

## Comprehensive Treatment for Depression in Patients With Drug Addiction Using Sulpirid and Phenotropil

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**The comparative evaluation of treatments for depression in patients with opioid addiction using sulpiride and phenotropil was made. The duration of treatment was 6 weeks. By the end of the study the almost complete disappearance of unmotivated fear, anxiety, reduced background mood was noted. The combination of amitriptyline with sulpiride made it possible to reduce the doses of antidepressants to a minimum while maintaining the reduction of emotional disorders and beneficial influence on behavior. The application of sulpiride and phenotropil in the comprehensive treatment for depression in patients with drug addiction leads to depression reduction, normalization of behavioral disorders and the whole nervous system.**

**Key words:** Withdrawal syndrome, depression, comprehensive treatment, Drug addiction, Hamilton scale for assessing depression.

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Substance abuse (psychoactive substance - PAS) is a problem in Russia, a serious threat not only to human health, but also to the security of the country as a whole. In Russia, as anywhere in the world, the majority of drug users are young people. The average age of drug abuse initiation nowadays is 13. Young people at this age are characterized as sensitive and they are the most vulnerable and psychologically helpless when face life's difficulties<sup>1,2</sup>, not having necessary life skills, not knowing how to choose an effective way to relieve stress that would help them maintain their personality and create a healthy and efficient

lifestyle. These young people cannot cope with various challenges. This leads to serious consequences, which are accompanied by a maladaptive and self-destructive behavior<sup>3</sup>.

Drug addiction among young people is currently one of the most pressing and painful problems of our society. It calls for strong and decisive rehabilitation activities in social welfare and health care institutions of various types that will engage medical psychologists, social work experts, physicians and social teachers. Besides, new forms and means of rehabilitation should be introduced<sup>4</sup>.

Traditionally, the centers of medical rehabilitation for young drug addicts in our country provide mainly medication correction and information seminars. This activity demonstrates its inconsistency as it ensures the effectiveness of remission at 15 - 20% of PAS users in a year which does not correspond to the growth and the

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spread of drug addiction among young people. There is a need for the comprehensive treatment in this contingent<sup>5</sup>.

A low efficiency of treatment in patients with opioid addiction is associated with the clinical manifestations of the disease, which are associated with feelings of pleasure and cause the patient's attitude to his suffering quite different from other diseases. The violations of attractions, the connection of the disease with vitally important feelings - all this makes therapeutic problem more difficult. The fact that the ground for drug abuse is a strong sensual reinforcement, the sense of pleasure, explains the small success of therapeutic efforts<sup>6,7</sup>. Currently the drug addiction treatment in most cases is limited to managing the drug withdrawal symptoms<sup>8,9</sup>.

A return to drug usage during the year is observed at 80-90% of patients<sup>1</sup>. Inefficient methods of treating drug addiction lead to a search for new approaches and methods of treatment. Despite the tendency to reassess either biological or psychosocial stimulation methods, two statements are obvious: a comprehensive approach to the treatment, i.e. the use of both methods is essential. The correlation of these methods in each case is individual and depends on the disease stage and disease patterns of the patient<sup>2</sup>.

As drug addicts' care involves the use of neuroleptics, it is prospective to use sulpiride<sup>10</sup>. It is derived from benzamide and is chemically quite different from the most conventional neuroleptics. It is interesting that there are two forms of sulpiride stereoisomers and the substance applied in clinics is in fact the racemic mixture of dextro- and sinistrorotatory isomers. It exerts moderate antipsychotic and antidepressive action in combination with an activating action. The mechanism of antipsychotic action is associated with selective blockade of central dopamine D<sub>2</sub>-receptors. The sedative effect is weak, the alpha-adrenergic blocking activity is low, and it practically does not cause antimuscarinic effects. It rarely causes extrapyramidal disorders. Sulpiride, having orienting response exclusively to the dopaminergic system, demonstrates a really wide range of therapeutic effects in the clinic that cannot be compared to any other range. This drug rapidly penetrates into all tissues of the body, faster in the liver and kidneys, slower in the brain

tissue (the major amount accumulates in the pituitary gland). It is excreted unchanged by the kidneys after glomerular filtration (92%). The total clearance (usually equal to renal) is 126 ml/min. T<sub>1/2</sub> is about 7 hours.

It is essential that the clinical effect is achieved not only in patients with schizophrenia, but also in patients with psychosomatic disorders (peptic ulcer disease, irritable bowel syndrome, bronchial asthma, various algia symptoms).

The analysis of sulpiride pharmacological action relying on the available studies suggests the drug effectiveness and applicability for treating patients with various psychopathological manifestations and especially in addictive patients with depressive disorders<sup>9</sup>.

The purpose of the research is to study the effectiveness of using sulpiride and phenotropil for the comprehensive treatment of depressive disorders in men aged 19 – 28 with opiate addiction.

## MATERIALS AND METHODS

63 patients aged 19-28 (the mean age of the examinees was 23.72 ± 5.28 years) with opioid addiction who had sought medical advice have been examined. In addition to a standard clinical examination (history, study of somatic neurological and mental status), a 6-weeks treatment of post withdrawal state was administered.

A coupling of acute withdrawal syndrome used to occur within 10-14 days from the last drug use.

By this time algic and vegetative symptoms almost completely disappeared, sleep normalized, the intensity of affective and behavioral disorders significantly reduced, and a compulsive drug addiction became inactive to a certain extent. Structurally different depressive disorders were mainly manifested in a post withdrawal period. On the basis of the clinical follow-up a depressive-dysphoric and asthenodepressive types of post withdrawal state were identified.

There were three groups of patients: 25 patients with opioid addiction in the first group who were prescribed only antidepressants (amitriptyline 100-200 mg/day divided in 3 doses) in post withdrawal period; the patients of the second group (n = 18) in the study period were

prescribed amitriptyline 100-200 mg/day divided in 3 doses combined with sulphiride 250-300 mg/day divided in 3 doses; and the third group of patients (n = 20) was prescribed a comprehensive treatment including amitriptyline 100-200 mg/day divided in 3 doses and combined with sulphiride 250-300 mg/day divided in 3 doses, and fenotropil 200 mg/day divided in 2 doses.

The study of the patients' education revealed the following: 24 people had basic vocational education; 19 people had special secondary education; 7 people had incomplete higher education; and 7 people had higher education. By the nature of employment the main part of the people (n = 54) did not work. The average length of opiate use was  $4.2 \pm 1.9$  years. All patients had been repeatedly treated for drug addiction in various hospitals and rehabilitation centers prior to the study. The daily doses of narcotic substance ranged from 0.25 to 4 grams.

The criteria of including a patient in the study were the second stage of obligate clinical signs of drug addiction, the patient's age older than 18, a consent to treatment and participation in the study.

The main methods used were clinical psychopathological, experimental psychological (Hamilton scale for assessing depression), clinical follow-up study and statistical methods. The clinical psychopathological method of research includes: a purposeful questioning of patients, finding out in compliance with the certain rules their mental state at the given time and in the past, their psycho-physiological development, hereditary psychiatric load and other pathology, their biography, the situation in the family, earlier diseases; dynamic observation of their behavior, interpersonal relationships, affects, expressive manifestations, response to the treatment used; interview with the patient's relatives and those who know him well, and the collection and evaluation of information from other sources (his character reference from educational institutions or places of work, written and artistic products of patients, audio and video recordings, etc.); clinical psychological experiment (to study attention, memory, thought disorder and intellectual deterioration, etc. using special assignments that simulate natural real life situations); analysis, evaluation and synthesis of the information

received, collection of follow-up data for monitoring the adequacy of the conclusion of the patient's condition and predictive hypotheses; follow-up study, which included the patient's questioning during the examination, as well as the information gathered from the relatives, friends, co-workers, from medical and other documentation of various types.

Statistical data analysis was carried out using a package of standard applications «Statistica for Widows» (V. 6.0). The simple average, square deviation and standard error of the simple average for the quantitative indicators were computed. When comparing the qualitative indicators the criteria  $X^2$  were used in accordance with the terms of use. The differences at the achieved level of  $p < 0.05$  were taken for statistically significant.

## RESULTS AND DISCUSSION

The analysis showed the specificity of the clinical manifestations and a well-defined temporal structure of the conditions observed after withdrawal, which made it possible to interpret them as an independent drug pathologic depressive syndrome.

All patients in the observed post withdrawal period had depressive disorders with dysphoric, asthenic manifestations. Almost all patients reported that when they were teenagers they felt lonely, isolated from peers, they had fluctuation of mood with a predominance of depressive component. They began to use drugs for relief or mitigation of negative emotional experiences.

The period of abstinence was characterized by mental block, ineffective contact with a doctor, intermittent dysphoric episodes. The compulsion was rude and viscous, poorly manageable by medical correction.

On the 12-14-th day there occasionally arose dysphoric episodes on the background of depressive affect with anxiety. They were considered as paroxysms of compulsive desire. In some cases of paroxysmal states the dysphoric component with unmotivated anger and aggression towards others predominated, in other cases a depressive component of raptus melancholicus (grim obsession) type with a sense

of utter despair prevailed; the patients were thrashing about, moaning, trying to soothe the unbearable craving for the drug. In the initial stages of the explosive reaction development the patients tried to prove to the others that they needed to leave the room where they were under any excuse, they produced the most diverse reasons, often ridiculous.

At the formed paroxysmal state those reasons were swept aside and replaced by an unappeasable drug hunger. The consciousness was affectively tenebrous, and at the altitude of scintillation the state was like a compulsion at abstinence.

The minority of patients ( $n = 16$ ) beginning from the 10-14-th day of cessation of use manifested easy irritability and fatigue, exhausted attention and increased sensitivity on

the depressed mood background. The subjective feeling of constant fatigue, more pronounced after awakening, was accompanied by a general drop in the tone, depression, pessimistic assessment of their health and their living circumstances in general. They had occasional headaches, which were classical "neurotic" in nature. Moreover, the patients became incapable of making any emotional, intellectual and physical efforts, their affective lability, sensitiveness, the tendency to inadequate response to all sorts of psycho-traumatic effect intensified.

The obtained data of depression evaluation in patients by the Hamilton scale in different periods of treatment are shown in Table 1.

As it can be seen from Table 1 the administration of amitriptyline and sulpiride in the

**Table 1.** The indicators of Hamilton scale in drug addicts treated by various methods

Observation period (days)	Hamilton scale indicators (scores)		
	First group (n=25)	Second group (n=18)	Third group (n=20)
1	42.4±1.3	42.4±1.3	42.4±1.3
10-14	37.1±1.5	37.1±1.5	37.1±1.5
28-30	14.3±1.1	12.1±1.0	11.4±0.9
36	13.5±1.2	10.3±1.1	7.2±1.0

comprehensive treatment, and the combined use of amitriptyline, sulpiride and phenotropil showed a significant decline of the Hamilton depression scale scores by the 28-30-th day treatment. This is especially pronounced in the third group. By the 36 day of care the maximum effect was observed in amitriptyline, sulpiride and phenotropil combined use.

The first group patients have shown a slight reduction of anxio-depressive symptoms after the clinical study, which was manifested in the complaints reduction of bad mood and internal tension. The declined excitability level made patients more balanced, self-collected and responsive to the psychotherapeutic treatment, and also led to the relative normalization of relations with relatives.

The patients in the second and third groups by the end of the study manifested the almost complete disappearance of unmotivated fear, anxiety and low mood.

The groups with the complex use of

medicine have shown a faster and more pronounced improvement of the Hamilton scale indicators than with single-agent therapy.

The combination of antidepressants with sulpiride allowed reducing their doses to a minimum while maintaining the reduction of emotional disorders and healthy influence on behavior. The positive dynamics of major psychopathology manifestations (anxiety, depressed mood, irritability) was achieved by relatively low doses of amitriptyline<sup>11</sup> through the catalytic influence of sulpiride. Moreover, there was neither excessive sedation nor clouding of consciousness, which improved the psychotherapeutic contact with the patient.

The detected effectiveness of sulpiride normalizing behavioral disorders can be regarded as an indirect effect of the medicine on the emotional sphere. In addition, the optimal therapeutic regimens using sulpiride have been developed, which allowed effective management of the psychopathological signs that are

attributable to the clinical performance of drug addiction. It should be noted that during the observation period not any possible side effects of sulpiride were noted.

Phenotropil in its turn has a positive effect on metabolism and cerebral blood circulation, stimulates redox processes, increases the body's energy potential by utilizing glucose and improves regional blood flow in the ischemic brain regions<sup>12, 13, 14</sup>. It increases noradrenaline, dopamine and serotonin in the brain, does not affect the level of gamma-aminobutyric acid (GABA), and has no pronounced effect on the brain spontaneous bioelectric activity. These factors dynamize sulpiride action and encourage the patients' nervous system recovery<sup>15-17</sup>.

Thus, sulpiride used in the comprehensive treatment for depression in patients with drug addiction reduces depression, normalizes behavioral disorders and the whole nervous system. These therapeutic effects are especially marked if the treatment regimen includes phenotropil.

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