

**UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA  
DOCTORAL SCHOOL**

**PhD THESIS  
- Abstract -**

**CLINICAL, THERAPEUTICAL AND  
NEUROBIOLOGICAL PARTICULARITIES OF  
DEPRESSION IN SUBALPINE CLIMATE**

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**Key words:** depression, subalpine climate, treatment.

## **I. General part**

Depression is defined as a pervasive emotional tone profoundly influencing the views and perceptions of self, others and, generally, the environment. Mood disorders are common conditions, potentially lethal and highly treatable, where patients feel states abnormally high or low. Affectivity's multiple abnormalities are accompanied by signs and symptoms affecting almost all areas of functionality. Vegetative symptoms include changes in sleep, appetite, libido and energy.

Mood disorders include major depressive disorder, bipolar disorders (I and II), dysthymic disorder, cyclothymic disorder, mood disorder due to a general medical condition, substance-induced mood disorder and general categories of depressive and bipolar disorders otherwise specified.

Advances in treatment include an increasingly wide range of pharmacological agents, greater understanding of the combined interventions - biological and psychosocial - recognition of chronicity of these disorders and importance of a long-term maintenance treatment [1].

Depression is a mental disorder characterized by profound changes in thymic status, in the sense of sadness, suffering moral and psychomotor slowing, generally associating anxiety. It maintains the patient a global impression of helplessness, painful, desperate fatality and sometimes leads to subdelusional rumination of guilt, indignity, low self-esteem and may lead to suicide.

After Kielholtz, depressive syndrome is a basic way of response to various conditions and situations with somatogenic effect, psychogenic or endogenous, which is manifested by the triad of depressive mood, psychomotor inhibition and impaired psychomotor skills.

## **II. Objectives and method of study**

### **1.1. Hypothesis**

Starting from the premises of the neurobiological model, that demonstrated the importance of metabolic substrate and oxygenation in the neural structures, we followed the efficiency antidepressant medication therapy in depressive disorders hospitalized in subalpine climate and their report with somatic comorbidities.

### **1.2. Objectives**

1. To assess the role of subalpine climate as an adjuvant therapeutic tool in the treatment of depressive disorders, combined with drug therapy (serotonin reuptake selective inhibitors - SSRIs).
2. To highlight the main somatic cardiovascular and cerebrovascular comorbidities associated, depending on the geographical environment of origin of patients (coastal, lowland plains, hills, mountains).
3. To identify the potential markers of outcome of depressive disorder specific for psychiatric sanatorium in subalpine climate (hemoglobin oxygenation).

### **1.3. Methods**

Retrospective / prospective study for a period of 5 years (1 January 2006 - 31 December 2010) performed in the Sanatorium of Neurosis Predeal, located at an altitude of 1,100 m; patients hospitalized with a diagnosis of depressive disorder and anxious depressive disorder; follow-up of the therapeutic response after 21 days of treatment with SSRIs. Assessment of the intensity of depression in day 0 and 21 was done by using the scales Hamilton Depressive Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), Clinical Global Impression (CGI) and the Mini Mental State Examination (MMSE) to assess possible cognitive impairment.

Based on the inclusion and exclusion criteria, we selected the sample N = 352 patients. A series of demographic, clinical, bioclinical items and therapeutic management issues were extracted and processed from observation sheets.

### **1.4. Methodology**

For patients who met the inclusion criteria we proceeded to extract the items in order of statistical processing and to assess the intensity of depressive disorder using Hamilton and CGI scales at day 0 (prior to the introduction of antidepressant therapy and complementary therapeutic methods - psychotherapy) and day 21, performing subsequent comparative analysis of the main items of scores obtained by comparative evaluation and validation and studies based on associated and dependent variables.

For the whole sample, antidepressant therapy was initiated between day 1 and day 21. In order to uniform the evaluation of the results, we used antidepressants from the same group, namely serotonin selective reuptake inhibitors (SSRIs) sertraline at a dose of 50-100 mg / day and Cipralext in doses of 10-20 mg / day, associating benzodiazepines (alprazolam at a dose of 1 mg / day) and mood stabilizers (carbamazepine at doses of 200-400 mg / day).

We performed separated and compared analysis of demographic indicators using statistical analysis method.

### III. Results and discussions

Our study deals with depression in subalpine climate, depending on demographic and clinical differences in response to SSRI medication depending on the particularities of evolution prior to study entry and potential corrective alpine environment on neurobiological substrate, by increasing the blood oxygenation. The large sample of patients (352 patients) can support the development of therapeutic particularities of depression in this climate.

The main individual factors of the study group were represented in both men and women by psychic stress, significant social factors in personal history, especially in females (57 women and 24 men). Another category of psychic stress factors in the study group was socio-economic psychostress, represented by loss of employment or unemployment (64 women and 31 men) or homelessness (30 women, 29 men).

Major psychotrauma, represented by the deaths in the family over the past two years accounted also important, twice higher for females (60 women, 31 men); the same for those represented by traumatic medical experiences (19 women, 11 men).

Analyzing the altitude of the usual environment is justified because patients admitted to Sanatorium of Neurosis Predeal constitute a study group from all over the country, with different relief (coastal, lowland plains, hills, mountains). It was noted that most patients are either women or men, young or old, from rural plain (67.30%), littoral zone was represented at a much lower rate (17%) and the least (15.70%) of hill-mountain area. Difference of altitude may represent an important component of the pathophysiology of depression sanogenetic mechanisms.

We used the rating scale HAM-D (21 items) to assess the condition of the patient from the day "0" and day 21 of hospitalization.

We considered a 0-21 day interval admission. So, at women in the day "0" average HAM-D score was 16.20 and the 21 day average score 8.5. In men the day '0' average score was 15.79 and 9.68 at day 21 scores, suggesting a partial remission with residual factors depending on somatic condition, with relatively low duration (3 weeks to assess therapeutic efficacy).

#### 3.1. Comorbidities in depression

Cardio-vascular, then metabolic diseases prevailed between somatic comorbidities that significantly influenced the outcome of women's depression. In the 20 men, 7 (35%) under 40 and 13 (65%) for over 40 years, we observed the predominance of cardio-vascular and metabolic diseases.

Correlation between somatic diseases and gender is statistically significant.

In the assessment of outcome risks for major depressive disorder, named comorbidities that we have presented detailed above can be summarized group into 3 broad categories, namely:

- Cardiovascular and cerebrovascular
- Dysmetabolic disorders
- Neoplastic disorders.

Neurobiological, clinical and therapeutic features of the outcome of the study sample led to the classification of depressive pathology into three subtypes:

- Depressive Disorder - Depressive Episode 144 cases
- Depressive-anxious disorder - 123 cases
- Vascular depression - 85 cases

The first two categories are overlapping neurobiological model of depression by serotonin deficiency, which is the reason why the first therapeutic option in 0-21 period consisted of substances of SSRIs, while the third category could be correlated to the neurobiological model of depression by serotonin deficiency associated with cerebral hypoperfusion.

Somatic comorbidity means two or more disorders in the same person at the same time for a defined period of time.

The concept originated in general medicine but was subsequently applied in psychiatry as a consequence of the introduction of explicit criteria, operational for neurometabolic diseases. Psychiatric comorbidities refers to three classes:

- Anxious disorders - 2/3 of patients with major depression experienced in lifetime at least yet another mental disorder. The strongest comorbidity is between depression and panic disorder
- Comorbidities between psychoactive substance abuse and depressive disorders are commonly found. The prevalence of depressive disorder in patients with alcohol dependence abuse or when entering a therapeutic program is 15-67%, over 15% of them commit suicide, an issue of great interest and responsibility for psychiatrists worldwide
- The third section of psychiatric comorbidities refers to personality disorders, as affective psychopathology may lead to maladaptive responses that can be encoded as cognitive distortions and conflicts caused by emotional imbalance. Also they can be interpreted in the context of personogenesis. Most problems occur when borderline PD frequently emerges in adolescents and young women with a family history of dispositional disorder. The risk of depression in these patients increases with life expectancy, and such patients are a concern for both psychiatrists and family physicians. In these patients, the occurrence of depression affects not only their level of functioning but also the disease outcome. Somatic and psychiatric disorders of influence each other, which leads to difficulties in those cases and requires a complex approach in psychiatric terms.

### **3.2. Optimization of hemoglobin oxygenation in subalpine climate conditions**

An essential point of the study is the affinity of hemoglobin to oxygen under subalpine climate, concerning, as expected, in the study sample at an increasing in hemoglobin oxygenation ranged from 12.6% to 13.2% and from 15.9 also often % to 16.5% in patients coming from lowland area which translates in a greater effect in the plains than in the mountains or on the seaside hill, where the increasing was less than those mentioned above (from 14.1% to 14.7 % and 13.7% from 14.3%) whether it concerns men or women.

Results characterized by favorable outcome of depression in alpine climate using proserotonergic medication (SSRI) can be explained by improving the quality of vascular perfusion, by improving oxygenation of hemoglobin in subalpine climate. We studied the possibilities to increase hemoglobin in subalpine climate, namely hemoglobin affinity to oxygen, which in our study originated from seaside plain hill - mountain, is growing in all categories from these different environments.

In our study, we selected cases from the three mentioned areas – coastal, lowland and mountain, reflecting and strengthening the supposition that in all hospitalized cases, level of hemoglobin obviously grew after admission. Also, we should mention that in cases selected, we tried to select predominantly those of the lowlands, followed by hill-mountain and coastal, each case with a variety of disorders: somatic disorders or anxious depressive disorder: hypertension, ischemic heart disease, peripheral arterial disease, obesity, diabetes mellitus type II, left carotid stenosis, organic affective disorder.

We studied the affinity of hemoglobin to oxygen in climate conditions, in men and women who came from different altitudes (coastal, lowland, hill), aged between 29 and 65 years with severe recurrent depressive disorder prevailing, cardiomyopathy, organic depression, hypertension, organic affective disorder, obesity, diabetes, cerebral atherosclerosis. We observed that men and women, regardless of where they originated, had an increase of hemoglobin oxygenation, ranging from 12.6 % to 13.2%, 15.4% to 16%, from 14.4% to 15.2% and from 15.9% to 16.5% of that from the flat. On the hill from rural regions, variations are between 14.1% - 14.7%, 14.2% - 14.9%. On those from the coastline, variations were between 13.7% and 14.3%.

### **3.3. Distribution of depressive disorders according to the number of days, number of cases, the average length of stay (ALOS) and the cost of a depressive episode between 2006 and 2010**

We analyzed the relationship in terms of the cost of hospitalization (ALOS) and the number of cases by the number of days.

Depending on the number of days, since 2006 and ending with 2010, we noted some variation in the sense that the lowest number of days is in 2006 and is the largest number in 2009 (21,586 days in

2006 and 28,226 days in 2009). Between these values are situated other years, 2007, 2008 and 2010. Depending on the number of cases, we observed an increase from 1222 in 2006 to 1577 in 2009, the remaining values being close. Considering the ALOS, we noticed that it ranges from 16.95 days in 2010 to 18.66 days in 2006. Between these two values, we observed quite similar values for other years. Finally, with reference to the cost of a depressive episode, it was found a greater variation in correlation with the number of days, the number of cases and ALOS, namely:

- The lowest cost of an episode was in 2006 and 2007,
- It follows a significant increase for the years 2008, 2009 and a slight decrease in 2010 (949.25 RON)
- Referring to the cost of an episode, we observed an increase of over 700 RON between the first two years comparing to the next three, which shows an increase in costs related to the economic crisis of recent years, from 2008 to the present.

The number of days between 2006 and 2010 increased, excepting of 2010. The number of cases increased during first four years (2006-2009) from 1200 to 1600 cases, with a slight descent in 2010 (1400 cases).

Average length of stay is between 16.95 and 18.66 days. The lowest average length of stay was registered in 2010 and 2007, and the highest in 2006 and 2008.

Regarding the cost of an episode, we found lower values in the first two years – 2006 and 2007. In 2008 and 2009 there has been a significant increase, and in 2010 values are decreasing.

## IV. Conclusions

1. Depressive Disorder in the study sample N = 352 patients, was twice more frequent in women than in men (65.34% versus 34.65%), the average age being 44.03 years for men, with a dispersion of 71.27 and standard deviation of 8.44 and 37.77 years for women, with a dispersion of 71.46 and standard deviation of 8.45.
2. Analysis of variables that could influence the development of therapy of depression revealed that a significant number (more than 4 episodes) was the preserve of women (38.6%), and social environment of urban origin prevailed both for women and men (65.1% to 65.8% in men and women). The educational level in the whole study group for both sexes was predominantly secondary education level training (53.3% of all patients - 47.6% women and 51.2% men).
3. Distribution of the sample by geographical environment of origin according to altitude revealed that most patients came from rural lowland plains (total 67.3%), from the coast 17% and hill-mountain environment 15.7%.
4. Mean gender distribution of scores on Hamilton depression scale revealed that at day 0 for women, HAM-D mean score was 16, 0% and 15.79% for men and at day 21, 8.85 (residue phenomenon 17.35) for women and 9 men 68 (residue phenomenon 6.11). For operational purposes, the whole sample was divided for homogenization of results in statistical processing for both genders into two categories, under and over 40 years, allowing batch splitting into three categories according to the therapeutic results day 21: treatment failure, incomplete therapeutic success and total therapeutic success. Significant differences ( $t = 9.81$ ,  $p < 0.01$ ) are relevant between the group with total therapeutic success and treatment failure.
5. Analyzing the results by geographical environment of origin, there is an absolute majority (62%) of those from lowlands, plains, regardless of urban or rural, age and gender of the total successful therapeutic subgroup over 40 years, while for treatment failure and incomplete therapeutic success, the vast majority (66%) was among those from the hill-mountain.
6. In the subgroup of patients under age 40, regardless of gender, geographical environment of origin did not correlate significantly with total therapeutic success.
7. The main somatic comorbidity which strongly influenced the outcome of depression ( $p < 0.05$ ) were for women: hypertension (17.39%), ischemic heart disease (16.96%), polyneuropathy (11.30%), obesity (10.43%), diabetes mellitus type II (9.13%) and for men hypertension (14.75%), ischemic heart disease (13.11%), diabetes mellitus type II (11.48), obesity (7.38%) and dyslipidemia (dependence between somatic and gender is statistically significant). Analyzing somatic comorbidities, we highlighted many neoplasms (7 women and 8 men) in association with an equal number of brain tumors (5 women and 5 men).
8. Study of hemoglobin affinity to oxygen in subalpine climate conditions in the study group revealed an increase in hemoglobin oxygenation which ranged from 12.6% to 13.2%, respectively, 15.9% 16.5% for patients from the lowlands, while for those coming from the hill-mountain environment and from the coast, the increase was less spectacular (14.1% to 14.7% and 13.7% to 14.3%), regardless of gender, outlining the potential value of a biological marker of the outcome of depressive disorder in alpine climate.
9. Treatment with SSRIs in subalpine climate can significantly improve the severity of depression. Positive results of treatment can be augmented in subalpine climate by improving the quality of vascular perfusion by increasing the oxygenation of hemoglobin.

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