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A Randomized Controlled Study of the Efficacy of Pregabalin in the Treatment of Opiate Withdrawal Syndrome

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Objective. To study the efficacy and safety of pregabalin (Lyrica) in the complex therapy of opioid withdrawal syndrome (OWS). **Materials and methods.** The study design was a randomized, symptom-controlled, simple, blind study with active controls. A total of 34 patients with OWS were randomized to two groups. Patients of group 1 (19 subjects) received pregabalin at a dose of up to 600 mg/day as the main substance for treating OWS, in combination with symptomatic treatment (basal and symptom-triggered). Patients of group 2 (15 subjects) received clonidine (Clofelin, up to 600 mg/day) as the main treatment agent, in combination with basal and symptom-triggered treatment. The severity of OWS, cravings for opiates, sleep disorders, anxiety, depression, and side effects were assessed daily using international validated quantified assessment scales. **Results.** In group 1, 15 patients (79%) completed OWS treatment, compared with seven (47%) in group 2 ($p = 0.05$, Fisher's exact test). There were no statistically significant differences between groups in terms of the dynamics of the severity of OWS (perhaps because of the limited number of patients). In the pregabalin-treated group, measures of the intensity of opiate cravings decreased during treatment as compared with group 2 ($p = 0.05$), and similar changes were seen in relation to anxiety ($p = 0.05$) and depression ($p < 0.05$); self-assessments of wellbeing increased ($p < 0.05$). There were no significant between-group differences in the overall incidence of side effects, though treatment tolerance was better in group 1. **Conclusions.** The treatment scheme including pregabalin was effective and safe and was well tolerated by patients, providing more successful completion of detoxification programs.

Keywords: pregabalin, opioid withdrawal syndrome, pharmacotherapy.

Treatment of opioid withdrawal syndrome (OWS) is now quite well developed [1–3], though curing this state (detoxification) continues to be one of the most important challenges in narcology.

Despite a variety of pharmacotherapy schemes, OWS is not infrequently poorly tolerated by patients. A significant proportion of patients therefore fail to complete treatment of OWS, with reinitiation of opiate consumption [2]. Methods for the accelerated cure of OWS using general anesthetics, although significantly increasing the proportion of people completing therapy, is associated with significant risks of severe complications [1] and has not found wide use in narcology. There are currently two schemes (protocols) with confirmed efficacy for curing OWS: the clonidine scheme and the buprenorphine protocol [4, 5]. The use of buprenorphine to cure OWS is forbidden in the Russian Federation. This treatment method is widely used in other countries, though it has drawbacks linked with difficulties with the necessary transfer to treatment with opiate antagonists (naltrexone): there has to be an interval of several days between the last

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dose of buprenorphine and the first dose of naltrexone, during which many patients experience recurrence of opioid dependence syndrome [6]. The main disadvantages of the clonidine protocol are its severe central depriming action and its low efficacy, which prevent patients from returning to narcology care and successful completion of OWS treatment. An important and relevant task is therefore that of developing novel treatment methods for OWS – effective and not involving the use of opiate receptor agonists.

One potential novel approach to the treatment of OWS consists of using pregabalin, an agent which blocks the α2-σ-subunit of voltage-dependent calcium channels in neurons, thus decreasing glutamate release from hyperexcited glutamatergic neurons [7]. The main indications for using pregabalin are neuropathic pain, generalized anxiety disorder, and epilepsy. A marked pain component and sleep disturbance combined with anxiety are among the major symptoms of OWS – so we suggested that pregabalin (Lyrica), which has analgesic, anxiolytic, and sedative actions, may be effective in the complex treatment of OWS.

Animal experiments have shown that pregabalin decreases morphine-induced tolerance and dependence syndrome [8]. Data from several authors indicate that addition of gabapentin, which has a similar mechanism of action to pregabalin, to OWS treatment protocols using methadone [9, 10] and buprenorphine [11] increases treatment efficacy. The authors of two non-Russian studies [12, 13] published reports of cases of the successful use of pregabalin for the treatment of OWS. Earlier reports were also published [14, 15] on the use of pregabalin in patients with opiate dependence syndrome for self-treatment of withdrawal syndrome.

These points impelled us to carry out a correct (evidence-based) study of the efficacy of using pregabalin for treating OWS.

The aim of the present work was to study the efficacy and safety of pregabalin in the complex treatment of opiate withdrawal syndrome.

Materials and Methods. The study was performed at the Murmansk Regional Narcology Dispensary and the Department of Narcology, Bekhterev St. Petersburg Research Psychoneurology Institute.

Inclusion criteria for patients were: diagnosed heroin dependence (ICD-10 criteria), regular consumption of heroin during the last year; age 18–60 years; all patients had to be in the initial phase of OWS; patients had to read Russian and complete the required questionnaires and scales; patients had to have permanent addresses and telephone numbers and had to provide an address and telephone number for a person able to contact them.

Exclusion criteria were: patients meeting the diagnostic criteria for dependence on another psychoactive substance apart from heroin and nicotine (patients with methadone dependence were also not included in the present study because of differences in the clinical dynamics of OWS from those in patients with heroin dependence); regular ingestion of psychotropic medications, including tranquillizers and antidepressants; ongoing comorbid mental illness (schizophrenia, bipolar affective disorder (BAD), epilepsy, etc.); history (six months before the recruitment visit) of suicidal intent or attempted suicide; history of psychoses and convulsive seizures; ingestion of depot neuroleptics within the four weeks before the start of the study; marked decreases in intellectual/memory functions; marked somatic pathology (liver, kidneys, cardiovascular system, nervous system); AIDS-associated illnesses, antiretroviral treatment; allergic reactions to the medicines used in the study; individual intolerance of the medicines used in the treatment of OWS; decompensation of existing disease; need for patient to take psychotropic medications not allowed for by the study protocol; recurrence of illnesses causing detoxification (i.e., reinitiation of opioid consumption); refusal to take part in the study.

A total of 85 patients were screened for possible participation in the study. Of these, 34 were included. The other 51 were excluded – 32 because they did not meet the inclusion criteria and 19 refused to take part.

Study scheme. The study design was a simple, blinded, randomized, symptom-controlled study with active control. The 34 patients with opiate withdrawal syndrome (F11.30) were randomized (using a random number generator) to two groups: patients of the study group (group 1) received six days of treatment of OWS with a protocol based on pregabalin, while patients of the reference group (group 2) received the traditional standard scheme based on clonidine.

Treatment protocols. Patients of group 1 (19 subjects) received pregabalin (Lyrica) at a dose of up to 600 mg/day as the main agent for the treatment of OWS combined with symptomatic therapy, which consisted of basal (prescribed as standard to all patients) medications, i.e., doxylamine (Donormil) 30 mg/day, and symptom-controlled (prescribed where needed because of the patient's requirements and physician's decisions based on quantitative assessments of OWS severity), i.e., ketorolac (Ketanov), loperamide (Imodium), metoclopramide (Cerucal), naphazoline (Naftizin, Sanorin), and phenazepam. Patients of group 2 (15 subjects) received clonidine (Clofelin, up to 600 mg/day) as the main substance for the treatment of OWS, along with basal and symptom-controlled therapy analogous to that in group 1. Patients were not prescribed other drugs. The treatment protocols in the two groups are shown in Table 1.

The main demographic and clinical characteristics of the patients by group are shown in Table 2. There were no between-group differences in most of these measures, with the exception of a greater proportion of men in the pregabalin group. Groups of patients did not initially differ in terms of the severity of OWS (see Table 2).

Clinical scales and psychometric tools. The severities of OWS (subjective and objective scales), cravings for opiates, sleep impairment, pain, anxiety, depression, and global clinical impression, wellbeing, and side effects were as-

TABLE 1. OWS Treatment Protocols

Treatment target	Treatment protocol									
	drugs (pharmacological group)	medicinal form	number of doses	dosage time	study days					
					1	2	3	4	5	6
Pregabalin treatment group										
OWS	Pregabalin (anxiolytic, anticonvulsant)	Capsules 150 mg	Once	9.30	300	300	300	150	150	150
				16.00				150	150	150
				20.00	300	300	300			
				22.30				150	150	150
				Daily dose, mg	600	600	600	450	450	450
Sleep impairment	Doxylamine (sedative, H1 histamine receptor blocker, m-cholinoblocker)	Tablets 30 mg		23.00	30	30	30	30	30	30
Clonidine treatment group										
OWS	Clonidine (sedative, α2-adrenoreceptor agonist)	Tablets 150 μg	Once	9.30	150	150	150	150	150	150
				13.30	150	150	150	75	75	75
				18.30	150	150	150	75	75	75
				22.30	150	150	150	150	150	150
				Daily dose, μg	600	600	600	450	450	450
Sleep impairment	Doxylamine (sedative, H1 histamine receptor blocker, m-cholinoblocker)	Tablets 30 mg		23.00	30	30	30	30	30	30

Symptom-regulated treatment protocol in both groups[1]

Indications	Drug	Pharmacological action	Medicinal form	Daily dose, mg
Pain	Ketorolac* (Ketanov)	Analgesic, NSAID, COX-1 and COX-2 inhibitor	Solution for i.m. injections, 1 ml (30 mg)	I.m., 30 mg, until effect obtained but no more than 90 mg/day
Sleep impairment, psychomotor arousal	Phenazepam*	Sedative, anxiolytic, benzodiazepine receptor ligand	Solution for i.m. administration, 1 ml (1 mg)	Single dose, 2 mg, repeat 2 mg if ineffective; total maximum dose 4 mg; maximum daily dose 10 mg
Vomiting	Metoclopramide (Cerucal)	Antiemetic, dopamine (D_2) receptor antagonist	Solution for i.m. administration, ampule, 2 ml (10 mg)	I.m., 10 mg, until effect obtained; maximum daily dose 60 mg
Constipation	Loperamide* (Imodium)	Antidiarrheal, antagonist of opiate receptors in GIT	Capsules, 2 mg	P.o., 4 mg, then 2 mg, until effect obtained; maximum daily dose 16 mg
Rhinorrhea	Naphazoline* (Naftizin, Sanorin)	Vasoconstrictor, α-adrenomimetic	Intranasal drops, 0.5% solution (0.005 g in 10 ml)	1–3 drops of solution in each nostril 3–4 times a day

*Drugs addressing the main symptoms of OWS prescribed in accordance with the protocol or after medical consultation.

TABLE 2. Characteristics of Patient Groups

Characteristics of patients	Group	
	1	2
Gender (men)	15	6*
Age, years	31.9 ± 1.1	28.7 ± 1.1
Duration of drug addiction, years	9.9 ± 1.4	7.9 ± 1.3
Duration of abstinence, h	11.8 ± 1.3	12.5 ± 2.8
Number of previous hospitalizations	3.8 ± 1.1	3.2 ± 1.2
Initial severity of OWS, OWSS, points	6.9 ± 1.1	7.7 ± 1.1

Data presented as $M \pm m$; *statistically significant between-group differences, $p < 0.05$ (Fishers' exact test).

sessed daily using the appropriate validated quantitative scales by physicians who, like patients, were not aware of which treatment group they were in.

The investigators taking part in running the tests were specially trained to use psychometric tools before the study, to ensure consistency in the results. The following assessment tools were used in the study: standardized clinical record cards were used to guide structured clinical interviews and document patients' medical observations; subjective and objective assessment scales for the severity of OWS (s-OWSS and o-OWSS) [16]; the overall scale for assessment of the severity of opiate withdrawal syndrome (OWSS) [17]; retrospective analysis of opioid consumption in the last 30 days (TLFB – timeline followback) [18]; visual analog scales for pain (VAS-p) [19], opiate cravings (VAS-c), impaired sleep and state of health (wellbeing) (VAS-w); the hospital anxiety and depression scale (HADS) [20]; the global clinical impression scale [21]; behavior and special events recording sheets; medication record sheets; side effects record sheets.

Lab methods. These methods included biochemical and clinical blood tests and urine tests at the beginning and end of the study; daily urine tests for opiates (including methadone) and other narcotics and weekly exhaled air tests for alcohol.

Statistical analysis. The main measure of efficacy was OWS treatment completion (detoxification). Secondary efficacy indicators were additional prescription of ketorolac, changes in measures on clinical and psychometric scales, and safety (number of side effects).

A study database was run using SPSS and a double input method to avoid data input errors. Groups were compared in terms of OWS treatment completion using Kaplan–Meier survival analysis (between-group comparisons by the Mantel–Cox and Gehan–Wilcoxon tests) in terms of the *elimination from the study (OWS treatment)* event. Groups were compared in terms of indicators such as the cause of completing OWS treatment, with construction of linkage tables and use of Fisher's exact test. The distributions of alternative signs were also evaluated using Fisher's exact test (FET). Processing of variables assessed during the study was by analysis of variance with independent time and treatment group factors and the post hoc Bonferroni test for between-group comparisons. Between-group comparisons for several indicators used a general linear model with repeat measurements, which, when there were statistically significant differences in the results of analysis of variance, allowed the result to be tested and significant differences to be confirmed.

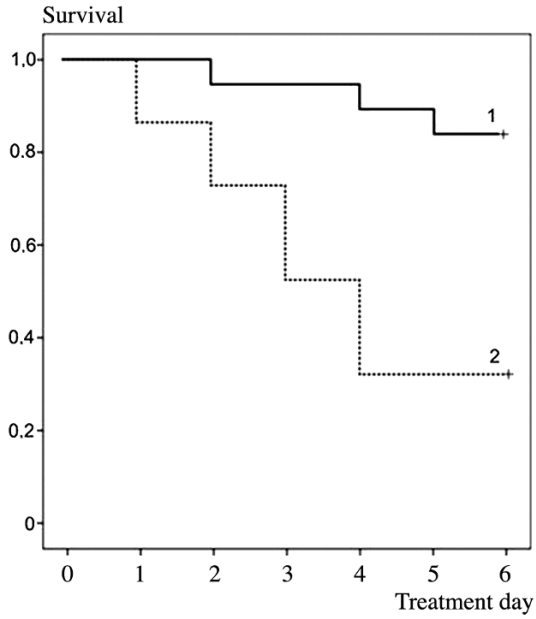

Fig. 1. Completion of OWS treatment programs by patients of groups 1 and 2. Kaplan–Meyer survival analysis. Statistically significant between-group differences: $p = 0.001$; Log Rank (Mantel–Cox) criterion.

Results. In group 1 (pregabalin), OWS treatment was completed by 15 patients (79%) versus seven patients (47%)

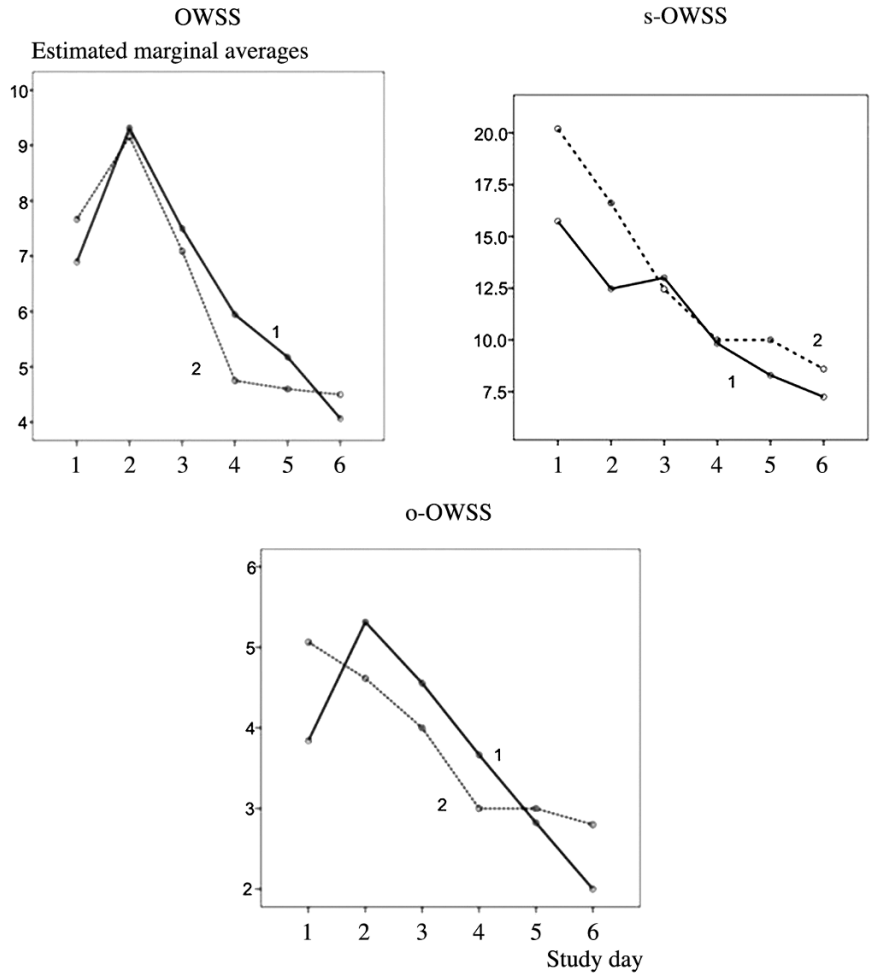

Fig. 2. Dynamics of severity of OWS in patients of groups 1 and 2, various scales. There were no significant between-group differences.

in group 2 (clonidine) ($p = 0.05$; FET). Analysis of Kaplan–Meyer survival also confirmed significantly better retention of patients in the pregabalin group ($p = 0.001$, log rank (Mantel–Cox) criterion) (Fig. 1).

There were no statistically significant between-group differences in measures of changes in the severity of OWS on any of the severity assessment scales, evidently because of the symptom-controlled protocol and small cohort size (limited number of patients) (Fig. 2). There were also no statistically significant between-group differences in the severity of the pain component of OWS.

During treatment, VAS-c was lower in group 1 (group effect, $p = 0.05$), as were anxiety ($p = 0.05$) and depression ($p < 0.05$) on the HADS; self-assessment of wellbeing on the VAS-w was significantly higher ($p < 0.05$) (Fig. 3). It should, however, be noted that none of the measures of the interaction of the group effect and the treatment day effect reached statistical significance, which may be indirect evidence of the cause of between-group differences, mainly the initial difference in values between groups.

In the symptom-controlled protocols, the number of additional drug prescriptions was one of the most important efficacy indicators, as these control the severity of patients' status and did not exceed the specified threshold value for additional prescriptions in either treatment group. Because of this, it is important that group 2 patients (the clonidine scheme) showed greater additional prescription of the analgesic ketorolac in the framework of symptom-controlled treatment: 60.5 ± 8.2 mg versus 36.0 ± 7.8 mg ($p < 0.05$).

There were no significant differences in the overall (total) frequency of side effects between the two groups of patients (73.7% in the pregabalin group versus 73.3% in the clonidine group), though significantly less severe asthenia and central depriming effects of treatment in the pregabalin group should be noted (16% versus 47% of patients, $p < 0.05$), which is evidence for subjectively better tolerance of OWS treatment by patients receiving pregabalin (this may explain the larger proportion completing detoxification).

Discussion. The results presented here are based on data from interim analysis of parts of a continuing clinical

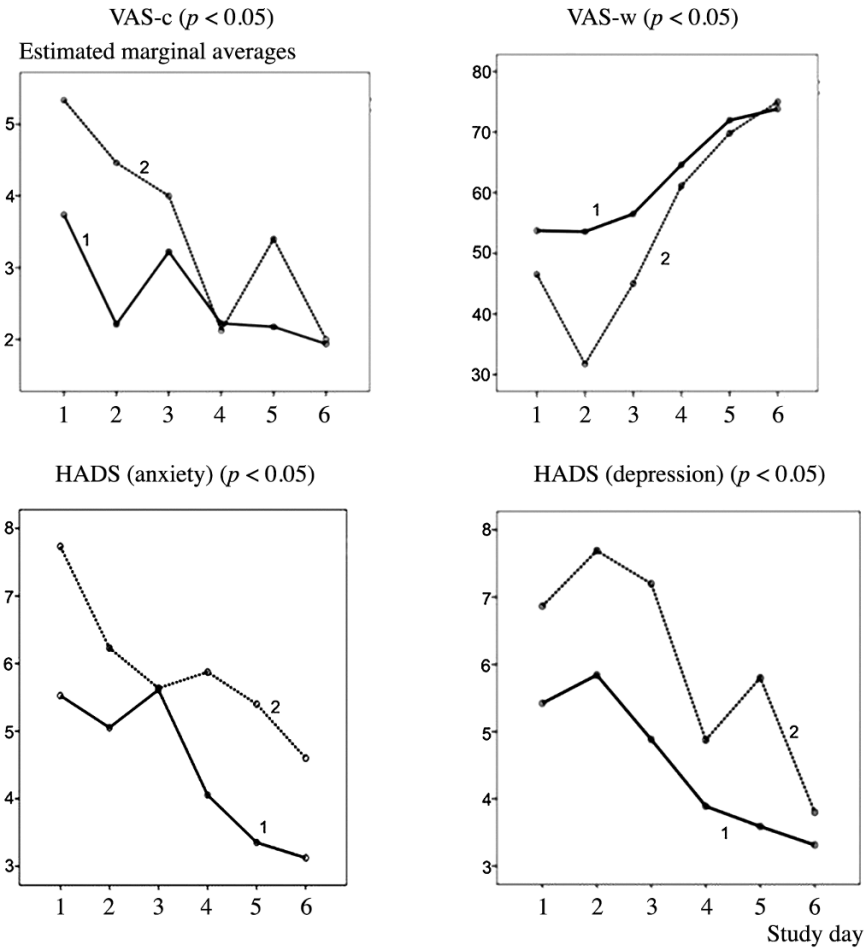

Fig. 3. Dynamics of indicators (marginal means) of opiate cravings (VAS-c), wellbeing (VAS-w), anxiety, and depression (HADS) in patients of groups 1 and 2.

trial and, because of the limited cohort of patients included in the analysis, must be regarded as preliminary. Nonetheless, the data obtained provide convincing evidence of the potential efficacy of pregabalin for the treatment of OWS.

The group of patients treated with pregabalin included significantly more patients who completed OWS treatment, which not only supports the efficacy of pregabalin in OWS and its advantages over the clonidine detoxification protocol, but is also an important result for practical clinical narcology. The second important result evidencing the high efficacy of pregabalin in OWS is the significantly greater (almost twofold) number of additional prescriptions of the analgesic ketorolac in the clonidine group. As noted above, in clinical trials performed using a symptom-controlled protocol, the number of additional prescriptions for drugs influencing the basic symptoms of the illness is one of the most important efficacy indicators. Thus, the number of additional prescriptions in a study with a symptom-controlled design is to a significant extent a more important indicator than changes in clinical variables, as the latter prevent the patient's clinical status and his or her main symptoms from developing above a particular limit. Such a situation applies in the present study, in which changes in the severity of OWS and its basic pain component, controlled by additional prescriptions (primarily ketorolac), did not differ between groups, while the number of additional prescriptions regulating this change did differ and was significantly greater in the clonidine group. It is important to note that there was a significant treatment effect on changes in individual symptoms of OWS which were not used as triggers for prescription of additional treatment – opiate cravings, anxiety, depression, and general wellbeing, which were significantly better in the pregabalin group. However, assistant of the effects of pregabalin on this symptomatology in the framework of OWS should be addressed with caution, as indicators of an interaction between group effects and treatment day effects did not reach statistical significance for any of these variables, which may be indirect evidence that between-group differences were due to a significant extent to initial between-group differences in these indicators.

The OWS treatment protocol based on the use of pregabalin showed better treatment tolerance than the clonidine protocol, because of less marked central depriming actions and asthenia. It is possible that the better tolerance of OWS treatment with pregabalin is due largely to the greater proportion of patients completing treatment of OWS in this group.

It should be noted that the results obtained here are in good agreement with published data on the potential efficacy of pregabalin in OWS [8, 12, 13]. These results were also supported by reports on the use of pregabalin for the self-treatment of OWS [14, 15]. In the context of data on the potential efficacy of pregabalin in OWS, recently published information on pregabalin abuse must be considered [7, 14].

Reports of pregabalin abuse in the specialist medical literature and mass media led to inclusion of this drug in the controlled substances class in the Russian Federation at the end of 2015. However, it is important to discriminate rare cases of abuse of and dependence on pregabalin from the large-scale use of this drug for the self-treatment of OWS by patients with opiate dependence syndrome. That pregabalin is much more frequently used for the self-treatment of OWS and post-abstinence disorders is evidenced by a series of data presented in recent publications: consumption of pregabalin without a doctor's prescription is seen in a vast majority of cases among opiate addicts – initially to ameliorate the symptoms of OWS and post-abstinence disorders; the doses used exceed the therapeutic by mean factors of 2–4, which is unusual and relatively low for the phenomenon of tolerance on development of dependence; the oral route is virtually always used; many patients did not experience euphoria even with high doss of pregabalin (2400 mg) [14]; pregabalin decreases opiate consumption and is used by patients instead of opiates as a legal drug; pregabalin withdrawal syndrome is relatively mild and its addictive potential is low.

From the point of view of clinical psychopharmacology, there is particular interest in the correcting action of the drug, whose main mechanism consists of decreasing glutamate release from hyperexcited glutamatergic neurons (by pregabalin) on the patient's state (OWS), i.e., the etiologically produced dysfunction of the opioidergic system of the brain. Our data provide evidence of the regulatory influence of glutamatergic neurotransmission on the functioning of the endogenous opioid neuropeptide system.

Thus, our results provide evidence that the OWS treatment scheme using pregabalin (Lyrica) instead of clonidine as the main agent is effective and safe, is well tolerated by patients, and support completion of detoxification programs (curing of OWS) in a larger proportion of patients than the traditional treatment scheme based on clonidine. These data provide evidence of the regulatory effect of glutamatergic neurotransmission on the functioning of the endogenous opioid neuropeptide system.

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