UNIVERSITY OF MEDICINE AND PHARMACY

"CAROL DAVILA", BUCHAREST

DOCTORAL SCHOOL

DOMAIN: MEDICINE

PhD THESIS

(Summary)

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PhD-candidate:

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Benefits of Naltrexone Association in the Treatment of Alcohol Addiction Associated to Schizophrenia

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Summary

Introduction

Alcohol is integral part of the life of human society, the substance being appreciated for its euphoric and anxiolytic effects. Schizophrenia is a mental disorder characterized by a series of positive, negative and/or cognitive symptoms, with the particularity of exposing a high rate of comorbid substance use, in an abusive way. While more than 80% of schizophrenics are smokers, the second substance consumed is alcohol, with dramatic consequences on the frequency and intensity of psychotic episodes and on life expectancy. Alcohol addiction is a key negative prognostic factor in patients diagnosed with schizophrenia, leading to a more difficult diagnosis, to a higher number of hospitalizations, and more severe disease episodes.

Recently, there has been a worrying increase in alcohol consumption globally, determining since 1967 the World Health Organization to initiate special programs to combat alcohol abuse, the goal becoming a priority, because alcoholism is considered to be the fourth public health problem in the world.

Although schizophrenia-alcoholism comorbidity is one of the most frequently encountered among the psychiatric population, there are currently various research hypotheses on which the authors of the relevant studies have failed to pronounce. This comorbidity is a challenge for clinicians, which they face both within the process of diagnosis, as well as of elaboration of a customized psychiatric treatment.

The novelty of the thesis consists in the administration of psychological instruments that measure different scales of psychopathology, to identify the rate of associated comorbidities as regards the group of patients with schizophrenia and alcoholism. The pathologies surveyed are from several planes, among which: somatic (hepatic, cerebral, neurological, metabolic, addictive disorder), cognitive, affective, motivational, aggressive and/or of hostility, of social functioning, of intra-family functioning, of life quality. The originality of the c comes from the survey of a small and specific group of patients with alcoholism-schizophrenia comorbidity, using the observation method, with an initial and a final test, with an interval of 6 months between them, during which the work group received additional anti-craving treatment, and the control group received only the treatment of basic diseases.

The central objective of this thesis is to argue the need for additional anti-craving treatment in patients with alcohol addiction associated with schizophrenia, as this management

emphasizes the idea of multidisciplinarity and interdisciplinarity. Being in agreement with the specialty literature, these patients suffer from two major psychiatric pathologies, for which the treatment is more complex and involves not only the identification of psychiatric signs and symptoms, but a psychological and medicinal therapeutic approach.

The secondary objective of this thesis was to provide comprehensive data on the functioning of a schizophrenic patient with comorbid alcohol consumption disorder. We applied, from a psychological perspective, a multitude of tests to identify a psychopathological profile of the patient with dual diagnosis, the ultimate goal being to identify the most effective mode of therapeutic management.

Current stage of knowledge

Schizophrenia-alcoholism comorbidity

Comorbidity is defined as the presence of a distinct clinical entity that existed or may occur throughout the clinical course of another underlying disease [1]. Alcohol consumption is usual among people with schizophrenia and leads to unfavourable treatment results [2].

Incidence

The consumption of psychotropic substances has a prevalence of almost 50% in patients diagnosed with schizophrenia, a percentage 3 times higher compared to the general population [3]. The rate of substance use is 2-3 times higher in men, compared to women with schizophrenia [4]. The mortality rates in patients with comorbid consumption are higher [5], and the most frequently used substances are: nicotine (80-95%), alcohol (20-60%), cannabis (12-42%), and cocaine (15-50%) [6].

The patients diagnosed with schizophrenia, compared to those without this diagnostic, are more likely to smoke, consume large amounts of alcohol, cannabis or recreational drugs [7] - a percentage of 47%, compared to the risk of 16% of the general population. Abdel-Baki and collab. [8] discovered an incidence of substance use varying from 30 to 70% in patients in the first psychotic episode. Alcohol addiction is a key negative prognostic factor in patients diagnosed with schizophrenia, leading to a more difficult diagnosis, a higher number of hospitalizations, and more severe disease episodes.

There are many uncertainties about the etiology of each of the pathologies of schizophrenia-alcoholism comorbidity, in terms of the onset of the disease, and the implications the symptoms of one pathology have over the other. Comorbidity leads to *higher intensity signs and symptoms*, compared to subjects diagnosed with only one of the pathologies. However, the most difficult thing is to establish a therapeutic plan. Comorbidity predisposes to more clinical exacerbations, reduced overall functioning, violence, suicide and higher risk of recurrence and rehospitalisation [9].

The study of Hunt and collab. [10] claims a 42% prevalence of alcoholism among patients with schizophrenia. The researchers also highlighted that the prevalence is higher in men and that those with alcohol consumption had an earlier onset of schizophrenia.

Norwegian researchers [11] identified a prevalence of alcohol consumption disorder of 25.1% among individuals born between 1950 and 1989, and who, between 2009 and 2013, were diagnosed with schizophrenia. The researchers also highlighted that middle-aged patients

with bipolar disorder had the highest prevalence of alcohol use disorder, while young people with schizophrenia had the highest prevalence of non-alcoholic use disorder. The study of Nielsen [12] highlighted an association between schizophrenia and almost all substances of which one may abuse. The highest risk of developing schizophrenia has been identified among cannabis users, but considerable risks have also been identified in case of consumption of hallucinogens and sedatives. **Cannabis and alcohol abuse increased** the risk 5, respectively **3 times** to develop schizophrenia, compared to 40% for cannabis and 0.4-12.36%, as it was provided in previous studies [13-15]. Therefore, the hypothesis is raised that *consumption of more dangerous substances* would be more strongly associated with the development of schizophrenia *than the frequency of consumption itself*. The tendency to consume substances more regularly and more intensively has been reported more frequently in men, and the risk of developing schizophrenia is however higher in men than in women [16].

Recent literature studies suggest that this dual diagnosis is found in a percentage that varies between 35% and 80% [17] of psychiatric population. Differences in epidemiological data have their origin, among others, in different diagnostic criteria, different investigation tools used by researchers, and in geographical criteria [18]. In the study of Leposavic [17], researchers identified a percentage of 54% of the 50 patients analyzed, who fulfilled the dual diagnosis. They also highlighted that the risk of comorbidity is higher in men diagnosed with schizophrenia at a young age and those with a family history of alcoholism. The percentages are probably even higher for high-risk groups, such as young people with a history of violence or homelessness. The prevalence is higher among men.

A Taiwan study showed a 10.5% prevalence of alcoholism among patients with schizophrenia [19], while in India it seems that the percentage is lower, of 5.5%. In his study, Subramaniam [20] identified a 6.4% prevalence of alcohol consumption among patients diagnosed with schizophrenia in Singapore.

Another study sought to compare the prevalence of alcohol consumption among schizophrenic patients in relation to the general population from India [21]. Researchers have shown a *much lower* prevalence among patients (10.2%) compared to healthy controls (18.3%). In addition, they also identified a percentage of 5.5% of the patients and 10.3% of subjects from the control group, who consumed alcohol in a risky way. Risky consumption was associated with the *rural environment* and *a lower level of education*.

Schizophrenia has a rate of comorbidity with alcohol in the maintenance phase of schizophrenia of 23.4% [22] but some studies have even identified a higher rate of 43.1-65% [23]. The risk factors for comorbidity [24] include:

- a low level of education;
- family history of alcoholism;
- violent offences in the background;

In a meta-analysis of 60 studies from around the world, Koskinen [22] demonstrated a median prevalence of current alcohol consumption disorder of 9% and a lifetime prevalence of 21%. Another study [25] mentioned that, among patients with schizophrenia and anxiety disorders, after one year of follow-up, alcohol abuse occurred in a percentage of 24-37%.

Genetic etiology of comorbidity

A study from 2017 aimed at predicting addiction disorders in patients without a diagnostic of psychotic disorder, using polygenic risk scores for schizophrenia and bipolarity. This statistical analysis is performed on subjects without underlying disease, to exclude the effect that the disease itself has on genetic risk factors. A common genetic etiology between psychosis and addiction has been demonstrated [26].

The common etiology for the two pathologies, schizophrenia and alcoholism, is also suggested by other studies, such as Hartz's [27], who claim that the dual diagnosis is partly due to a polygenic genetic liability. This liability explains a general risk of consumption disorder and not certain specific risks. In addition, it reiterates the idea that there is a fine demarcation line between the two disorders.

Zai [28] claim a 20% percentage of alcoholism comorbidity with schizophrenia. The brain-derived neurotrophic factor (BDNF) and the dopamine D3 receptor (DRD3) are involved in alcohol consumption-related behaviors. BDNF is involved in regulating nerve cell proliferation and cell survival, in addition to dopaminergic support [29]. DRD3 it is found in the nucleus accumbens of the limbic system, which plays an important role in strengthening stimuli [30]. The study of Zai [28] identified that **Val66Met BDNF gene** is associated with alcohol addiction in patients with schizophrenia, but also certain haplotypes of the gene. Low levels of BDNF have been identified in both schizophrenic and non-schizophrenic patients, as well as in those who were not following any treatment [31]. DRD3 gene did not identify positive associations.

Cognitive deficits from schizophrenia include deficits in the area of attention, memory, learning and executive function [32]. Cognitive deficits from alcoholism include deficits in working memory, choice of goals, strategic planning, and inhibition of the response [33]. Therefore, comorbidity will lead to more severe deficits. In an article [34] Ventriglio sought to notice the cognitive functioning of patients with a primary diagnostic of schizophrenia, some of them consuming alcohol and others without consumption, being noticed that cognitive

performance was affected in both groups (compared to the healthy population), but only by 6.2% more among alcoholic patients. Deficits have been reported in the area of *verbal and working memory, executive functioning, planning, and physiognomy recognition* [35]. Ventriglio [34] analyzed, using MODA questionnaires (for cognitive deficits) and MAST (for alcohol consumption), three groups of patients (schizophrenics, alcoholic and healthy schizophrenics) and identified a significant correlation of moderate intensity between the two scores.

There are various hypotheses about the causes that *determine schizophrenic patients to consume alcohol*, among them being, most frequently, the belief that [2]:

- they can *more easily* overcome the characteristic symptoms of psychotic episodes;
- they are more tolerated if they are perceived as addicted to alcohol*, compared to when they would be diagnosed with schizophrenia*;
- they attribute *the degradation of personal functioning to alcohol consumption*, which seems to be a reversible condition;
- *they attribute aggressive behavior to alcohol consumption*, considering that they are more easily accepted by the society.

Applied research

According to the specialty literature presented, it clearly results the need for a scientific and practical approach to patients diagnosed with alcoholism-schizophrenia comorbidity.

Research objectives

- The study of differences in symptomatology between the group of patients having received anti-craving treatment and those from the control group (patients with schizophrenia, alcohol consumers, but who have not received long-term anti-craving medication).
- Emphasizing the importance of anti-craving medication on three components: reducing the apatho-abulic dimension, increasing the quality of life, increasing the motivational-volitional dimension.
- Identification of psychopathological comorbidities in patients with alcoholism-schizophrenia comorbidity.

Research hypotheses

- There is a statistically significant difference in psychometric test results between the group of patients having received anti-craving treatment and the group of patients without anti-craving treatment.
- There are differences between the two groups, depending on: heredo-collateral history, pathological personal history, social support network, and the treatment scheme.
- We can predict the score for quality-of-life variable in patients with comorbidity, depending on the other variables surveyed.
- We can predict the score for the alcoholism variable, depending on the other variables surveyed.

Methodology

Participants

The research was carried out on patients admitted to the VX Department of Psychiatry within the Psychiatry Hospital “Prof. dr. Alexandru Obregia”. All participants in the group had the main diagnostic of axis I of Schizophrenia. In the evolution of the underlying disease, they associated alcoholism, either addiction or “in binge” consumption.

We chose to focus on alcohol addiction compared to abuse, the latter being rather a residual diagnosis that would not meet the criteria for addiction. Our definition as regards dual diagnosis was based on ICD-10 criteria for alcohol addiction and DSM-5 criteria for

schizophrenia. We also quantified other addictions, such as psychoactive substances or nicotine.

The group of participants in the research consists of 88 subjects, men, from urban environment 61 (69.3%) and rural environment 27 (30.7%), with ages comprised between 23-80 years, with an average age (M) of 47.20 years and with a standard deviation (DS) of 13.15. They have the following levels of education: primary 11 (12.5%), professional 16 (18.2%), high-school 31 (35.2%), higher education 24 (27.3%), postgraduate studies 6 (6.8%). The research participants are at the first hospitalization – 24 (27.3%) and with several hospitalizations – 64 (72.7). Of the 88 subjects, 46 (52.3%) were hospitalized voluntarily and 42 (47.7%) – non-voluntarily.

Sampling procedure

The study was carried out between June 2019 and August 2020, within the Psychiatry Hospital "Prof. dr. Alexandru Obregia" Bucharest, within XV department.

Upon admission to the clinic, there were patients who associated uncomplicated withdrawal and/or complicated withdrawal with delirium tremens. The hospitalization period of the patients introduced in the study was between 7 and 21 days. For this reason, the psychological evaluation was performed between the 7th day and the 12th day of hospitalization, when the patients had clarified the field of consciousness and could participate in the interview, respectively they could fill in the questionnaires. Similarly, the final test was performed after 6 months of treatment.

The group of randomly selected participants was divided into two approximately equal groups, 45 of them being allotted to the work group (GE) – those who received anti-craving medication and the other 43 in the control group (GC) – those who did not receive anti-craving medication. Tests were applied before and after the end of the study period.

Measurements, evaluation tools, research variables

The variables collected and the questionnaires applied were chosen in agreement with the limits of the previously reviewed studies. Thus, we define the following psychological dimensions of alcoholism, *in agreement with symptomatology made explicit in the psychological examinations* of alcoholic patients admitted to psychiatry departments, dimensions representing *a reflection in the clinical psychology of the main psychiatric diagnostics associated with alcoholism*.

1. The psychotic dimension. This included surveying on:

- maintaining confusion, disorientation, difficult testing of reality;

- insufficient understanding of the situation in which the person concerned is;
- feeling of unreal and implausible.

2. The apatho-abulic dimension.

3. The depressive dimension. We checked is the following are associated in patients:

- guilt, culpability, remorse;
- risk of suicide;
- risk of extended depressive episodes;
- the need to associate treatment schemes that include dual antidepressants and SSRIs, eventually with the inclusion of antipsychotics.

4. The psychopathy dimension. We have searched:

- if family pathology 1 is associated;
- the importance of the *other* in the dynamics of relapse and in the administration of medication;
- if the profile of addiction is also played in other areas, and if this happens more in the psychological space than in the physical one

5. The disbehavioral dimension (association of mental and behavioral disorders due to alcohol use, association of explosive impulsive, excitable personality structures, loaded with indices of cerebral micro-organicity, aggression, hostility, acting-out pathology with short-circuiting the field of consciousness and mentalization deficit).

6. The amnestic dimension. We have surveyed:

- association of fixation amnesia;
- association of confabulations;
- association of disorientation;
- inability to regain the level of functioning reached before the last hospitalization;
- cognitive impairment;
- personality deterioration;
- lack of involvement in personal hygiene;
- the need of family involvement in care.

7. The dimension of somatic sequelae of alcoholism. We have searched:

- somatic dysfunction;
- indifference to the degradation of the body's functioning;
- the association of apatho-abulia that goes up to affective indifference towards oneself;

- the category of those most willing to maintain abstinence (and due to the late involvement of families);

8. The cognitive dimension (assessed by cognitive functioning questionnaires).

Two types of measurements were used: the binary type (with yes/no answers) and clinical scales whose result is scoreable.

The psychological instruments used were: MAST scale, HAM-D depression scale, PANSS scale (where the following were measured: the positive dimension, the negative dimension and the general dimension), WHOQOL quality of life scale, MMSE score, cognitive error questionnaire, absurd story test, hostility questionnaire (of which only three scales were used: negativism, resentments, indirect hostility). An introductory questionnaire for factual data was added, which highlighted: age, level of education, background. The associated comorbidities were also noted.

Research design

The research took place in a natural environment and it was an observation study, which involved an initial test and a final test. The time distance between the two tests was 6 months. The database was processed in SPSS, variant 26. To test the hypotheses, we divided the hypotheses into sub-hypotheses, for operationalization.

Results

Results obtained from testing the first two working hypotheses:

H1: *There is a statistically significant difference in the results of psychometric tests between the group of patients who received anti-craving treatment and the group of patients without anti-craving treatment.*

H2: *There are differences between the groups depending on heredo-collateral history, personal pathological history, social support network, and the treatment scheme.*

- *The anti-craving medication had an effect on relapses of alcoholism*.
- *We notice that there are significant differences in the values of the MAST test in the two tests*. The size of the effect (d) will show us the influence of the medication on alcoholic patients. An above-average effect size was obtained for the control group (d=0.72) while for the research group a large effect size was obtained (d=1.17)
- *The anti-craving medication had (low) effect on inter-episodic self-care capacity.*
- *The anti-craving medication had very low effect on maintaining a job.*
- *Patients without comitial seizures and normal biological outcomes and without somatic dysfunction will have a lower cognitive deficit at cognitive failure (CFQ), absurd story test (PAC) both upon admission and 6 months after admission.*
- *Patients without comitial seizures and without somatic dysfunction will have a lower deficit at confusion (both upon admission and 6 months after admission). Those without comitial seizures and without somatic dysfunction will have a lower deficit at disorientation 6 months after admission. Financial planning capacity* will be higher in those ***without*** *comitial seizures* and *without somatic dysfunction* upon admission. 6 months after admission, the percentage of those *without comitial seizures and without degradation* is higher compared to admission at *confusion* (94.5% compared to 59.3%) and *disorientation* (98.2% compared to 29.6%). 6 months after admission, the percentage of those *without comitial seizures and without degradation* is higher compared to admission at financial planning capacity (85.5% compared to 40.7%)
- *The global intensity of the depressive syndrome (HAM D)* decreased 6 months after admission in both groups, in the control group (without AD medication) more than in the research group (with AD medication). AD medication had a negative effect on *the global intensity of the depressive syndrome.*
- *Antidepressant medication has a positive effect (small) on the risk of suicide.*

- *AD medication has a positive effect on prolonged depression*. The effect is higher 6 months after admission for the research group and small for the control group.
- *Because the value of increase is higher for the control group, we conclude that antidepressant medication had no effect on increasing motivation.*
- *In the control group (those without AD medication) the presence of curiosity increased more compared to the research group (those with AD medication) so we conclude that AD medication had no effect on curiosity.*
- *The quality of life decreased in both groups, more in the research group than in the control group. AD medication had a negative effect on the quality of life.*
- *Personality deterioration is not influenced by AD medication. The decreases are approximately equal.*
- *Professional abandonment is not influenced by AD medication. The decreases are higher in those who did not receive AD medication (control group).*
- *Concerns about the future are not influenced by AD medication. The increase is higher in those who did not receive AD medication (control group), by 12.8%.*

- The quality of life increased in both groups. We note that there are significant differences in WHOQOL test values in the two studies. The size of the effect (d) will show us the influence of anti-craving + AD medication on the quality of life of alcoholic patients. For both groups the effect size is above average: d = 0.90 for the control group and d = 0.80 for the research group. Although not too much, the quality of life has increased more in those who did not receive anti-craving medication.
- The difference in terms of *"Personality deterioration"* between those who received anti-craving + AD medication and those who did not receive is of 16.6%.
- Cognitive errors decreased in both groups. We note that there are significant differences in CFQ test values in the two tests. The size of the effect (d) will show us the influence of voluntary/involuntary hospitalization on the cognitive errors of alcoholic patients. The effect size is average (d=0.52) for patients who are hospitalized voluntarily and weak (0.38) for the patients who are hospitalized involuntarily.
- Cognitive errors decreased in all three groups. The size of the effect (d) will show us the influence of the level of education on *"cognitive errors"* of alcoholic patients. For the group *"gymnasium"* a weak effect size was obtained (d=0.35), for the group *"high-school"* an effect size towards average was obtained (d=0.44) while for the group *"higher education"* an above-average effect size was obtained (d=0.57) Admission of

alcoholic patients with or without anti-craving medication had a positive effect on *"cognitive errors"* differentiated according to the level of education.

- Family support has a positive effect on *Risk of suicide and depression*. The effect is higher 6 months after admission because the effect of the medication is added and the number of those with family support increases. Family support has little effect on *guilt and culpability*. If we also consider medication, family support may have no effect on *guilt and culpability.* Family support has little effect on *satellite anxiety*. If we also consider medication, family support may have no effect on *satellite anxiety.*

Results obtained from the testing of the third working hypothesis

H3: We can predict the score for the variable quality of life based on the other variables surveyed. More precisely:

We can predict the score for *the quality of life* by the variables: *alcoholism* (MAST), *psychotic impairment* (PANSS), *social variables*, variables related to *medication, hospitalization*, *demographic* variables.

INITIAL TESTING

We carried out a multiple regression analysis, using as variable the criterion *the quality of life.* The following were introduced into the same equation, as predictive variables:

- *alcoholism* (measured by MAST);
- *psychotic impairment* (measured by PANSS): *PANSS_P, PANSS_N, PANSS_G;*

- *social variables: Self-care capacity, The presence of social support upon admission, Maintaining the job, Association of medical complications, Public safety impairment, Association of social stress, Financial planning capacity, Family support;* the answers were of the type: *no (0)* and *yes (1)*;

- variables related to *medication and hospitalization: AP, AD, method of hospitalization, number of hospitalizations*; the answers were of the type: *no (0)* and *yes (1)*;

- *demographic variables: level of education* (gymnasium(1), professional(2), high-school(3) higher education(4), post-graduate(5), *the environment* from where those concerned are coming (rural, urban), *age*.

As a method, we choose the Backward analysis, method that will ultimately provide a correct statistical pattern, after trying in turn all possible patterns, initially including all variables, then eliminating one by one those that are not relevant (variables that are correlated with other variables in the pattern). Thus, 15 patterns were generated.

We have followed the value of $R^2_{adjusted}$, which will indicate us the relevance of the pattern. The higher value will indicate us the better pattern. This is 0.456 in the pattern 10. The coefficients F are significant (at $p<0.01$) to all 15 regression patterns, so all patterns are effective in prediction. The highest value is that of pattern 15, $F=13.75$, $p<0.01$.

ANOVA analysis of variance for regression pattern 15, on the influence of independent variables on the dependent variable **upon admission**:

Pattern		The square sum	Freedom degree	Square average	F	p.
15	Regression	19439.207	5	3887.841	13.753	.000[o]
	Residual	23180.748	82	282.692		
	Total	42619.955	87			

We will choose *pattern 15* as being the most adequate.

Pattern	R	R square	R square adjusted
15	.675[o]	.456	.423

Pattern 15 explains 42.3 % of the variation of cognitive functioning (R2adjusted = 0.423), the global effect being high.

Standardized Beta coefficients indicating a significant influence of independent variables on the dependent variable (the quality of life_WHOQOL) **upon admission**:

Pattern 15	Non-standardized coefficients	Standardized coefficients		t	p	Correlations		
	B	Std. Error	Beta			Zero-order	Partial	Part
(Constant)	45.93	8.17		5.62	.000			
PANSS_P	.46	.18	.211	2.46	.016	.095	.262	.201
FS1_Self-care_capacity	17.42	4.16	.375	4.19	.000	.530	.420	.341
FS2_Presence_social_support	9.80	4.00	.211	2.45	.016	.384	.261	.200
FS7_Financial_plan._cap.	7.87	4.56	.167	1.73	.088	.385	.187	.140
AP	-15.92	5.88	-.248	-2.70	.008	-.370	-.286	-.220

The table above shows for pattern 15 each independent variable, standardized and non-standardized regression coefficients are presented, the standard error of non-standardized coefficients, t tests to test the null hypothesis, according to which the non-standardized coefficients are zero, zero-order correlations, partial and semi-partial.

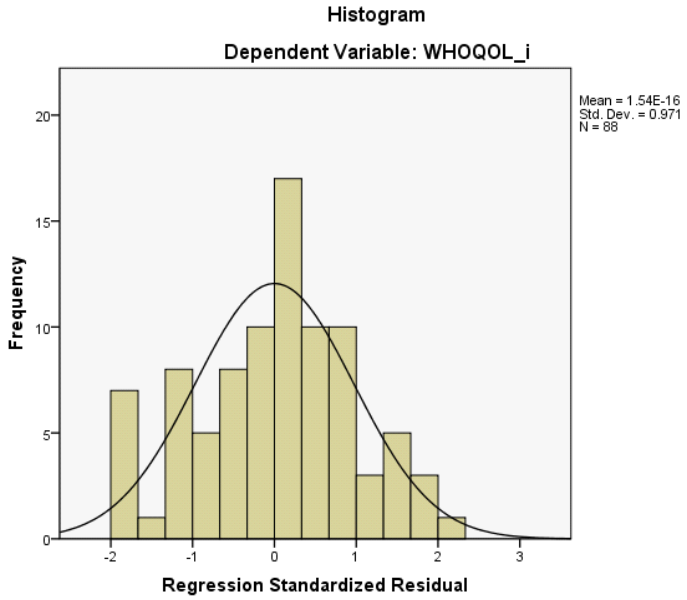
The largest share of the five variables of the pattern 15 is that of *Self-care capacity*. The effect size indicators for each of the five variables of the pattern 15 are r_{sp}=-0.341 for *Self-care capacity (FS1)*, r_{sp}=-0.220 for *AP,* r_{sp}=0.201 for *PANSS(P),* r_{sp}=0.200 for *The presence of social support (FS2),* r_{sp}=-0.140 for *Financial planning capacity (FS7).*

Following the presentation and analysis of the table with the β coefficients of the regression equation, as well as of their statistical significance, the corresponding multiple regression equation is as follows:

$Y=a+b_1*X_1+b_2*X_2+b_3*X_3+b_4*X_4+b_5*X_5$

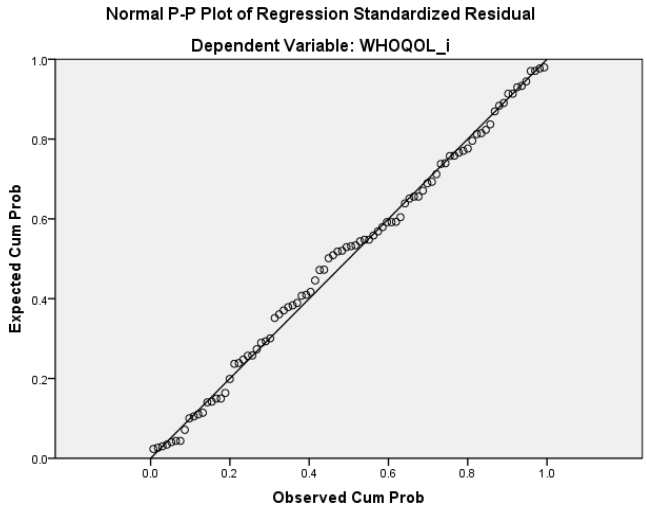
WHOQOL = 45.93 + 0.46*PANSS(P) + 17.42*FS1 + 9.80*FS2 + 7.87*FS7 - 15.92*AP

Another condition that must be met for the application of multiple regression is that the errors (residues) be normally distributed (fact indicated by the histogram below).



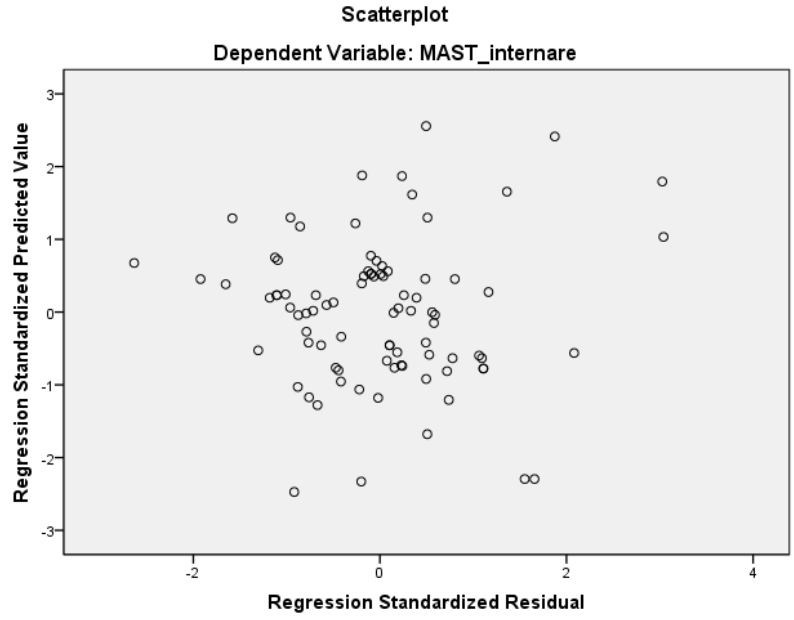
GRAPH 1: Residue distribution.

Graph 1 checks the normality of the standardized residue distribution, by comparison with the deviations from the normal curve. We notice that the condition of normality of the residue distribution is met.



GRAPH 2: Deviations of residue distribution.

In graph 2 one can notice the representation of the correlation of the data predicted by the independent variables (test scores) and the measured ones, which represent the performances for the criterion (WHOQOL).



GRAPH 3: Representation of scatter plot between the values of the criterion and those of the predictors.

We check the existence of influential cases by inspecting Cook's distance. As the value obtained is 0.012 (<1), it results that there are no influential cases [36].

Conclusion:

Upon admission, the value of the score PANSS (P), Self-care capacity (FS1), The presence of social support (FS2), Financial planning capacity (FS7) are positive predictors of the quality of life. AP is a negative predictor. In other words, the lower the PANSS score of a patient, the better is the self-care capacity, the more social support he benefits, he is able to plan his daily actions and activities, the more these aspects will positively influence his the quality of life. As the person in question requires high doses of antipsychotic medication, this correlates negatively with the long-term prognosis, in terms of the quality of life. This may be due either to a resistant form of schizophrenia, or to the persistence of residual symptoms, or to the association of the organicity factors of psychosis.

FINAL TESTING

We achieved the same algorithm as in the initial testing. 14 patterns have been generated. We have followed the value of $R^2_{adjusted}$, which will indicate us the relevance of the pattern. The highest value will indicate us the best pattern. This is 0.696 in the pattern 10. The coefficients F are significant (at $p<0.01$) in all 14 regression patterns, so all patterns are effective in the prediction. The highest value is that of pattern 14, $F=27.45$, $p<0.01$.

Table ANOVA variance analysis for regression pattern 14 on the influence of independent variables on the dependent variable **upon admission**:

Pattern		The square sum	Freedom degree	Square average	F	p.
15	Regression	39825.736	7	5689.391	27.450	.000[n]
	Residual	16581.344	80	207.267		
	Total	56407.080	87			

We will choose *pattern 14* as being the most adequate.

Pattern	R	R square	R square adjusted
14	.840[n]	.706	.680

Pattern 14 explains 68.0 % of the variation of cognitive functioning ($R^2_{adjusted} = 0.680$), the global effect being high.

Table Standardized Beta coefficients indicating a significant influence of independent variables on the dependent variable (the quality of life_WHOQOL) **6 months after admission**:

Pattern 14	Non-standardized coefficients	Standardized coefficients		t	p	Correlations		
	B	Std. Error	Beta			Zero-order	Partial	Part
(Constant)	115.72	9.31		12.43	.000			
PANSS (N)	-.60	.25	-.233	-2.41	.018	-.657	-.261	-.146
PANSS (G)	-.39	.12	-.303	-3.18	.002	-.605	-.335	-.193
FS1_Self-care_capacity	24.24	4.86	.329	4.99	.000	.553	.487	.302
FS4_Medico_legal_compl._assoc.	-13.06	5.05	-.164	-2.58	.012	-.205	-.278	-.157
AD	-11.89	3.32	-.235	-3.59	.001	-.246	-.372	-.217
Anti-craving medication	7.40	3.24	.146	2.29	.025	.284	.248	.139
Level of education(5)	3.93	1.45	.172	2.72	.008	.322	.291	.165

The table above shows for pattern 14 and for each independent variable the standardized and non-standardized regression coefficients, the standard error of non-standardized coefficients, t tests to test the null hypothesis, according to which the non-standardized coefficients are zero, zero-order correlations, partial and semi-partial.

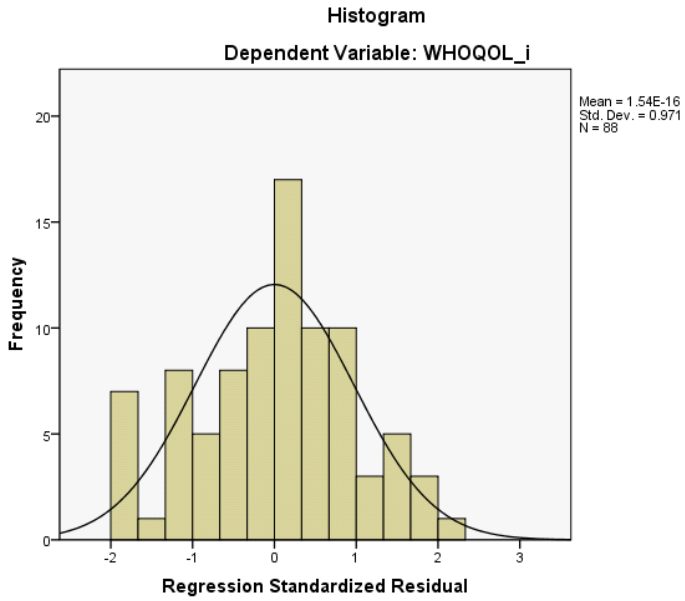
The largest share of the seven variables of the pattern15 is that of *Self-care capacity*. The effect size indicators for each of the seven variables of the pattern 14 are r_{sp}=-0.302 for *Self-care capacity (FS1)*, r_{sp}=-0.217 for *AD,* r_{sp}=-0.193 for *PANSS (G),* r_{sp}=0.165 for *Level of education*, r_{sp}=-0.157 for *Association of forensic complications* (FS4), r_{sp}=-0.146 for *PANSS (N),* r_{sp}=0.139 for *Anti-craving medication.*

Following the presentation and analysis of the table with the β coefficients of the regression equation, as well as of their statistical significance, the corresponding multiple regression equation is as follows:

$Y=a+b_1*X_1+b_2*X_2+b_3*X_3+b_4*X_4+b_5*X_5+b_6*X_6+b_7*X_7$

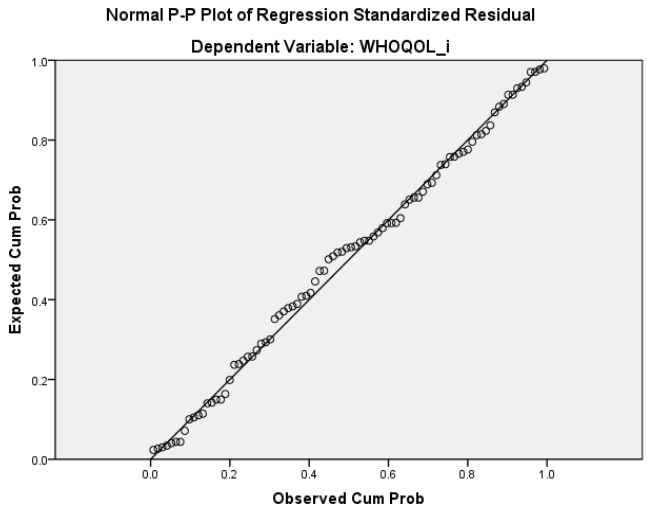
WHOQOL = 115.72 - 0.60*PANSS(N) - 0.39*PANSS(G) + 24.24*FS1 - 13.06*FS4 - 11.89*AD + 7.4*Medication + 3.93*Education level

Another condition that must be met for the application of multiple regression is that the errors (residues) be normally distributed (fact indicated by the histogram below).



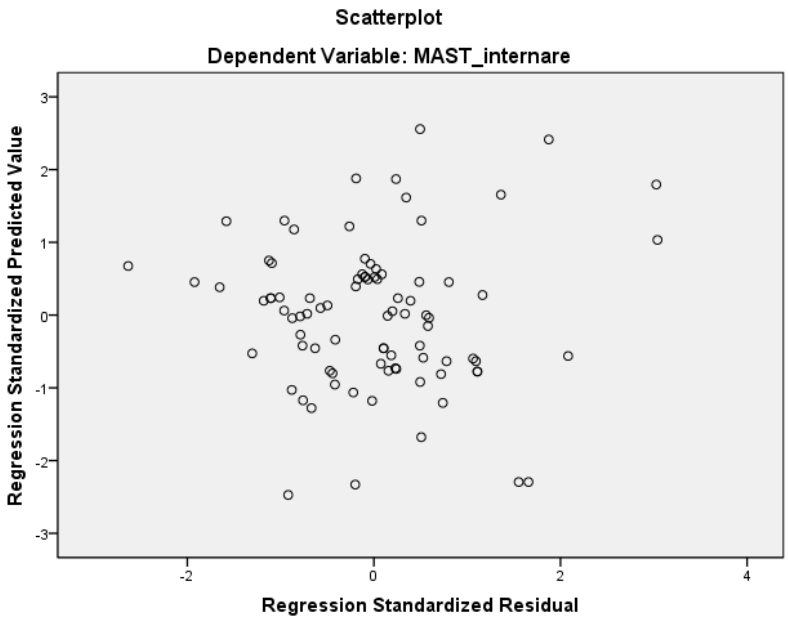
GRAPH 4: Residue distribution.

Graph 4 checks the normality of the standardized residue distribution by comparison with the deviations from the normal curve. We notice that the condition of normality of the residue distribution is met.



GRAPH 5: Deviations of residue distribution.

In graph 5 one can notice the representation of the correlation of the data predicted by the independent variables (test scores) and the measured ones that represent the performances for the criterion (WHOQOL).



GRAPH 6: Representation of scatter plot between the values of the criterion and those of the predictors.

We check the existence of influential cases by inspecting Cook's distance. As the value obtained is 0.014 (<1), it results that there are no influential cases.

Conclusion:

6 months after admission, Self-care capacity (FS1), Anti-craving medication, and Level of education, are positive predictors of the quality of life. The other variables analyzed are negative predictors. In other words, the patients with a high level of education are those who can more easily become aware of the prodromal signs of disease in case of recurrences, as well as those whose intellectual level helps to support their insight, which in turn is responsible for treatment compliance. At the same time, in this multiple regression equation Anti-craving medication becomes important, which, by minimizing alcoholic recurrences, supports a quality remission and an appropriate capacity for reality testing. At the same time, the possibility of self-care is an important predictor, because it includes in itself long-term existential strategies, of which those related to health become basal.

Table Comparison between the two patterns:

Upon admission			6 months after admission	
Pattern 15 R square adjusted=.423	Part		Pattern 14 R square adjusted=.680	Part

(Constant)			(Constant)	
PANSS_P	.201		PANSS (N)	-.146
FS1_Self-care_capacity	.341		PANSS (G)	-.193
FS2_Presence_social_support	.200		FS1_Self-care_capacity	.302
FS7_Financial_plan._cap.	.140		FS4_Medico_legal_compl._assoc.	-.157
AP	-.220		AD	-.217
			Anti-craving medication	.139
			Level of education	.165

Upon admission*, Self-care capacity, The presence of social support, Financial planning capacity* lead to a better quality of life. 6 months after admission, the subjects having *self-care capacity*, with *anti-craving medication* and *higher education level* also have better quality of life.

The results of testing the fourth working hypothesis

H4: *We can predict the score for the variable alcoholism depending on the other variables surveyed*. More precisely:

We can predict the score for *alcoholism* (MAST) by the variables: *social variables, psychotic impairment* (measured by PANSS), variables related to *medication, hospitalization* and *hostility.*

INITIAL TESTING

A standard multiple linear regression analysis was performed, having as variable the criterion alcoholism. The variable *alcoholism* was included in the regression analysis as a dependent variable and the following were introduced together as predictive variables:

- *social variables: Self-care capacity, The presence of social support upon admission, Maintaining a job, Association of medical complications, Public safety impairment, Association of social stress, Financial planning capacity, Family support*; the answers were of the type: *no (0)* and *yes (1)*.

- *psychotic impairment* (measured by PANSS): *PANSS_P, PANSS_N, PANSS_G*;

- variables related to *medication and hospitalization*: *AP, AD, the mode of hospitalization, number of hospitalizations*; the answers are of the type: *no (0)* and *yes (1)*.

- *the hostility* (measured by the hostility questionnaire), by the 3 sub-scales: negativism, resentments, hostility.

As a method we choose the Backward analysis, the method that will ultimately provide a correct statistical pattern, after trying all possible patterns in turn, including all variables, then eliminating one by one those that are not relevant (variables that are correlated with other variables in the pattern). 13 patterns were generated. We have followed the value of $R^2_{adjusted}$, which will indicate us the relevance of the pattern. The highest value will indicate us the best pattern. This is 0.392 in the pattern 13. The coefficients F are significant (at $p<0.01$) in all 13 regression patterns, so all patterns are effective in prediction. The highest value is that of pattern 13, $F=10.35$, $p<0.01$.

Table ANOVA variance analysis for regression pattern 13 on the influence of independent variables on the dependent variable **upon admission**:

Pattern		The square sum	Freedom degree	Square average	F	p.
13	Regression	10129.119	6	1688.187	23.019	.000[q]
	Residual	5940.324	81	73.337		
	Total	16069.443	87			

We will choose *pattern 13* as being the most adequate.

Pattern	R	R square	R square adjusted
13	.659[m]	.434	.392

Pattern 13 explains 39.2 % of the variation of cognitive functioning ($R^2_{adjusted}$ = 0.392), the global effect being high.

Table Standardized Beta coefficients indicating a significant influence of independent variables on the dependent variable (alcoholism_MAST) **upon admission**:

Pattern 13	Non-standardized coefficients		Standardized coefficients	t	p	Correlations		
	B	Std. Error	Beta			Zero-order	Partial	Part
(Constant)	33.89	5.90		5.74	.000			

FS2 The presence of social support	-5.25	2.37	-.205	-2.21	.030	-.220	-.239	-.185
FS4 Forensic complications	-7.29	3.68	-.231	-1.98	.050	.061	-.215	-.165
FS5 Public safety impairment	10.54	3.36	.404	3.13	.002	.311	.329	.262
FS6 Association of social stress	-9.62	2.15	-.391	-4.48	.000	-.329	-.446	-.375
PANSS (N)	.29	.166	.191	1.73	.088	.243	.188	.144
AP	9.07	3.77	.256	2.41	.018	.401	.258	.201

The above table presents for pattern 13 and for each independent variable the standardized and non-standardized regression coefficients, the standard error of non-standardized coefficients, t tests to test the null hypothesis, according to which the non-standardized coefficients are zero, zero-order correlations, partial and semi-partial.

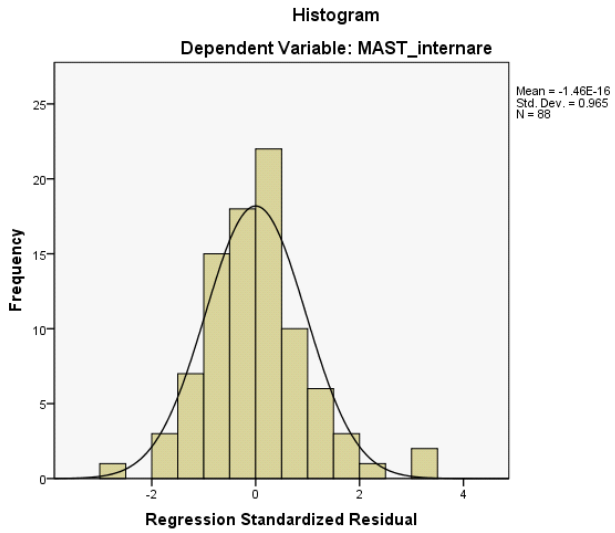
The largest share of the six variables of the pattern 17 is that of *Association of social stress*. The effect size indicators for each of the six pattern variables 13 are r_{sp}=-0.375 for *Association of social stress (FS6)*, r_{sp}=0.262 for *Public safety impairment (FS5)*, r_{sp}=0.201 for *AP*, r_{sp}=-0.185 for *The presence of social support (FS2),* r_{sp}=-0.165 for *Association of forensic complications* (*FS4),* r_{sp}=0.144 for *PANSS (N)*.

Following the presentation and analysis of the table with the β coefficients of the regression equation, as well as of their statistical significance, the corresponding multiple regression equation is as follows:

$Y=a+b_1*X_1+b_2*X_2+b_3*X_3+b_4*X_4+b_5*X_5+b_6*X_6$

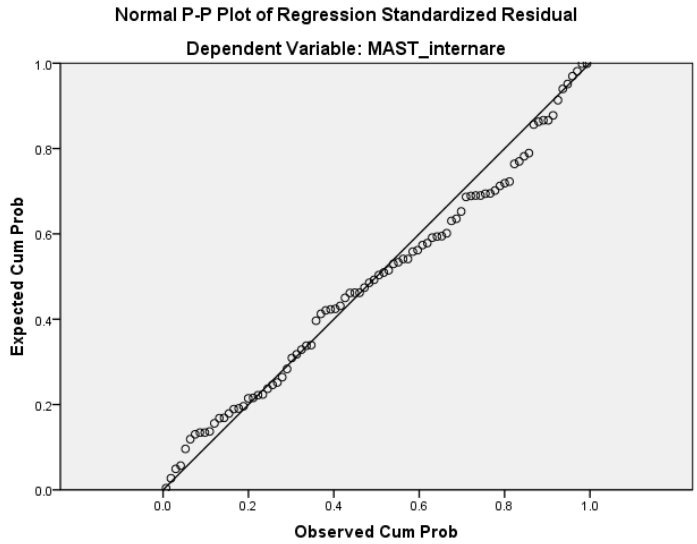
MAST = 33.89 - 5.25*FS2 - 7.29*FS4 + 10.54*FS5 - 9.62*FS6 + 0.29*PANSS(N) + 9.07*AP

Another condition that must be met for the application of multiple regression is that the errors (residues) be normally distributed (fact indicated by the histogram below).



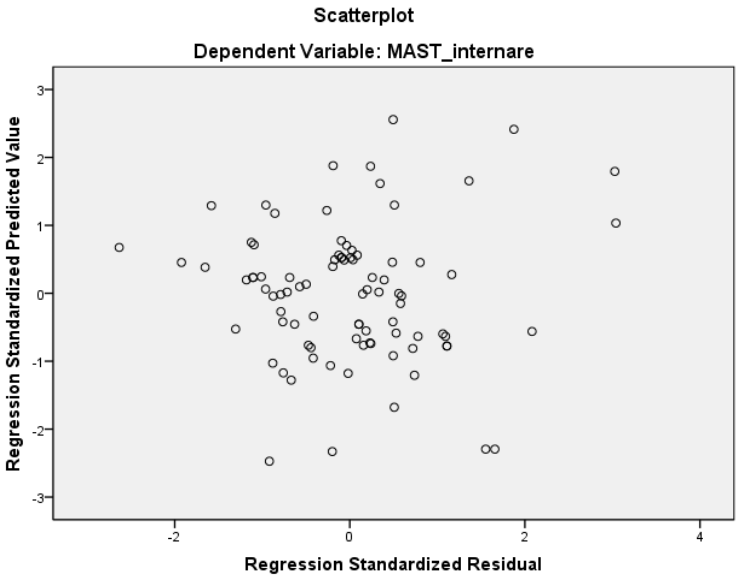
GRAPH 7: Residue distribution.

Graph 7 checks the normality of the standardized residue distribution by comparison with the deviations from the normal curve. We notice that the condition of normality of the residue distribution is met.



GRAPH 8: Deviations of residue distribution.

In graph 8 one can notice the graphical representation of the correlation of the data predicted by the independent variables (test scores) and the measured ones, which represent the performances for the criterion (MAST).



GRAPH 9: Representation of scatter plot between the values of the criterion and those of the predictors.

We check the existence of influential cases by inspecting Cook's distance. As the value obtained is 0.015 (<1), it results that there are no influential cases [36].

Conclusion:

The presence of social support (FS2) is a negative predictor for alcoholism. Public safety impairment (FS5), Negative dimension PANSS (N), AP, Association of forensic complications (FS4), Association of social stress (FS6) are positive predictors. Forensic complications, among which public safety impairment, are directly related to insufficient reality testing. Social stress is a powerful enhancer for patients with schizophrenia, even when we talk about eustress. The specialty literature quotes a threefold higher frequency of positive emotional events present in the lives of subjects with schizophrenia about three weeks before the onset of a new acute psychotic episode. The negative dimension of the disease is also cumulative with insufficient contact with reality, while social support is correlated with emotional openness and pleasant life events, with trials from both the patient with schizophrenia-alcoholism comorbidity and those around, to normalize the situation he is facing and to help him return to the broad borders of normality.

FINAL TESTING

We used the same algorithm used for the initial testing. 17 patterns were generated. We have followed the value of $R^2_{adjusted}$, which will indicate us the relevance of the pattern. The

highest value will indicate us the best pattern. This is 0.605 in the patterns: 15, 16 and 0.603 in the pattern 17. The coefficients F are significant (at $p<0.01$) in all 17 regression patterns, therefore all patterns are effective in the prediction. The highest value is that of pattern 17, $F=23.019$, $p<0.01$.

Table ANOVA analysis of variance for the regression pattern 17 on the influence of independent variables on the dependent variable:

Pattern		The square sum	Freedom degree	Square average	F	p.
17	Regression	10129.119	6	1688.187	23.019	.000[q]
	Residual	5940.324	81	73.337		
	Total	16069.443	87			

We will choose *pattern 17* as being the most adequate.

Pattern	R	R square	R square adjusted
17	.794[q]	.630	.603

Table Standardized Beta coefficients indicating a significant influence of independent variables on the dependent variable (alcoholism_MAST) **6 months after admission**:

Pattern 17		Non-standardized coefficients	Standardized coefficients		t	p	Correlations		
		B	Std. Error	Beta			Zero-order	Partial	Part
	(Constant)	28.41	4.99		5.69	.000			
	FS1 Self-care capacity	-11.36	2.97	-.289	-3.82	.000	-.480	-.391	-.258
	FS4 Forensic complications	9.80	2.90	.230	3.37	.001	.250	.351	.228
	FS5 Association of public safety	16.22	3.18	.364	5.09	.000	.458	.492	.344
	Medication	-5.56	1.98	-.206	-2.80	.006	-.362	-.297	-.189
	PANSS (P)	.32	.10	.228	3.16	.002	.229	.331	.213
	Negativism	2.71	.83	.256	3.26	.002	.551	.341	-.220

The table above shows for pattern 17 and for each independent variable the standardized and non-standardized regression coefficients, the standard error of non-standardized coefficients, t tests to test the null hypothesis, according to which the non-standardized coefficients are zero, zero-order correlations, partial and semi-partial.

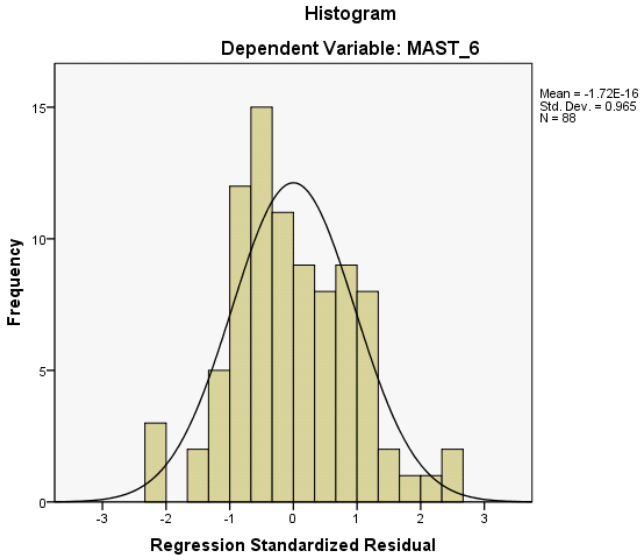
The largest share of the six variables of the pattern 17 is that of *Public safety impairment (FS5)*. The effect size indicators for each of the six pattern variables 17 are: r_{sp}=0.344 for *Public safety impairment (FS5)*, r_{sp}=-0.258 for *Self-care capacity (FS1)*, r_{sp}=0.228 for *Association of forensic complications (FS4)*, r_{sp}=0.220 for *Negativism*, r_{sp}=0.213 for *PANSS (P)*, r_{sp}=-0.189 for *Medication*.

Following the presentation and analysis of the table with the β coefficients of the regression equation, as well as of their statistical significance, the corresponding multiple regression equation is as follows:

$Y=a+b_1*X_1+b_2*X_2+b_3*X_3+b_4*X_4+b_5*X_5+b_6*X_6$

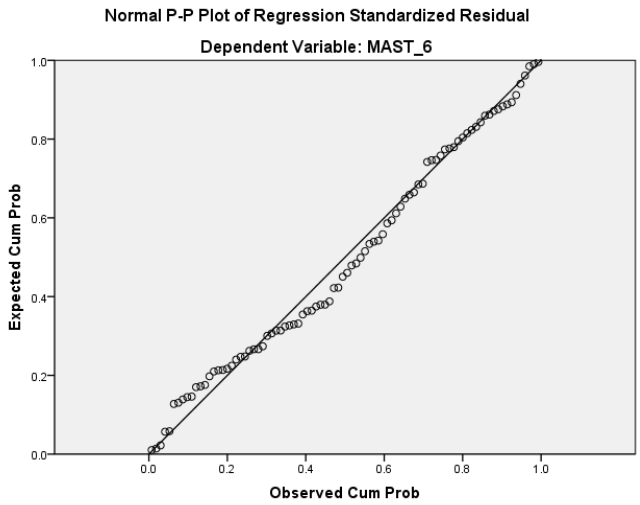
MAST = 28.41 - 11.64*FS1 + 9.80*FS4 + 16.22*FS5 - 5.56*Medication + 0.32*PANSS(P)+ 2.71*Negativism

Another condition that must be met for the application of multiple regression is that the errors (residues) be normally distributed (fact indicated by the histogram below).



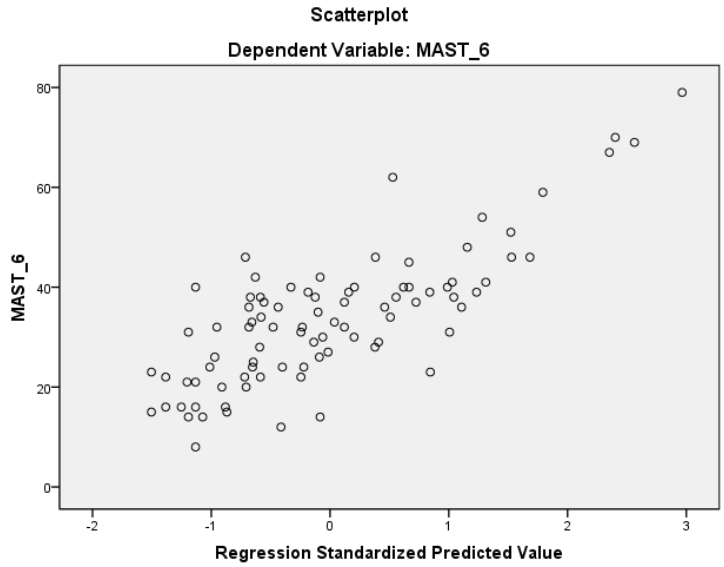
GRAPH 10: Residue distribution.

Graph 10 checks the normality of the standardized residue distribution by comparison with the deviations from the normal curve. We notice that the condition of normality of the residue distribution is met.



GRAPH 11: Deviations of residue distribution.

In graph 11 one can notice the representation of the correlation of the data predicted by the independent variables (test scores) and the measured ones that represent the performances for the criterion.



GRAPH 12: Representation of scatter plot between the values of the criterion and those of the predictors.

We check the existence of influential cases by inspecting Cook's distance. As the value obtained is 0.013 (<1), it results that there are no influential cases [36].

Conclusion:

Self-care capacity and Anti-craving medication are negative predictors for alcoholism. Association of forensic complications, Public safety impairment, Positive

dimension PANSS (P), Negativism are positive predictors. The highest prediction is that of Association of forensic complications. Forensic complications can be caused by both alcoholism (mental and behavioral disorders due to acute ethanol poisoning, alcoholic psychosis, blackout states, narrowing of the field of consciousness with the association of crepuscular states), as well as the positive productive dimension of the disease (imperative auditory hallucinations, delusional ideation of hetero-aggressive action). When the two pathologies are associated, they potentiate each other, there being cases in which schizophrenics resort to alcohol to have the instinctual force to put into practice what the delusional hallucinatory pathology dictates to them. This is all the more dangerous when what is being pursued is, in fact, to lower the censorship of the consciousness and the criticism, to produce confusing dreamlike states.

Table Comparison between the two patterns:

Upon admission			6 months after admission	
Pattern 13 R square adjusted=.392	Part		Pattern 17 R square adjusted=.603	Part
(Constant)			(Constant)	
FS2 The presence of social support	-.185		FS1 Self-care capacity	-.258
FS4 Forensic complications	-.165		FS4 Forensic complications	.228
FS5 Association of public safety	.262		FS5 Association of public safety	.344
FS6 Association of social stress	-.375		Anti-craving medication	-.189
PANSS (N)	.144		PANSS (P)	.213
AP	.201		Negativism	.220

Upon admission, *The presence of social support, Association of forensic complications and Association of social stress* lead to a lower value of alcoholism. 6 months after admission, the subjects having *Self-care capacity and take anti-craving medication* have the value of *Alcoholism* lower.

Conclusions

Anti-craving medication had effects on relapses related to alcoholism. There are significant differences in the MAST test values in the two tests. Anti-craving medication had (small) effect on inter-episodic self-care capacity. Anti-craving medication had very little effect on maintaining a job.

The subjects without comitial seizures, with normal biological results and without somatic dysfunction will have a lower cognitive deficit in: *Cognitive failures (CFQ)*, *Absurd story test (PAC)*, both upon admission, and 6 months after admission.

The patients without comitial seizures and without somatic dysfunction will have a lower deficit in *Confusion*, both upon admission, and 6 months after admission. Those without comitial seizures and without somatic dysfunction will have a lower deficit in disorientation 6 months after admission. *Financial planning capacity* will be higher in those ***without comitial seizures*** and *without somatic dysfunction* upon admission.

6 months after admission, the percentage of those *without comitial seizures and without degradation* is higher compared to hospitalization moment in *Confusion* (94.5% compared to 59.3%) and *Disorientation* (98.2% compared to 29.6%). 6 months after admission, the percentage of those *without comitial seizures and without degradation* is higher compared to hospitalization moment in financial planning capacity (85.5% compared to 40.7%).

The global intensity of the depressive syndrome (HAM-D) decreased 6 months after admission in both groups, in the control group (without AD medication) more than in the research group (with AD medication). Antidepressant medication had a negative effect on *the overall intensity of the depressive syndrome.*

Antidepressant medication has a positive effect (small) on the risk of suicide. Antidepressant medication has a positive effect on prolonged depression. The effect is higher 6 months after admission for the research group and small for the control group. Because the value of the increase is higher for the control group, we draw the conclusion that antidepressant medication had no effect. In the control group (those without AD medication) the presence of curiosity increased more, compared to the research group (those with AD medication), therefore, we draw the conclusion that AD medication had no effect. The quality of life decreased in both groups of patients treated with AD, more in the research group than in the control group. AD medication had a negative effect on the quality of life. Personality deterioration is not influenced by AD medication. The decreases are approximately equal.

Professional abandonment is not influenced by AD medication. The decreases are higher in those who did not receive AD medication (control group). Concerns about the future are not influenced by AD medication. The increase is higher in those who did not receive AD medication (control group), by 12.8%.

When we measured differences between the group that received antidepressant and anti-craving medication, and the group that did not receive the anti-craving medication, the quality of life increased in both groups. Although not too much, the quality of life has increased more in those who did not receive anti-craving medication.

Cognitive errors decreased in both groups (the one with antidepressant + anti-craving and the ones with antidepressant only). We note that there are significant differences in CFQ test values in the two studies. The effect size is average (d=0.52) for the patients who are hospitalized voluntarily and weak (d=0.38) for the patients who are involuntarily hospitalized.

There are significant differences in cognitive errors between the "gymnasium" group and the "higher education" group upon admission and between the "gymnasium", "high-school" and "higher education" groups, 6 months after admission. Cognitive errors decreased in all three groups. For the "*gymnasium"* group, a weak effect size was obtained (d=0.35), for the "*high-school"* group, an effect size towards average was obtained (d=0.44), while for the "*higher education"* group, an above-average effect size was obtained (d=0.57). Admission of alcoholic patients with or without anti-craving medication had a positive effect on "*cognitive errors"*, differentiated according to the level of education. Cognitive failures have decreased in both groups. We note that there are significant differences in CFQ test values in the two studies. For the control group, a weak effect size was obtained (d=0.34), while for the research group, an average effect size was obtained (d=0.52). Although not very high, anti-craving medication had an effect on cognitive failures. Cognitive errors decreased in both groups. We note that there are significant differences in CFQ test values in the two studies. For the control group, a weak effect size was obtained (d=0.34), while for the research group, an average effect size was obtained (d=0.52) AD treatment decreased the size of the effect of "*cognitive failures"* from 0.52 to 0.37 for the research group. The control group, the group that received only anti-craving medication had an increase from 0.34 to 0.52. The values of *absurd story test"* increased in both groups, significantly only in the research group, with an average effect size (d=0.47). MMSE has increased in both groups. We notice that there are significant differences of the values in the two studies. The effect size (d) will show us the influence of medication + AD on the *MMSE* values of alcoholic patients. An above-average effect size was obtained for the control group (d=0.84), while for the research group, a weak effect size was obtained

(d=0.37). Medication + AD decreased the effect size on the MMSE from 0.84 in the control group to 0.37 for the research group.

Family support has a positive effect on *personality deterioration*. The effect is higher 6 months after admission, because the effect of medication is added and the number of those with family support increases. Family support has a positive effect on *Involvement in personal hygiene*. The effect is higher 6 months after admission, because the effect of the medication is added and the number of those with family support increases. Family support has a positive effect on *The presence of curiosity and concerns for the future*. The effect is higher 6 months after admission, because the effect of the medication is added and the number of those with family support increases. Family support has a positive effect on the *risk of suicide and depression*. The effect is higher 6 months after admission, because the effect of medication is added and the number of those with family support increases. Family support has little effect on *guilt and culpability*. If we also consider the medication, family support may not have any effect on *guilt and culpability.* Family support has little effect on *satellite anxiety*. If we also consider the medication, family support may not have any effect on *satellite anxiety.*

From the regression analysis, which sought to predict especially *the quality of life*, upon admission: *PANSS (P)*, *Self-care capacity*, *The presence of social support*, *Financial planning capacity* are positive predictors of the quality of life. AP is a negative predictor. For the regression analysis from the final testing, *Self-care capacity*, *Anti-craving medication*, *Level of education* are positive predictors of the quality of life. The other variables analyzed are negative predictors.

From the regression analysis, which sought to predict the score for *Alcoholism*, *Public safety impairment*, *Negative dimension PANSS (N)*, *AP* are positive predictors. *The presence of social support*, *Association of forensic complications*, *Association of social stress* are negative predictors. As regards the final testing, *Self-care capacity* and *Anti-craving medication* are negative predictors for alcoholism. *Association of forensic complications*, *Public safety impairment*, *Positive dimension PANSS (P)*, *Negativism* are positive predictors. The highest prediction is that of *Association of forensic complications*.

Discussions

Our study focused on demonstrating the benefits of using Naltrexone as an anti-craving treatment in patients with schizophrenia-alcoholism comorbidity. It is known from the specialty literature [37] that Naltrexone, together with Acamprosate and Disulfiram are treatments that reduce the craving for alcohol through various mechanisms of action [38], but the benefits have been intensively studied in patients with singular pathology, addiction or alcohol abuse. The present study was conducted on a group of men addicted to alcohol, whose underlying disease is schizophrenia. The decision to work only with males is influenced on the one hand by the profile of the hospital department where the study was conducted and on the other hand- by the higher prevalence of males for both pathologies.

We have highlighted in the theoretical section notions about the prevalence of comorbidity, possible aetiologies of comorbidity, but also genetic studies that explain a polygenic association of diseases, clinical symptomatology of the patient with dual diagnosis, anatomical changes in brain volume in these patients and treatment possibilities.

Further, in the study, we used a consistent battery of tests to better understand how patients with dual diagnosis work, focusing on factual data (age, environment of origin), clinical data related to the underlying disease (first episode or chronic disease), clinical data related to consumption (abuse or addiction), data on other psychostimulants used, social support network, quality of life, cognitive deficits, patient motivation for recovery, concerns for suicide and guilt ideation, to objective results related to somatic dysfunction of patients. The aim of the thesis was to detail a profile of the patient with comorbidity, which adhere or not to the results of previous studies that tried to emphasize the profile of this patient. The secondary purpose was to emphasize the importance of using anti-craving treatment, as comorbid alcohol consumption was associated with negative effects on the course of the disease, with relapses of the underlying disease, with more negative symptoms and, of course, a more reserved prognosis. Therefore, we tried to highlight the benefits of using Naltrexone in our group of patients.

Among **the benefits of using Naltrexone** identified in our study, we can list:

- decrease the number of relapses of alcohol consumption - by identifying differences in the MAST (alcoholism) score between initial and final testing;
- inter-episodic self-care capacity increased (in a small but statistically significant percentage);

- it had a beneficial effect on patients' ability to maintain a job;
- it decreased the overall intensity of the depressive syndrome associated with comorbidity for these patients;
- the quality of life increased;
- they diminished the cognitive deficits (objectified by the cognitive error questionnaire), and the effect size produced on the decrease of cognitive deficits is more important for those who are hospitalized voluntarily – probably due to the fact that the patients who are hospitalized voluntarily have a degree of orientation on their own person and they are more aware of the negative effects of the disease. In addition, we have examined the influence of the level of premorbid education of patients on the decrease in cognitive abilities in patients with dual diagnosis. We have identified that cognitive deficits improved in all three groups (gymnasium, high-school and higher education), but with an increase in the effect directly proportional to the level of education (poor for gymnasium, average for high school and above average for higher education);
- Cognitive deficits decreased (objectified by the test of absurd stories);
- The value of the MMSE has increased;

Profile of the patient with dual diagnosis can be highlighted as follows:

- those without somatic dysfunction and without comitial seizures will have cognitive deficits, confusion and disorientation more reduced and they will have a better financial planning capacity;
- has depressive symptoms, and the patients who needed antidepressant treatment had benefits on the risk of suicide (reducing it), prolonged depression (diminishing it), increasing their curiosity about the disease and its prognosis;
- support (through the social support network or through the family present) has a positive effect on personality deterioration, significantly delaying it;
- Family support also supports involvement in the personal hygiene, the presence of curiosity and of concerns for the future;
- Family support decreases the risk of suicide and depression, as well as satellite anxiety;

These results complement the profile of the patient with schizophrenia – alcoholism comorbidity, male, who has a family history of alcoholism, who developed in a conflicting family environment and who has more severe cognitive deficits than patients with a single primary diagnostic. [17].

Other impressive results of the thesis would be related to **predicting the quality of life** for the patients:

- For **initial testing**: The quality of life is predicted by: the positive psychopathological scale in PANSS, self-care capacity, social support, financial planning capacity, these being positive predictors. The need to introduce a new antipsychotic into the treatment is a negative predictor on the quality of life.
- For **final testing**: The quality of life is influenced by: self-care capacity, the level of education and anti-craving medication.

These results explain the beneficial involvement of Naltrexone in the quality of life of patients with dual diagnosis.

For **alcoholism testing**, it seems that the variables that predict would be:

- For **initial testing**: public safety impairment, the negative dimension of the PANSS scale, and the need to introduce a new antipsychotic, are positive predictors for alcoholism.
- For **final testing**: Association of forensic complications, public safety impairment, positive dimension of PANSS, are positive predictors for alcoholism. Self-care capacity and anti-craving medication are negative predictors.

The result that Naltrexone is a negative predictor for alcoholism score in the final testing demonstrates the beneficial effects it has on this group of patients with dual diagnosis. The fact that the positive dimension of PANSS predicts a higher score for alcoholism is in agreement with the specialty literature, speculating that the reasons why schizophrenics consume alcohol are to reduce the psychotic symptoms of the underlying disease or to reduce the side effects of neuroleptic medication. We highlight the importance of surveying the forensic complications and those in the area of public safety impairment for these patients, as their presence may explain a more dangerous consumption of alcohol, compared to other patients who do not have such behaviors.

Limits and future directions

A limitation of this research is given by the relatively small number of patients, who cannot extrapolate the research results to a higher level. However, it is important to mention that it is difficult to find patients with schizophrenia-alcoholism comorbidity, being an extremely selective working group.

Another limitation of the research comes from the design of the study, the work group differing from the control group by the administration of Naltrexone. This is an anti-craving drug that has a high price (about 200-300 RON) and is not subsidized by the National Health Insurance Fund, which made it difficult for all patients to purchase the drug after hospitalization period.

On the other hand, from a psychological perspective, it is and it has been difficult to change the irrational cognitions in the mind of the patient with schizophrenia related to the usefulness of stopping alcohol consumption. We are talking, on the one hand, about a physical and mental addiction for a human being who already has some limits because of the underlying disease (which must also be controlled).

Another argument that led to the stratification of the working group was that the schizophrenics who were included in the study had to have a certain level of pre-morbid functioning in order to successfully fill in the questionnaires, to maintain the compliance with the treatment, to give their consent to participate in the study. In addition, we had to choose patients who did not have a severe somatic pathology, on which the subject diagnosed with schizophrenia would have focused his entire psychic system.

Although the study was quite extensive in terms of the psychic dimensions surveyed, it is difficult to delimit whether the low motivation for abstinence we encountered in some patients came from their side of alcohol addiction or the dimension related to schizophrenia (from apatho-abulic perspective).

In the specialty literature it is discussed on *the suicide attempts* of the patients with comorbidity, but this is a limitation of our study, namely that we did not have a large number of patients with suicide concerns and/or suicide attempts, and the attending physician administered preventative sedative antidepressant for most patients (except for 8 subjects), throughout the hospitalization, so that during the testing the patients were protected from the expression of affects and feelings in this area. For a more in-depth study of this dimension, a

comparison between two groups with equal number of patients would have been necessary (with AD medication versus without AD medication).

Future research in the field of psychiatry, doubled by finesse neuropsychological assessments, could also consider assessing the cognitive functioning of these patients under *administration of antidemential drugs* (In clinical practice, Memantine is used in patients with schizophrenia to increase cognitive function and prevent thought disorder, regardless of their age).

We consider that psychopharmacology has evolved a lot with the state-of-the-art antipsychotics, which aim at eliminating the negative phenomenology from schizophrenia and reduce the dimension of thought disorder. Thus, the schizophrenic patient can receive for the underlying disease deposit injectable medication, once a month (Rispolept Consta, Abilify Maintena, Xeplion, Trevicta, Zypadhera) and he/she will become more compliant with the idea of receiving anti-craving medication for the pathology of alcoholism, only one tablet a day (Naltrexone and/or Acamprosate).

Comorbidity is best treated when both pathologies are approached simultaneously [39], which emphasizes the idea that alcohol abuse must be identified quickly and treated effectively. Since 2002 [40], the idea has been argued that the integration of substance abuse and mental health treatments is more effective than treating diseases in parallel. A multidisciplinary, comprehensive, empathic and step-by-step approach is needed to achieve recovery.

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APPENDIX 1
PUBLISHED WORKS FROM THE DOCTORAL THESIS
(Web of Science)

Drăgoi AM, Voicu T, Chipeşiu AM, Costea RV. Morphopathological approaches in alcoholism. Rom J Morphol Embryol 2020; 61(2):345–351. doi: 10.47162/RJME.61.2.04. (FI=1,411)

Drăgoi AM, Trifu AI, Trifu S. Socio-demographic characteristics of the psychiatric population with comorbid alcoholism. Revista de Cercetare si Intervenție Sociala 2020;70:265-287. doi: 10.33788/rcis.70.16. (FI=0,736)

Popescu A, Marian AM, **Drăgoi AM***, Costea RV. Understanding the genetics and neurobiological pathways behind addiction (Review). Experimental and Therapeutic Medicine 2021;21:544. doi: 10.3892/etm.2021.9976 – FI = 1,785

Trifu S, Istrate D, **Drăgoi AM**. Gaps or links between hormonal therapy and schizophrenia? (Review). Experimental and Therapeutic Medicine 2020.4: 3508-3512. doi: 10.3892/etm.2020.9017. FI = 1,785

Stan, F. **Drăgoi A.M.**, Costea R.V. (2020). The impact of socio-cultural factors in addiction comorbidities. Journal of Educational Sciences & Psychology 2020;10(2):177-191.

Drăgoi AM, Vlăduti A (2020). The comorbidity between schizophrenia and alcohol. Substance addiction and alcohol use link to schizophrenia. Journal of Educational Science & Psychology 2020;10(1):141 – 148.

Sofia AD, Ionescu TC, **Drăgoi AM** (2020). Comorbidity of schizophrenia and alcohol use disorder: implications for clinical practice. Journal of Educational Science & Psychology 2020;10(1):93 – 100.

Drăgoi AM, Popescu A, Trifu AD. Antisocial personality in paranoid schizophrenia - the forensic risk. The European Proceedings of Social & Behavioural Sciences EpSBS; 2019;72:731-742. doi: 10.15405/epsbs.2019.11.82

Trifu S, **Drăgoi AM**, Trifu AD (2019). Evolutive possibilities of acute and transitory psychotic disorder. The European Proceedings of Social & Behavioural Sciences EpSBS 2019;72:754-764. doi: 10.15405/epsbs.2019.11.84

Drăgoi AM, Enache A, Trifu S (2019). Obsessive-compulsive particularities before and after remission of acute phase episodes of schizophrenia. The European Proceedings of Social & Behavioural Sciences EpSBS 2019;72:775-786. doi: 10.15405/epsbs.2019.11.86

Trifu A.I., Popa I.M., **Drăgoi A.M.** The comorbidity of schizophrenia and alcohol: from cognitive destruction to social isolation. The European Proceedings of Social & Behavioural Sciences EpSBS 2019;72:787-794. doi: 10.15405/epsbs.2019.11.87

APPENDIX 2

OTHER WORKS PUBLISHED DURING DOCTORAL STUDIES

Published books:

Trifu S., Patrichi, B. **Drăgoi, A.M.** (coordonatori) (2021). *Psihiatrie - clinică, psihodinamică și elemente de farmacologie.* București: Editura Medicală. ISBN 978-973-39-0919-4

Trifu S., **Dragoi A.M.** (coordonatori) (2021). Interferențe clinice în psihiatrie. Experiențe diagnostice. București: Editura Universitară. ISBN 978-606-28-1325-3

Trifu S., **Drăgoi A.M.**, Vlaicu I. (coordonatori) (2019). Psychodynamic Psychiatriy. Clinical Theories. Beau Bassin: LAP LAMBERT Academic Publishing. ISBN 978-620-0-31198-6

Trifu S., **Drăgoi A.M.**, Andronache D. (coordonatori) (2018). Psihiatrie Psihodinamică. Studii de caz. București: Editura Medicală. ISBN 978-606-28-0803-7.

Other published works (Web of Science):

Drăgoi AM, Rădulescu I, Năsui BA, Pop AL, Varlas VN, Trifu S. Clozapine: An Updated Overview of Pharmacogenetic Biomarkers, Risks, and Safety — Particularities in the Context of COVID-19. Brain Sci. 2020; 10(11):840 (FI = 3,332)

Trifu S, Țîbîrnă A, **Drăgoi AM***, Cristea MB. Immunological and hormonal mechanisms in Alzheimer's disease. Rom J Morphol Embryol 2020;61(4):1033–1038. doi: 10.47162/RJME.61.4.y (FI = 1,411)

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