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CLINICAL–EVOLUTIONARY FEATURES OF REFRACTORY DEPRESSION

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ABSTRACT:

In the recent decades, there was a rapid increase of depression among population, including its refractory variants, and researches show that in resistant depression predisposing causes are distinguished by a pronounced degree of expression [3, 7, 8, 16]. It is necessary that the research methods to be limited to the decisive ones, as well as establishing the correct amount of treatment, based on continuity of therapy, which effectively reduces the terms of hospitalization and financial costs [1, 4, 6, 10, 11]. The clinical analysis of patients suffering from refractory depression, admitted in Psychiatric Clinic, Chișinău, revealed psychopathological pathomorphosis, which included delusions of guilt, incurable somatic disease, accusatory hallucinations, suicidal attempts, as well as disturbance of depressive syndrome components with development of monotonous, rigid affect. The most characteristic variants for resistant depression are anxiety, melancholy, apathy and inhabitation. The complex therapy that included antidepressants, timostabilizers, sometimes, electroconvulsive therapy proved to be effective in overcoming the acute states and establishing remission. Treatment with antidepressants was initiated in moderate doses, but augmentation was relatively rapid, avoiding polypragmasy. Psychotherapy, originally applied to explain the goal, therapeutic tactics, nature of disease, peculiarities of development, duration of treatment, proved to be one of the basic methods of numerous therapeutic interventions.

Keywords: *resistant depression, antidepressants, timostabilizers, electroconvulsive therapy, psychotherapy*

REZUMAT:

În ultimele decenii, s-a înregistrat o creștere rapidă a depresiei în rândul populației, inclusiv a variantei sale refractare, iar cercetările arată că, în depresia rezistentă, cauzele predispozante se disting printr-un grad pronunțat de exprimare [3, 7, 8, 16]. Este necesar ca metodele de cercetare să fie limitate la cele decisive, ca și stabilirea nivelului adecvat de asistență terapeutică, pe baza continuității tratamentului, ceea ce reduce, în mod eficient, durata spitalizării și costurile asistenței [1, 4, 6, 10, 11].

Analiza clinică a pacienților care suferă de depresie refractară, internați în Clinica de Psihiatrie, Chișinău, a dezvăluit o patomorfoză psihopatologică, care a inclus iluzii de vină, boală incurabilă somatică, halucinații cu tematică acuzatoare, tentative de suicid, precum și tulburări cu componentă depresivă, cu dezvoltare afectivă monotona, rigidă. Variantele cele mai caracteristice ale depresiei rezistente sunt anxietatea, melancolia, apatia și de locuire. Tratamentul complex, ce a inclus antidepresive, timostabilizatoare, uneori terapie cu electroconvulsivante, s-a dovedit a fi eficace în depășirea stărilor acute și a dus la instituirea remisie. Tratamentul cu antidepresive a fost inițiat în doze moderate, dar creșterea dozelor a fost relativ rapidă, evitând polipragmazia.

Psihoterapia, aplicată inițial pentru a explica scopul tratamentului, al tacticilor terapeutice, al naturii bolii, al particularităților de dezvoltare, precum și durata tratamentului, s-a dovedit a fi una dintre metodele de bază în numeroase intervenții terapeutice.

Cuvinte-cheie: *depresie rezistentă, antidepresive, timostabilizatoare, terapie electroconvulsivantă, psihoterapie*

INTRODUCTION

The goal of work

Assessing of clinical-evolutionary features of resistant depressions and establishing an appropriate treatment.

MATERIALS AND METHODS

This work was carried out in the Psychiatric Clinic, Chișinău, based on the study of 612 subjects with depressive disorders, resistant to treatment.

RESULTS AND DISCUSSIONS

306 patients from the basic group received complex treatment (antidepressants, timostabilizers, electroconvulsive therapy, psychotherapy). The study was complemented by the control group – 306 patients, who received treatment mixed with medicaments.

Tab. I: *Characteristics of researched material by gender, place of residence*

Basic group								Control group (306)							
Men 37 (12,09 %)				Women 269 (87,91 %)				Men 74 (24,19 %)				Women 232 (75,81 %)			
urban		rural		urban		rural		urban		rural		urban		rural	
abs	%	abs	%	abs	%	abs	%	abs	%	abs	%	abs	%	abs	%
25	8,2	12	3,9	176	57,5	93	30,3	56	18,3	18	5,9	174	56,9	58	18,9

For the recruitment of the people in the study, both inclusion and exclusion criteria were used. Thus, inclusion criteria were: patients aged 18 – 69; patients who underwent two consecutive ineffective courses of timoanaleptic with application of AD with different chemical structures.

Exclusion criteria included: people with a series of serious medical conditions at the stage of decompensating (somatic, endocrine and hematologic pathology, including diabetes type 1); asthma, severe HTS (gr. 3); pectoris angina; myocardial infarction; chronic heart failure; severe arrhythmias; renal failure; ulcerative colitis; neoplasia; anemia (gr. 3); chronic hepatitis; with maximum activity.

Eligibility criteria for study groups were:

1. Testing clinical parameters and estimation of its dynamic during 6 months of observation: – 1st – at the admission, 2nd – 14 days later, 3rd – at the discharge from hospital, 4th – after 6 months.
2. Accumulation of less than 50 %, according to Hamilton and Montgomery-Asberg evaluation scales of depression.

The average age of the patients from the basic group was $46,86 \pm 0,74$ years, but in the control group – $46,81 \pm 0,64$ years.

In the present study, the highest share of people were with secondary education – 360 cases, (58,8 %), followed by people with higher education – 179 cases (29,2 %) and, finally – people with incomplete secondary education (elementary) – 73 cases (11,9 %).

According to the social status, the highest number of people were permanent employees – 292 cases (47,70 %), followed by pensioners/welfare recipients – 196 cases (32,00 %), unemployed – 98 cases (16,00 %), and, finally, students – 26 cases (4,20 %).

Clinical and psychopathological examination included the research of particular issues investigated in this study by means of complex data evaluation. Psychological examination was oriented at investigation of individuals' personality particularities, their emotional states, study of interpersonal, family and work relationships, peculiarities of individual's reactions, the level of depression and other symptoms, conflict situations, personal aspirations. Investigation data were processed on computer by means of variation, descriptive and discriminate analysis.

The statistical processing of groups with regards to the eredo-family history demonstrated that affective disorders are the most frequent pathologies: in the basic group – 95 cases (31,05 %); in the control group – 63 cases (20,59 %) ($\chi^2 = 8,74$), with statistically reliable difference ($p < 0,01$). A significant number of cases was detected in families which abused psychoactive substances – in basic group – 37 cases (12,09 %), and in control group – 15 cases (4,90 %) ($\chi^2 = 10,17$), with obvious differences ($p < 0,01$); somatic disorders – in basic group – 60 cases (19,61 %), and in control group – 37 cases (12,09 %), ($\chi^2 = 6,48$), statistically conclusive ($p < 0,05$), etc.

By comparing groups on the acts of birth, it was shown that most of the cases were represented by individuals who had been born at term – basic group – 261 cases (85,29 %), control group – 281 cases (91,83 %), ($\chi^2 = 6,45$, $p < 0,05$). Data obtained demonstrated that in the basic group, most of the caretakers generated a sense of guilt in their offspring – 101 cases (33,01 %); in the control group – 69 cases (22,55 %) ($\chi^2 = 8,34$), with statistically reliable differences ($p < 0,01$). The same data was obtained on the deprivation – basic group – 80 cases (26,14 %) – control group – 54 cases (17,65 %) ($\chi^2 = 6,46$), with significant statistical difference ($p < 0,05$). It is statistically significant ($p < 0,05$) the parents' humiliating attitudes towards children ($\chi^2 = 5,69$). As to the living conditions, it is worth mentioning that, in the basic group, more than half of the patients – 155 cases (50,65 %) lacked material things compared to the control group – 117 cases (38,24 %) ($\chi^2 = 9,56$), the differences were statistically reliable ($p < 0,01$).

Peculiarities of psycho-traumatic situations, their duration, complexity, the difficulty of their resolution and the patients' impossibility to get out of them play an important role in emergence of persistent forms of these manifestations. Both in the basic group (45 cases – 14,71 %), and in the control group (35 cases – 11,44 %), a significant number of individuals suffered obsessive disorders ($\chi^2 = 1,44$, $p > 0,05$), but better statistically significant results ($p < 0,01$) showed children with sleep disorders. The largest number of individuals suffered disappointments, low emotional support, abandonment, separation in childhood, the results being statistically significant ($p < 0,001$).

In their own families, most of the individuals had abandonment, separation, divorce, decease – the basic group (149 cases – 48,69 %) – the control group (98 cases – 32,03 %) ($\chi^2 = 17,66$), demonstrating statistically significant differences ($p < 0,001$). The second place with regards to the frequency is taken by the low emotional support – the basic group (104 cases – 33,99 %), in the control group (65 cases – 21,4 %) ($\chi^2 = 12,43$), with obvious differences ($p < 0,001$). The following places are taken by patients with no trust relationships ($\chi^2 = 21,13$), with no intimate relationships ($\chi^2 = 15,49$), and with partner's emigration ($\chi^2 = 15,07$), the differences being statistically conclusive ($p < 0,001$).

The distribution of the harmful factors study in the observation period demonstrated that the number of individuals with somatic disorders was evidently higher than other harmful factors – the basic group (215 cases – 70,26 %), the control group (112 cases – 36,60 %) ($\chi^2 = 69,67$), as well as

the affective oscillation at the neurotic level – the basic group (141 cases – 46,08 %) – in the control group (88 cases – 28,76 %) ($\chi^2 = 23,26$), with statistically significant differences ($p < 0,001$).

Assessment of comorbidities during disease showed that, in the basic group, the largest number of individuals suffered from organic brain disorders – 210 cases (68,63 %), and in the control group – 140 cases (45,75 %) ($\chi^2 = 32,70$), this also happens in the cases of somatic pathology – in the basic group – 205 cases (66,99 %), and in the control group – 146 cases (47,71 %) ($\chi^2 = 23,26$), with statistically significant differences ($p < 0,001$).

The analysis of the study data with regards to psychiatric comorbidity during disease, revealed that the largest number of patients suffered posttraumatic stress disorders, the basic group (107 cases – 34,97 %), the control group (64 cases – 29,92 %) ($\chi^2 = 15,01$), personality disorders – the basic group (99 cases – 32,35 %), the control group (43 cases – 14,05 %) ($\chi^2 = 28,76$), the differences being statistically conclusive ($p < 0,001$).

In our observations, the disease was usually characterized by a relatively long development. Thus, the average duration of the disease in the basic group was $9,99 \pm 0,53$ years, in the control group – $14,84 \pm 0,46$ years, with statistically significant differences ($p < 0,01$). Complete picture of individuals' distribution according to disease duration has the following: from 1 to 10 years – 297 patients (48,5 %); from 11 to 19 years – 155 (25,4 %); from 20 to 29 years – 132 (21,5 %); 30 years and more – 28 (4,6 %) (Fig. 1).

Keyword. 1. from 1 to 10; 2. from 11 to 19; 3. from 20 to 29; 4. 30+. *** $p < 0,01$

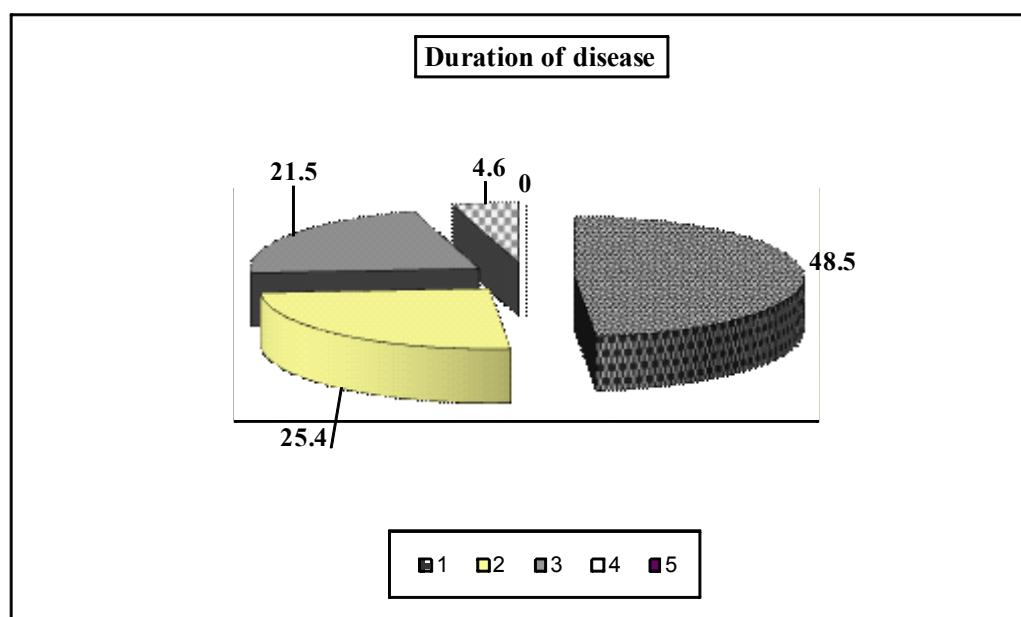


Fig. 1: *Distribution of individuals according to disease duration*

The average number of previous episodes among individuals in the basic group was $5,86 \pm 0,33$, and in the control group – $7,13 \pm 0,26$, with conclusive statistical differences ($p < 0,01$). The complete distribution of individuals according to previous episodes is as follows: up to 5 episodes – 326 patients (53,3 %); from 6 to 10 – 166 (27,1 %); from 11 to 15 – 90 (14,7 %); from 16 to 20 – 20 (3,3 %); over 21 episodes – 10 individuals (1,6 %). The obtained results are shown in the figure 2.

Keyword. 1. from 0 to 5; 2. from 5 to 10; 3. from 11 to 15; 4. from 16 to 20; 5. 21+ *** $p < 0,01$

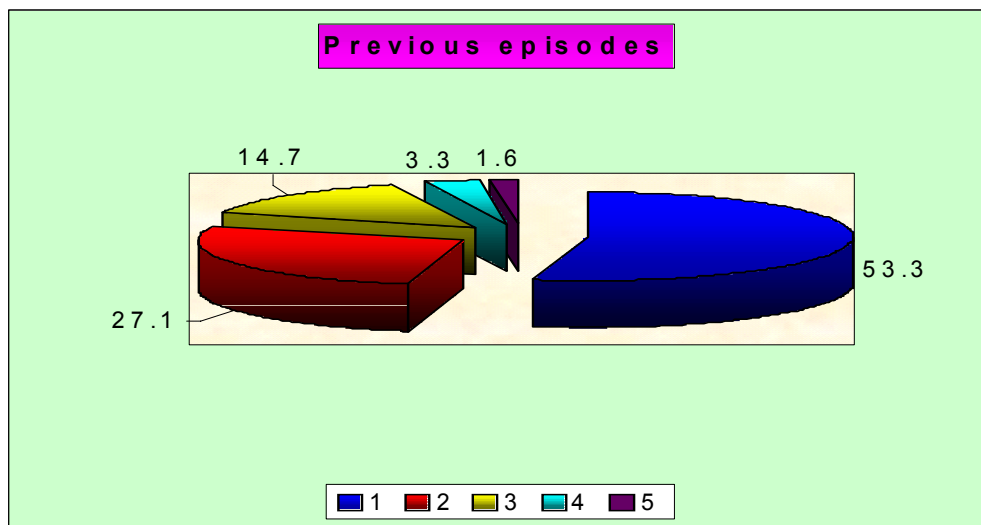


Fig. 2: Distribution of the individuals according to the number of previous episodes

The most frequent onset way of resistant depressive episode both, in the basic and control groups was a sudden one – 222 cases, 72,55 % in the first case, and 235 cases, 76,80 % – in the second case. Insidious offset in the basic group was detected in 84 cases, 27,45 %, and 71 cases, 23,20 % in the control group ($\chi^2 = 1,46$).

The most frequent psycho-traumatic situations at the manifestation of refractory depressive episode were personal ones, found in most of the patients – 167 cases in the basic group (54,58 %), and 146 cases in the control group (47,71%). 78 patients from the basic group – 25,49 % and 76 individuals from the control group – 24,84 % had no psycho-traumatic situations at the manifestation of the resistant depressive episode. The following positions are taken by patients with personal and professional psycho-traumatic situations – in the basic group – 38 cases (14,52 %); in the control group – 35 cases (11,44 %), then come individuals with only professional psycho-traumatic situations at the manifestation of resistant depressive disorders – 23 cases in the basic group (7,52 %), and 49 cases in the control group (16,01 %) ($\chi^2 = 10,95$).

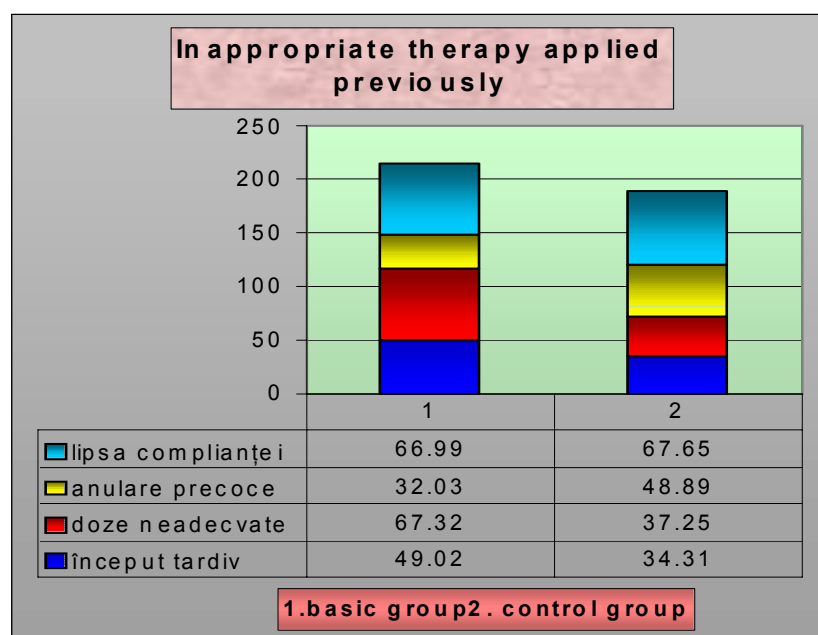


Fig. 3: Factors of inappropriate therapy previously applied in both groups

Inadequate doses (in the basic group – 206 cases – 67,32 %), in the control group – 114 cases – 37, 25 % ($\chi^2 = 55,44$, $p < 0,001$) and non-compliance (basic group – 205 cases – 66,99 %), in the control group – 207 cases – 67,65 % ($\chi^2 = 0,30$, $p > 0,05$) were the most frequent factors of inappropriate therapy applied before. As to other factors, we can mention that late onset was noted in 150 cases (34,31 %) ($\chi^2 = 13,61$, $p < 0,001$), but early cancellation was observed in 98 cases – 32,03 % – in the basic group), and 107 cases in the control group – 48, 89 % ($\chi^2 = 0,59$, $p > 0,05$).

Our observations demonstrated that major clinical variants of the disease are distributed as it following: anxious refractory depression – 248 cases (40,52 %), melancholic refractory depression – 214 cases (34,97 %) and apathic-inhibited depression – 150 cases (24,51 %) (figure 4), which are consistent with the literature [2, 5, 9, 14].

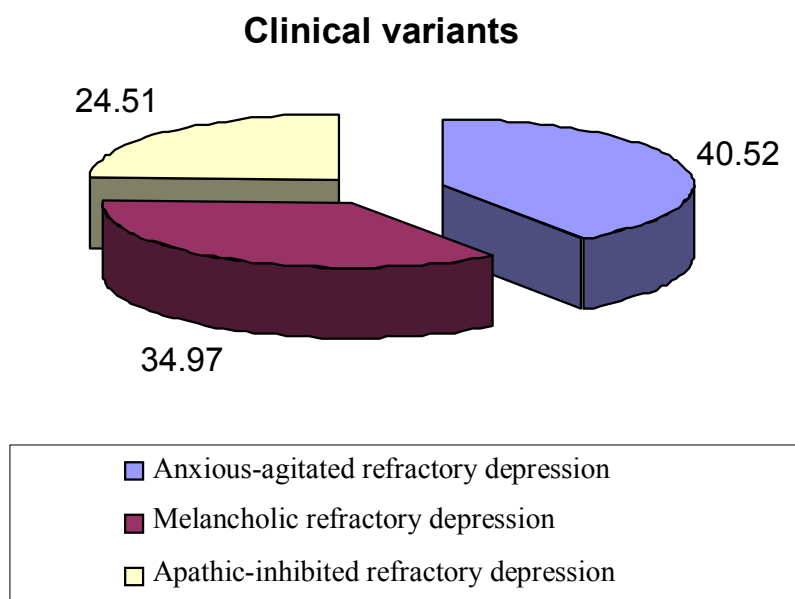


Fig. 4: *Major clinical variants of the refractory depression*

In compliance with the results from the Figure 4, anxious refractory depression is prevailed – (40,52 %), which is consistent with the specialty literature [12, 13, 15].

The psychopathological structure of anxious resistant depression is distinguished through the mobility of affective disorders, lability of anxious affect, the affect that did not only held dominant position, but, as a rule, was a decisive one. Agitation was sterile, messy, paradox, chaotic, with perplexity, patients permanently moving to and from, gesturing, always gazing at the exit. Anxiety (247 cases, 99,60 %) had an unconscious character, always accompanied by light psychomotor slowdown and melancholic affect, with retrosternal feeling of burden. Dominant anxious affect was experienced by patients as a feeling of restlessness, excitement, inner tension, psychomotor agitation – 193 cases (77,82 %), agitation that, in fact, masked the slowdown.

The clinical picture of the resistant melancholic depression is characterized by pronounced sadness (100 % in all 214 cases), with vital component, tension, psychomotor slowdown – 210 cases (98,13 %). However, the external manifestations of anxiety were insignificant or missing. Patients also suffered from had psychic anesthesia, being characterized by a decrease or a total lack of feelings towards relatives – 149 cases (69,63 %), or lack of emotional response. Most of the individuals manifested the idea of the lack of values – 177 cases (82,71 %), and indignity. Patients accused themselves of insignificant facts. These feelings amplified suicidal ideas and tendencies – 75 cases (35,05 %). Individuals considered that they had “to release themselves” of those “sins”, and the only chance, the only solution was to die.

In the clinical manifestations of resistant apathic-inhibited depression, there mainly was decrease of activity in all 150 cases and volitional impulses, emergence of spontaneity – 141 cases

(94,00 %), with feeling of drowsiness and physical weakness – 80 cases (53,33 %). The patients were sad and pessimistic about their future – 146 cases (97,33 %), having ideas of guilty and lack of value – 133 cases (88,67 %). The patients were indifferent and careless about everything that happened around them, they were not captivated by their yesterday interests and passions – 131 cases (87,33 %). In 8 cases (5,33 %), there was the state of stupor which manifested through intense psychomotor inhibition, verbal, motor, alimentary negativism. The patients stayed in the bed, were immobile, their mimics expressed despair, pain, they stared fixedly in front of themselves. The patients did not speak, or spoke slowly, whispering, being unable to exercise their will, with total avolition.

Therapeutic objectives of this study were to reduce vulnerability, and treatment syndromes, choice of methods was based on etiopathogenic background, nature of clinical picture, severity of symptoms. The treatment was aimed at remission of symptoms, improving the quality of life, resolving psychosocial factors, preventing risks of relapse and recurrence by means of education the patient with the goal of increasing compliance.

Initially, there were taken measures in order to reduce the affective tension, removing major morbid feelings of the patients, treatment of the associated diseases, including nutritional disorders. Later, it was established that productive psychological contact with the individuals, highlighting feelings within psychological conflict, are causes that trigger and maintain the disease.

Usage of pharmacological preparations by means of adjustment of doses served as an opening therapy in the combined treatment. It covered three ways of developing good therapeutic relationships: reducing symptoms and application of simple measures of psychotherapy; increasing the role of psychotherapy as medicament treatment overcomes first obstacles; adequacy of medicament doses after positive response to psychotherapy.

In developing therapeutical strategies, biological methods were used in combinations with psychological ones, however for patients unable to communicate, first of all, there were used pharmacotherapeutic methods, but avoiding the polypragmasia principle. Medicament treatment was mainly focused on antidepressants with dual action – venlafaxine, amitriptyline, clomipramine and imipramine, in doses over 200 mg/per day. The impact of the preparation on the basic disease syndrome was observed in the first weeks. However, the intensity of symptoms related to decreased mood, for instance, anxiety, insomnia, psychomotor slowness which were earlier reduced. Thus, the stimulatory impact of antidepressants proved to be favourable for the psychomotor functions, although the mood remained unchanged. This fact was been paid a special attention, because it increased the suicide risk.

At the beginning of treatment, we avoided the concomitant indication of an antidepressant and psychotropic medicaments. The combination of preparations was oriented towards increasing the curative impact, urging the healing process and decreasing the intensity of the psychopathological symptoms. The augmentation therapy was carried out by means of completing the treatment with timostabilizers (carbamazepine, valproic acid derivatives), which were indicated to stabilize the mood and prevent the depression relapse. The initial dose of carbamazepine was 200 mg, in the evening, in the first three days and then, gradually, increased from 100 mg/per day to 600 – 1200 mg/per day in the course of 3 – 4 days, thus we achieved an attenuation of the affective lability, but the depression manifestations became less prominent. The main indications for the prescription of valproic acid in doses up to 1000 mg/per day were psychotic phenomena of other co-morbidities, as well as prevention of the disease. In deep depressions, marked by anxiety, agitation, delirium ideas, hallucinations, insomnia, anxiety, the neuroleptics we used were able to efficiently control these symptoms, but in order to increase and remove these symptoms, we indicated Risperidone, in doses of 2 – 4 mg/per day, Olanzapine, in doses of 5 – 10 mg/per day, Amisulpride, in doses of 200 mg/per day, Clozapine, in doses of 50 – 100 mg/per day, Sulpiride, in the doses of 200 mg/per day, as well as classical neuroleptics – Haloperidol, in the doses of 5 – 10 mg/per day. Because tranquilizers act quickly upon certain components of depression, for instance, anxiety, we indicated these preparations (for instance, diazepam, 10 – 20 mg/per day), but for a term up to 3 – 4 weeks.

Ten individuals from the basic group combined preparation therapy with the electroconvulsive one. This combination was used only in cases of hazard to life, physical health harm of the patients, with high autolytic risk, persistent psychotic manifestations (for instance, stupor), in the case of dehydration and food refusal, or if patients do not respond to other treatments, and a rapid therapeutic effect was badly needed. The electroconvulsive therapy was conducted in intensive care department, in a safe environment, with available appropriate urgency equipment. The electroconvulsive therapy procedure lasts 2 days, the treatment course consisting of 7 – 12 sessions. In most of cases, electroconvulsive therapy contributed to improving the state. Insomnia disappeared after one session; negativism, including alimentary – after the second session; moral pain, delirium, including self-blame and suicide risk – after the 3rd session. Thus, after one week, problems of disease emergency were resolved.

Before starting psychotherapy sessions, we have profoundly studied individuals' personalities, peculiarities of their reactions, and motivation. Etiopathogenic mechanisms, which favoured the emergence and maintenance of symptoms were highlighted and researched. The patients were helped to understand the link between the peculiarities of their system of relationships and disease, meaning of psycho-traumatic situations, attitudes of individuals towards themselves, avoiding giving direct instructions. During sessions patients' vulnerability, caused by interpersonal disappointment that occurred on earlier stages of mental development was recognized. The patients admitted that those losses triggered ambivalent and contradictory feelings at the level of the *Ego*, while frustration inevitably led to a decrease of self-esteem and implicit emergence of depressive symptoms.

CONCLUSIONS

1. The most frequent predisposing factors in the researched groups proved to be previous significant eredo-collateral traumas through affective disorders in families, deprivation and humiliating attitudes coming from the parents in early childhood, lack of a stable and safe family, economic and moral decline of the family. Among the major determinants of the initiation and installation of resistant depression, there are personal psycho-traumatic situations and posttraumatic stress. Significant contributory facts in maintaining the resistant depressions and their long-term evolutions are negative somatic background and organic brain impairment.

2. In the case of resistant depression, the following variants are the most characteristic: anxious – agitated (40,52 %), melancholic (34,97 %), apathic – inhibited (24,51 %). The structure of the anxious – agitated refractory depressions is distinguished by mobility of affective disorders, periodical emotional releases, and, sometimes, melancholic raptus. The clinical picture of the melancholic refractory depressions is characterized by sadness, strong vital component, psychomotor slowness, suicidal ideas, psychic anesthesia. In the manifestations of apathetic – inhibited refractory depression, there prevail decreased activity, volitional impulses, depressive depersonalization, and states of stupor with food refuse.

3. Therapeutic objectives in resistant depression consisted of reducing the vulnerability, treatment of syndromes, prevention of relapses and recurrences. The choice of therapeutic methods was based on etiopathogenic background, nature of clinical picture, severity of symptoms. Antidepressants were indicated in combination with other medicaments, including timostabilizators and neuroleptics, as well as psychotherapy.

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The author declares that he has no potential conflicts of interest to disclose.

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