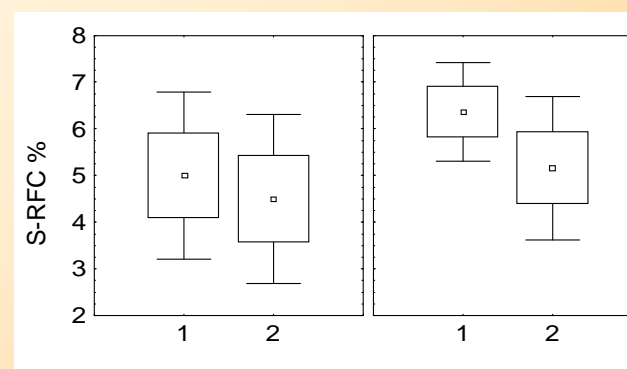
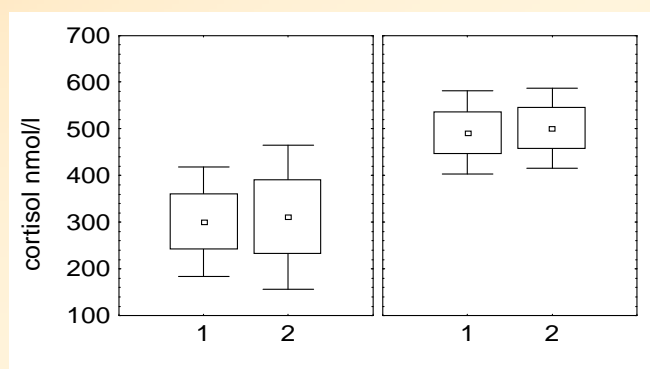
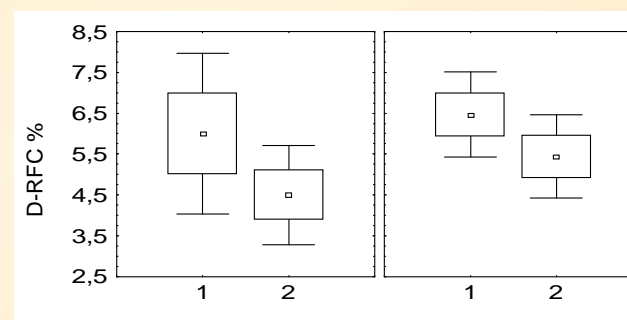
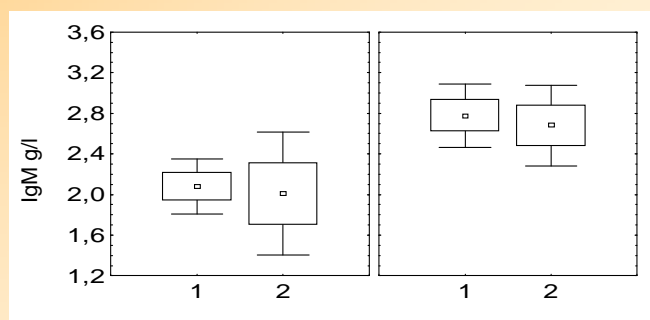
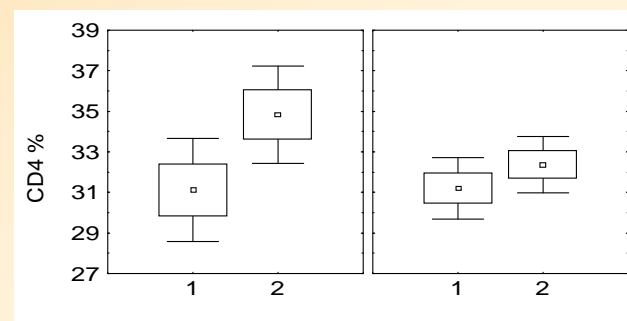
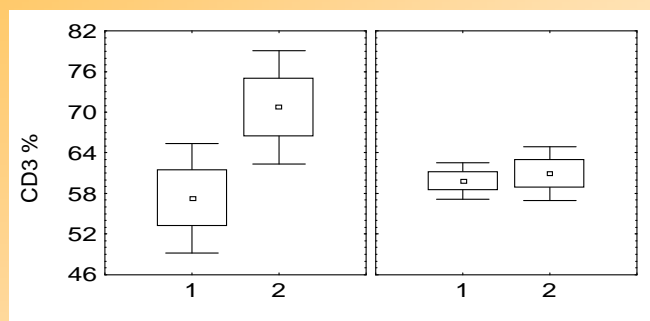
острый абстинентный синдром

постабстинентное состояние

Dynamics of cortisol and indicators neurotransmitter metabolism in patients with opioid withdrawal

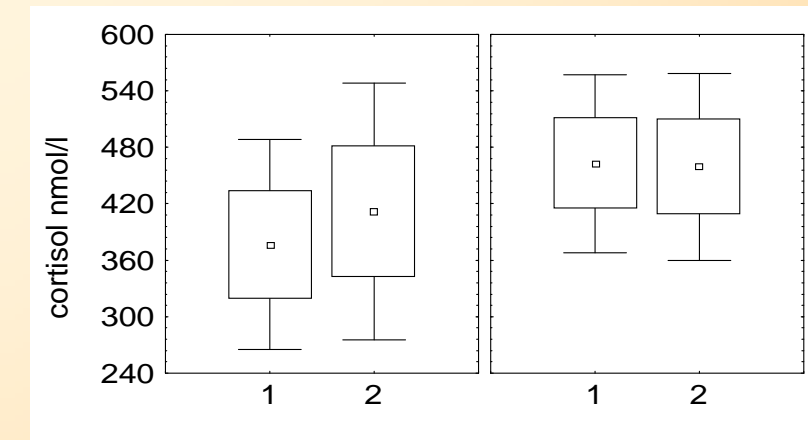
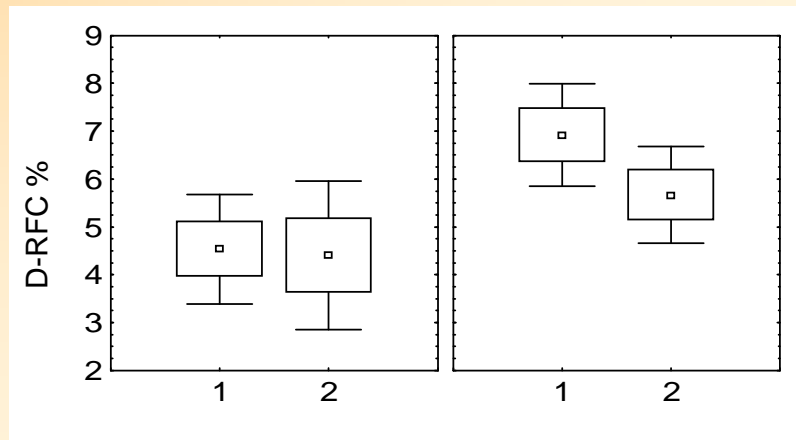
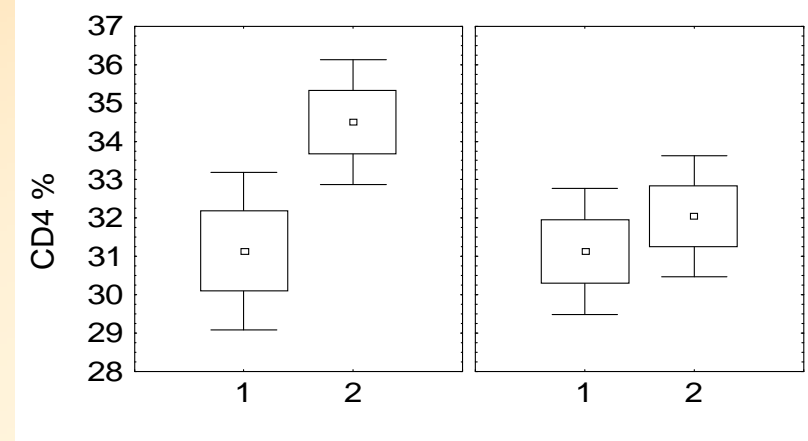
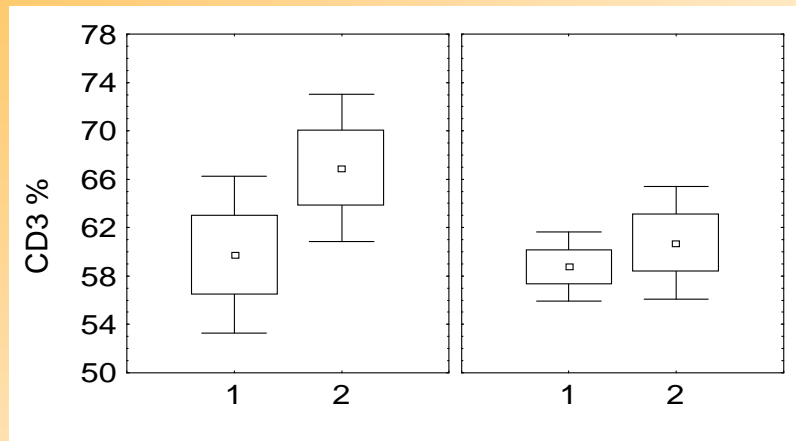
Parametrs	control	opioid drug abuse	
		PAS	TP
Cortisol, nmol/l	323,03±21,40	593,95±34,04***	574,57±34,02***
C-RFC (serotonine positive Cells), %	3,63±0,36	6,09±0,46***	5,03±0,65*
D-RFC (dopamine positive Cells), %	2,70±0,35	6,41±0,45***	5,26±0,44***
* $p<0,05$; *** $p<0,001$			

The dynamics of the studied parameters depending on duration of drug use



- 1 – Post-Abstinence Stage (PAS); 2 – Therapeutic Remission Stage (TR);
- A – duration of drug use of up to 3 years ($2,01 \pm 0,77$);
- B – duration of drug use of 4 years or more ($6,32 \pm 2,13$)

The dynamics of the studied parameters depending on the maximum tolerance



A

B

A

B

1 – Post-Abstinence Stage (PAS); 2 – Therapeutic Remission Stage (TR);
A – tolerance of up to 10 trade doses ($7,51 \pm 2,41$);
B – 11 trade doses or more ($22,55 \pm 7,49$)

- Thus, in opioid addiction pathophysiological psychoneuroimmune associativity is formed, indicating disturbance of intersystem relations and necessity to use various methods of therapeutic intervention to restore them (optimize), in particular, the use of immunomodulators.

The first phase of the rehabilitation cycle begins with detoxification (duration 7-10 days)

- SUMS-1 (Enterumin) - mineral matrix (aluminum oxide) coated with carbon, with developed meso- and macroporous structure, has high sorption activity, eliminates endo- and exotoxins from the body.
- Scheme of administration: 20-30 grams three times daily for 7 to 10 days in combined pharmacotherapy.
- The clinical picture of the opioid withdrawal syndrome in patients receiving the SUMS-1 differed from the classical description severe dyspeptic symptom complex was not observed, pains in the epigastric region decreased, appetite restored quickly and physiological functions normalized, patients reported improvement in general state of health.
- Repeated laboratory tests (day 14-15 of the initiation of intake of the sorbent) have shown decrease up to norm or tendency to normalization of the number of leukocytes, significant reduction in the level of aminotransferase, levels of IgM, IgG, CIC.

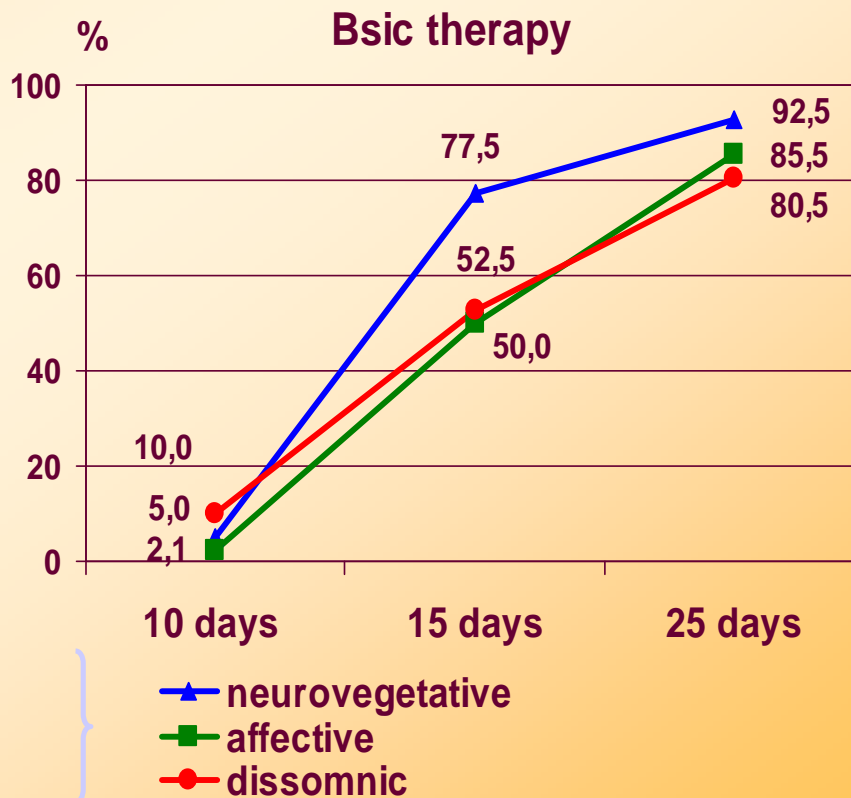
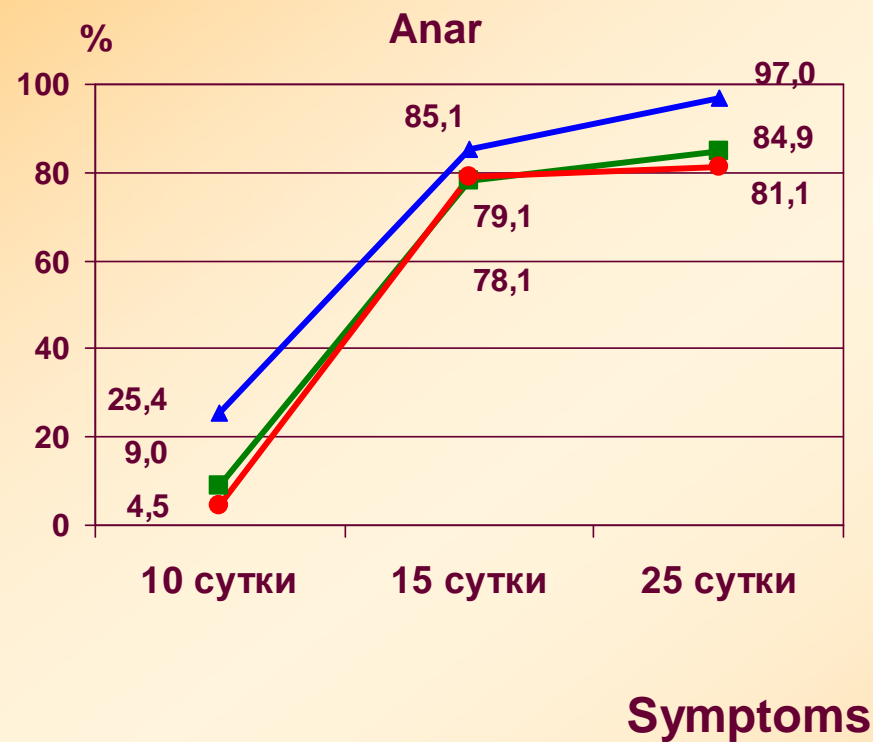
The second phase of the rehabilitation cycle at the stage of therapeutic remission

- **Galavit** (Aminodihydrophthalasindionum natrium) - immunomodulatory and anti-inflammatory agent, regulates the synthesis of cytokines, proliferative activity of T-lymphocytes, enhances phagocytosis, increases non-specific protection of the body, it has an antioxidant effect.
- Scheme of administration: 100 mg / day for 10 to 15 days in combined pharmacotherapy
- The use of immunomodulators has positive therapeutic effect most expressed with regard to asthenic symptoms.

Application of ANAR in monotherapy of drug addiction

- Anar contains ultra-high dilutions of affinity purified antibodies to morphine.
- New generation drugs containing ultrahigh dilutions of antibodies to endogenous regulators capable of modulating the function of molecules to which they were derived rather than suppressing or potentiating it and exerting adaptive effects and “sparing” balanced therapeutic effect are safe.
- Scheme of administration: monotherapy, 1 tablet 5-8 times daily for 28-35 days.

Reduction of symptoms at the stage of therapeutic remission (patients in %)



- The efficiency of monotherapy with Anar containing ultra-high dilutions of antibodies to morphine was comparable to the efficiency of the basic therapy and allowed to reduce volume of pharmacotherapy, especially in patients with little experience of narcotization (up to 3 years), with mild cognitive deficits. Clinical improvement was accompanied by an increase in natural killers CD 16⁺ and a decrease in serotonin positive lymphocytes compared to point 1 of the examination.

Conclusion

- Opioid addiction is accompanied by dysregulation of immune, neurotransmitter, hormonal systems and formation of abnormal intersystem interrelationships with their own peculiarities and stable patterns at various stages of drug withdrawal.
- Main psychoneuroimmune pattern in the dynamics opioid abstinence syndrome is characterized by quantitative deficiency of CD4⁺ lymphocyte populations, increased number of activated T-lymphocytes and B-lymphocyte HLADR⁺ phenotype, activation of humoral immunity factors, increased number of circulating lymphocytes having receptors for serotonin and dopamine, high concentrations of cortisol in the blood of patients.
- The most important predisposing factors of disturbance of psychoneuroimmunomodulation mechanisms and reduction of the effectiveness of treatment of patients with opioid addiction are the early age at onset of opioid use, long experience and high doses of drug.
- The inclusion in the treatment of drug addicts of immunomodulators has a positive therapeutic effect.

- **The report presents research materials obtained in the laboratory of clinical psychoneuroimmunology and the department of addictive disorders (head of Department Prof. Nikolay A. Bokhan, member of RAS) .**
- **I would like to mention the contribution to study the problem Elena Matafonofa, which is currently in the Vanderbilt University Medical Center is working (USA, Nashville).**

Thank you
for attention!

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