THE EFFICACY OF ASSOCIATING SYSTEMIC APPROACH TO STANDARD DRUG THERAPY IN PATIENTS WITH ALCOHOL DEPENDENCE

THESIS SUMMARY

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**KNOWLEDGE ACQUIRING STAGE**

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ABBREVIATIONS

AA - Alcoolici Anonimi
ANM – NATIONAL DRUG AGENCY
AUDIT - The Alcohol Use Disorders Identification Test
CE – NATIONAL COMITTEE OF ETHICS
CAT – CLUBS FOR ALCOHOLICS IN TREATMENT
CAR – CLUBS FOR ALCOHOLICS IN RECOVERY (în România)
DSM - Diagnostic and Statistical Manual of Mental Disorders
GABA - Acidul gamma-aminobutiric
GCP - Good Clinical Practice
GPX - Glutation peroxidaza
ICD -10 - International Classification of Diseases (ICD)
SOD - Superoxid dismutaza
MAST - The Michigan Alcohol Screening Test
MDA - Malondialdehide
OCDS - Obsessive Compulsive Drinking Scale
PUFA - Poly Unsaturated Fatty Acids

The Doctoral Thesis is illustrated by 65 de figures, 52 tables and 202 references.

This doctoral thesis couldn’t be realized without support of University Professor Vasile Chirita, UMF GR.T.Popa Iasi to whom I address distinguished thanks for his constant trust and support during doctoral stage.
CHAPTER 7. INTEGRATED THERAPY FOR ALCOHOL DEPENDENCE – ADVANTAGES OF ASSOCIATING SYSTEMIC APPROACH AND OXIDATIVE STRESS FLUCTUATIONS

7.1. OBJECTIVES OF THE STUDY

The study hereby followed two research directions. Within the first part of the research, the author proposed to make a research on the benefits of the Hudolin systemic therapy (Hudolin, 1991) with the help of the Clubs together with the standard therapy in case of alcohol dependence. The indexes that were evaluated in the efficiency of the therapy are the following: abstinence, quality of life, as well as the compulsive wish to drink alcohol. The study was conceived in a prospective manner, with periodical evaluations, as the visits timing has as a main goal to register the patients’ short-term and long-term evolution. One of the main medical objectives in case of alcohol dependence as well as of the study hereby is to obtain and maintain abstinence for a period as long as possible. Beside abstinence, I considered it useful to evaluate the evolution of quality of life and the index that evaluates the compulsive wish to drink alcohol, in time.

The second part of the study focused on the research of certain paraclinical indexes of oxidative stress in patients that are alcohol dependents in comparison with a control group and in relation with different moments from giving up alcohol. The goal of this study is to better understand the relationship between alcohol consumption and oxidative stress and to evaluate the impact of abstinence on the oxidative status of the system. The study developed over a 12-month period and the determination of the oxidative stress indictors was organized according to well-established periods. The reason of the research is represented by the fact that literature contains few studies on the way in which abstinence from alcohol influences the level of oxidative stress in addicts.

As a summary, the study hereby is a prospective study, a comparison between associated therapy (the Hudolin systemic therapy and the standard therapy) and the standard therapy of alcohol dependents.

The objectives of the study are the following:

1. This study aims to analyze the efficiency of the systemic, multi-familial approach in alcohol dependents under standard treatment, an efficiency that shall be first quantified by the maintaining of the 12-month period of abstinence.
2. On the second hand, I want to analyze the dynamics of the quality of life index in case of these patients during the treatment.
3. The analysis of the ideation dynamics regarding alcohol as well as the wish to drink alcohol.
4. The evaluation of the oxidative stress parameters.

7.2. WORKING HYPOTHESES

The working hypotheses for this research are the following:
There are significant differences between the groups of patients under standard therapy and Hudolin systemic therapy vs. patients that are under standard drug treatment only as regards the 12-month abstinence from alcohol.

Patients that benefit from a combined therapy (Hudolin systemic and standard) shall have a different quality of life index in comparison with the patients that are under standard therapy only.

From the point of view of the ideation and of the wish to drink in case of alcohol dependents, there are significant differences between the group of patients under Hudolin therapy and standard treatment vs. patients under standard therapy only.

The oxidative stress parameters shall have different values during the consumption period vs. the abstinence and control period.

7.3. INCLUSION AND EXCLUSION CRITERIA

The Inclusion Criteria

- Patients with ages between 18 and 65, with alcohol dependence, diagnosed according to the ICD-10 criteria.
- Patients must sign a consent regarding their participation in the study and respectively to the multi-familial communities meetings called Alcoholics Clubs (for those who accept).
- The patients included by the study must not have been previously followed a treatment or entered psychotherapy for alcohol dependence within the last 90 days.
- Patients must clearly express their wish to give up alcohol.
- As regards the alcohol dependence, patients must present at least 2 days of exaggerated alcohol consumption, defined as more than 5 “standard alcoholic beverages” per day in the case of men and more than 4 “standard alcoholic beverages” per day in the case of women during 30 consecutive days within a 90 days period before their inclusion in the study (there shall be used “the standard alcoholic beverage” defined by the AUDIT scale, having a value of 10 g of pure alcohol).
- The patients included in the study must have a stable social status, meaning identifiable and stable address and/or job as well as family next of kin willing to participate to the multi-familial communities (for those who will be included in the Alcoholics Clubs during their rehabilitation).

The Exclusion Criteria

- Any psychic disorder belonging to the 1 DSM IV-TR axis, under psychiatric record or treatment that could interfere with the patient’s judgment, ability to consent or follow the study’s procedures.
- Any other decompensated associated somatic disorder or that can aggravate the patient’s clinical condition in case of participation in the study.
- The patient’s non-compliance with the prescribed treatment or his/her refusal to adhere to the study’s program (for those who did not consent as regards systemic therapy).
7.4. MATERIAL AND METHOD

This study involved the dynamic clinical-therapeutic evaluation of 90 patients that were alcohol dependents for a 12-month period. The patients included in the study were among those from the records of the Socola Psychiatry University Hospital from Iași. The patients were diagnosed as alcohol dependents based on the ICD-10 criteria. These patients had or had not psychic or somatic comorbidities (except those specified by the exclusion criteria). All the patients received standard drug therapy for alcoholism (mood stabilizers, benzodiazepine, and vitamin therapy). Among these, 44 subjects accepted and were supplementary included in the Alcoholics’ Rehabilitation Club.

For the second part of the study that comprised the research on the oxidative stress, initially 33 patients were included and 18 alcohol non-consumer patients who were enrolled in the control group. Practically, two groups of patients were used for the evaluation of oxidative stress, meaning the alcohol dependent patients group and the control group. During the study period, the alcohol dependent patients’ group comprised only patients that were abstinent at the moment of the study visit, while the patients who relapsed were excluded from the study.

The study’s design:

- The clinical-therapeutic monitoring included a number of seven visits during the 12-month period, as follows:
  
  Visit 1 – screening
  Visit 2 – baseline, maximum 7 days after V1
  Visit 3 – 1 month later
  Visit 4 – 3 months later
  Visit 5 – 6 months later
  Visit 6 – 9 months later
  Visit 7 – at the end of the study, 12 months later

- In case of the 2-month visit (baseline), the patients were divided into 2 approximately equal groups (according to their consent to participate in the therapy program developed within the Alcoholics’ Rehabilitation Clubs). Thus, 44 alcohol dependent patients received a standard drug treatment and they entered the Hudolin systemic psycho-social intervention program and 46 alcohol dependent patients only benefited from standard drug treatment.
  
  - At the baseline moment, the following were evaluated: the quality of life – the QOL 16 scale, the compulsive wish to consume alcohol – the OCDS scale and the severity of the alcohol dependence. During the other visits, I continued with the evaluation of the quality of life, of the compulsive wish to consume alcohol as well as of abstinence.
  
  - The Hudolin systemic intervention program developed during a 12-month period, once a week, for 1 hour – 1 hour and a half.
- The concomitant pathology-patients included in the study also presented other psychiatric disorders, like anxiety, depression, cerebral chronic organic disorder, personality disorder, epilepsy, delirium and addiction to other substances like cocaine, cannabis, benzodiazepine and one gambling addict.
- During its development, the study had the following structure: the enrolment period (January 1st – December 30th 2012), the end of data collection (December 30th 2013), the evaluation period (12 months).
- The oxidative stress was evaluated by dosing the antioxidant enzymes (SOD and GPX) and a lipid peroxidation marker (MDA) on each study visit.

Investigation Instruments

The evaluation of alcohol dependent patients could be realized with the help of the quality of life scales, the AUDIT (184) scale and the OCDS scale.

The QOL 16 (The Quality of Life Scale) quality of life scale that was first conceived by John Flanagan in the ‘70s, is a scale used to evaluate the quality of life in case of the persons suffering from chronic disorders. It is a Likert scale whose items have 7 answer choices and they vary from delighted (7), satisfied (6), rather satisfied (5), mixed (4), rather unsatisfied (3), unhappy (2), and terrible (1). It is made of 16 items, having an extra item in comparison with the original version, namely item 16 that refers to the level of independence and self-care ability. The other five evaluated fields include physical and material wellness, relationships with the others, social, community and civic activities, personal development and fulfillment, recreational activities. It is a self-managing scale whose total scores vary between 16 and 112. Higher scores indicate a higher level of quality of life (Burckhardt et al.2003).

The OCDS scale (Obsessive Compulsive Drinking Scale) (Anton et.al, 1995).

It is a scale applied in case of the alcohol consumers and it evaluates the obsessive-compulsive behaviors associated with the wish to drink alcohol. The instrument presents sensitivity and specificity for the obsessive-compulsive behaviors associated with the alcohol consumption and they are not predictively valid in case of relapse. Researches show that the OCDS scale is also a useful instrument for the screening of abuse and alcohol dependence. It is a quiz made of 14 items that can be self-administered in a 5-minute interval. The scores for each item vary from 0 to 4, high scores indicating a high intensity of obsession and compulsion. The total score varies between 0 and 40 and a limit of 7 was chosen in order to discriminate between social consumption and alcohol dependents with 93% sensitivity and 98% specificity. Seen that the object of the study is represented by evaluation of reaching abstinence, the ideation regarding alcohol and the wish to consume alcohol in case of these patients during the treatment period shall be evaluated with the help of this scale (Drobes et al.1999).

The AUDIT (The Alcohol Use Disorders Identification Test) scale (Saunders et al.1993).

It is a self-administering quiz containing 10 items meant to evaluate the behavior and issues associated with alcoholism as well as the harmful alcohol consumption (items 1-3), the behavior associated with the consumption (items 4-6), the adverse reactions to alcohol (items 7-8) and the issues associated with alcohol (items 9-10). The scores of items 1-8 vary between 0 and 4, while items 9-10 can be scored with 0, 2 or 4. The scores vary between 0 and 40, with higher scores that are associated with a higher risk. The scores between 8 and 12 indicate a harmful consumption while the scores between 13 and 40 indicate alcohol dependence. The studies realized according to this scale show a high sensitivity and specificity (Dolman et al.2005).
dependence and alcohol consumption levels before the inclusion in the study shall be evaluated by means of this scale at the moment of the inclusion in the study.

The Evaluation of Oxidative Stress

The serum was put in Vacuettes. After being left to rest for a few hours, the serum was centrifuged then transferred in Ependorf vials. After a new centrifugation in the special centrifuge for the Ependorf vials, the samples were deposited at 80°C, until being taken for the biochemical analyses regarding the specific activity of some marker enzymes of the oxidative stress (superoxide dismutase and glutathione peroxidase), as well as some final products of lipid peroxidation, like the malondialdehyde. This experimental procedure was followed each time the serum was taken.

The Determination of the Glutathione Peroxidase Activity by the DNTB Method

This method measures the glutathione peroxidase activity in the serum and plasma, using as a substratum for the enzyme the hydrogen peroxide (H2O2) and the reduced glutathione (GSH). The color reaction is realized because of the dithiobis (2-nitrobenzoic acid) (DNTB), and the maximum absorbance is measured by spectral photometric means 412 nm over the blanks reagents.

Reagents

1. Sorensen tampon, disodium phosphate (Na2HPO4) pH =7.0 0.4 mM;
2. GSH 5mM;
3. Bidistilled water;
4. Meta-phosphoric acid 7%;
5. DNTB 0.04%.

Working Method

With the help of two vials the following reagents volumes are measured

\[
P \quad M
\]

<table>
<thead>
<tr>
<th>Phosphate tampon</th>
<th>1</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>GSH</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

The mixtures are incubated for 5 minutes at 37°C. After incubation, 1 ml of H2O2 is added to each vial, and then they are incubated again at 37°C for 5 minutes.
After the second incubation, the following reagents are measured in other two centrifuge vials:

<table>
<thead>
<tr>
<th>Reagent</th>
<th>P</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubated Meta-phosphoric acid</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>GSH</td>
<td>0.31</td>
<td></td>
</tr>
</tbody>
</table>

The mixtures are let to rest for 10 minutes, then they are centrifuged for 15 minutes at 30,000 rotations per minute.

In order to determine the GPx from the supernatant the following are used

<table>
<thead>
<tr>
<th>Reagent</th>
<th>P</th>
<th>M</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bi-distilled water</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supernatant</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Disodium phosphate</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>DNTB</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

They are let to rest for 5 minutes, then the extinction is read at $\lambda = 412$ nm.

The activity of the glutathione peroxidase is determined according to a glutathione standard curve. The activity of the enzyme is expressed in $\mu$m GSSG/ml/min.

*The determination of the superoxide dismutase, the Fluka kit.* A specialized kit produced by the Fluka company (figure 5-A) was used to determine the superoxide dismutase (SOD). The method’s principle is based on the reduction of a water soluble salt (WST 1 – water soluble tetrayolium salt), under the influence of the superoxide anion, to formazane dye. After preparing a working solution and the incubation at 37°C, for 20 de minutes, the samples absorbance is read with the help of a biochemical analyzer, at 450 nm.

*The Determination of Lipid Peroxides – the Malondialdehyde Reaction*

**The Method’s Principle**

In case of high temperature and in an acid environment, the malondialdehyde (MDA) resulted from the decomposition of the lipid peroxides responds to the 2-thiobarbituric acid (TBA) forming a pink trimetinic adduct MDA-TBA2 with a maximum absorption point at 532 nm.

Reagents
1. 50% Trichloroacetic acid solution;
2. 20% Trichloroacetic acid solution;
3. 0.67% Thiobarbituric acid solution;
4. N-butanol or ethyl acetate.

Working Method

Blood is sampled on heparin or sodium citrate. With the help of a dropper, 2 ml of blood are put in a centrifuge vial and 2 ml of distilled water are added. The mixture is then shaken, frozen and unfrozen. Two milliliters of 50% trichloroacetic solution is added. The mixture is then mixed with the help of the glass stirring rod and it is centrifuged for 15 minutes at 6000 rotations per minute.

Two vials shall be used. In the first vial (probe) we drop 2 ml of supernatant and in the second vial (control) – 2 ml from the solution obtained by mixing 4 ml of distilled water and 2 ml of 50% trichloroacetic acid. We introduce 2 ml of thiobarbituric acid solution in each vial. The vials, covered with a small glass cone shall be kept in a boiling bain-marie for 20 minutes. The vials shall be cooled under jet of water. After cooling, we add 4 ml of n-Butanol in each vial and we carefully shake for several times. We read the extinction of the organic phase from the sample 532 nm from the organic phase of the control.

Calculation of the Results

Taking into account the molar extinction coefficient of the MDA-TBA2 adduct, the MDA/ml serum n-Moles are calculated with the help of the following formula:

\[ \text{MDA/ml serum n-Moles} = \text{Ep} \times 39. \]

The normal values vary between 3 6 n-Moles/ml (11', 352).

Also, based on the above-described method, a simplified experimental protocol was established; within the said protocol, we use 0.1 ml of serum (5-A) for each sample and we add 1 ml of 50% trichloroacetic acid (ATC) and 1 ml of thiobarbituric acid (TBA). The administration of 50% ATC shall generate a precipitation of the protein from the sample. Of course, if we use 0.1 ml of serum, we shall add 1.1 ml of 50% ATC or another 0.1 ml of distilled water in order to have equal volumes. The control shall contain 0.2 ml of distilled water, 1 ml of ATC and 1 ml of TBA.

Next, there comes the bain-marie boiling for 20 minutes, the 10-minute centrifuging at 3000 rotations/minute and the spectral-photometrical reading 532 nm from the above-described control.
Statistic Processing Methods

The making of the sample comprised the following stages: the making of a survey base (the screening of the patients from the Socola Hospital), the statistical analysis with the proper use of the statistic tests. The following methods were used during the study: descriptive methods (for the analysis of the demographic data), comparative methods (the Anova single Factor test), as well as prospective methods to follow the evolution of the patients in time. The data were loaded and processed with the help of the statistic functions in Microsoft Excel (Microsoft Corp.) and of the SPSS 16 (SPSS Inc.) statistical analysis pack. The results are expressed as an average plus/minus standard deviation (SD). The statistic interpretation guide mark’s value is of 0.05, p(Sig.)<0.05 having a statistic signification.

7.5 RESULTS

THE AUDIT SCALE

The AUDIT scale was applied only once to all the patients in the study inclusion stage. The statistical analyses show average values close to the total scores of the AUDIT scale between two groups of patients, of around 30 points. As one can easily notice in the table below, from a statistic point of view, the Anova analysis indicates insignificant differences between the two groups as regards the total scores of the scale (p>0.5). Once more, these results confirm the homogeneity of the two studied groups F(1.89)=3.94, p=0.11.

Table 1. ANOVA single factor for AUDIT scale for the 2 groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Count</th>
<th>Sum</th>
<th>Average</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUDIT scale associated treatment</td>
<td>44</td>
<td>1245</td>
<td>28.29545</td>
<td>51.65486</td>
</tr>
<tr>
<td>AUDIT scale standard treatment</td>
<td>46</td>
<td>1410</td>
<td>30.65217</td>
<td>47.60966</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>P-value</th>
<th>F crit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>124.9061</td>
<td>1</td>
<td>124.9061</td>
<td>2.518965</td>
<td>0.116071</td>
<td>3.949321</td>
</tr>
<tr>
<td>Within Groups</td>
<td>4363.594</td>
<td>88</td>
<td>49.58629</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4488.5</td>
<td>89</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7.5.4. ABSTINENCE

The abstinence period was registered for all patients on each study visit and compared within the two treatment groups. As we can see from the chart below, there is a difference of almost 2 months between the two groups of patients as regards the average of the abstinence months. Thus, the group that benefited from both standard and systemic therapy had an abstinence average of almost seven months (M=6.92±3.2), in comparison with the group that received only standard medication and that manifested an abstinence period of only five months (M=5.1±3.8). The Anova single factor statistical analysis highlighted significant statistical differences, F(1.66)=4.29, p=0.04 (table 2).

Table 2. ANOVA single factor for abstinence for the 2 groups

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstinence Associated treatment</td>
<td>39</td>
<td>270</td>
<td>6.923077</td>
<td>10.80972</td>
</tr>
<tr>
<td>Abstinence Standard treatment</td>
<td>28</td>
<td>143</td>
<td>5.107143</td>
<td>14.91402</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>P-value</th>
<th>F crit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>53.74623</td>
<td>1</td>
<td>53.74623</td>
<td>4.294688</td>
<td>0.042202</td>
<td>3.98856</td>
</tr>
<tr>
<td>Within Groups</td>
<td>813.4478</td>
<td>65</td>
<td>12.51458</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>867.194</td>
<td>66</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
THE OCDS SCALE

The analysis of the OCDS scale scores for a 12-month treatment period (dynamic evaluation approach) indicates benefits of both therapy categories regarding the evolution of the OCDS scale scores. During the three months of treatment, there is a higher decrease of the scale scores for the patients under combined therapy, as one can notice from the chart below. After three months of treatment, we noticed slightly lower scores for the patients under standard treatment. From a statistic point of view, there are significant differences between the two groups of treatment during the study period (table 9) (p<0.05).

Table 9. ANOVA single factor for OCDS at 12 months

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>P-value</th>
<th>F crit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>7529.874</td>
<td>11</td>
<td>684.534</td>
<td>12.38922</td>
<td>5.98E-19</td>
<td>1.823568</td>
</tr>
<tr>
<td>Within Groups</td>
<td>15194.4</td>
<td>275</td>
<td>55.25238</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>22724.28</td>
<td>286</td>
<td>22724.28</td>
<td>286</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fig 21. The evolution of OCDS scores in 12 months

THE QUALITY OF LIFE SCALE

A comparison regarding the evolution of the quality of life scale’s scores for the two groups of patients can be observed in Figure 29. If both groups of patients start from almost equal average values, after one month we can already observe a significant difference from a statistic point of view, a difference that is maintained during the next months, $F(11.277)=16.36$, $p<<0.01$. 

Fig.29. Evolution of QOL 16 scores in 12 months
OXIDATIVE STRESS

The dynamic evaluation of the activity level of the SOD enzyme during the study indicates significant differences between the groups’ average values from a statistic point of view, F(6.116)=15.5, p<<0.01. As one can see in the figure below, the highest abatement of the activity of the SOD enzyme (M=0.4) is registered at the baseline moment and after a 12-month abstinence the enzymatic level has the highest value, in comparison with the control group (M=1.1). During the study, we observe a progressive increase of the level of enzymatic activity between the first and the twelfth month (Fig. 41). Twelve months after the interruption of the alcohol consumption, the activity of the SOD enzyme reaches the closest point to the level of the alcohol non-consumer patients (Mcontrol =1.3U/ml, M = 12 months 1.1U/ml).

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>18</td>
<td>2</td>
<td>24.98419</td>
<td>1.388011</td>
</tr>
<tr>
<td>baseline</td>
<td>33</td>
<td>3</td>
<td>14.21865</td>
<td>0.430868</td>
</tr>
<tr>
<td>1 week</td>
<td>33</td>
<td>3</td>
<td>30.36136</td>
<td>0.920041</td>
</tr>
<tr>
<td>1 month</td>
<td>19</td>
<td>1</td>
<td>12.34052</td>
<td>0.649501</td>
</tr>
<tr>
<td>3 months</td>
<td>7</td>
<td>1</td>
<td>4.521443</td>
<td>0.64592</td>
</tr>
<tr>
<td>6 months</td>
<td>4</td>
<td>1</td>
<td>3.687684</td>
<td>0.921921</td>
</tr>
<tr>
<td>12 months</td>
<td>3</td>
<td>1</td>
<td>3.483425</td>
<td>1.161142</td>
</tr>
</tbody>
</table>

Fig. 29. The evolution of QOL16 scores in 12 months
The Evaluation of the GPX enzyme (glutathione peroxidase)

In the figure below, one can notice that the highest GPX level is present in the case of non-alcoholic patients (the control group), and the lowest GPX activity level is registered at the baseline moment (immediately after the interruption of alcohol consumption) (Fig. 53). In alcohol dependent patients, we notice a progressive growth of the GPX activity, starting from the baseline moment and reaching a maximum of 12 months, in comparison with the control group. From a statistical point of view, the differences were significant, F(6,116)=2.8, p=0.01.

Table 40. ANOVA single factor for GPX scale in 12 months

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>18</td>
<td>4</td>
<td>0.226531</td>
<td>0.013882</td>
</tr>
<tr>
<td>baseline</td>
<td>33</td>
<td>4</td>
<td>0.129055</td>
<td>0.011953</td>
</tr>
<tr>
<td>1 week</td>
<td>33</td>
<td>4</td>
<td>0.152971</td>
<td>0.003519</td>
</tr>
<tr>
<td>1 month</td>
<td>19</td>
<td>4</td>
<td>0.128496</td>
<td>0.010991</td>
</tr>
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<td>3 months</td>
<td>7</td>
<td>4</td>
<td>0.142</td>
<td>0.000815</td>
</tr>
<tr>
<td>6 months</td>
<td>4</td>
<td>4</td>
<td>0.201168</td>
<td>0.000827</td>
</tr>
<tr>
<td>12 months</td>
<td>3</td>
<td>4</td>
<td>0.200773</td>
<td>0.000757</td>
</tr>
</tbody>
</table>
The MDA (malondialdehyde) Evaluation

Next, I will present the evolution of the patients’ plasmatic MDA level, comparatively, for different abstinence periods and in comparison with the group of non-consumer patients belonging to the control group. As one can notice in the chart below, the alcohol consumption leads to a significant increase of the MDA level at the baseline moment ($M_{\text{baseline}}=69\text{nmol/ml}$), followed by a progressive decrease up to twelve months, when it reaches a value that is close to the value of the control group ($M_{12\text{months}}=33\text{n-Mol/ml}$) (table 52). As one can notice in Figure 65, the highest MDA value is observed in patients that are in the baseline moment and the lowest value is observed in non-consumer patients. The MDA values tend to decrease in time, as they are not constant. For example, on the third month, the registered MDA level was higher in comparison with the first month of abstinence. The Anova statistical analysis for all the studied comparisons indicates highly significant differences, $F(6.116)=3.7$, $p=0.001$ (Fig. 65).

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>Source of Variation</th>
<th>SS</th>
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</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>0.143719</td>
<td>6</td>
<td>0.023953</td>
<td>2.809548</td>
<td>0.013948</td>
<td>2.182082</td>
</tr>
<tr>
<td>Within Groups</td>
<td>0.937821</td>
<td>110</td>
<td>0.008526</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.081541</td>
<td>116</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Fig 65. Comparirasion of MDA level for a period of 12 months between patients and control group

Table 52. ANOVA single factor for MDA level in 12 months of abstinence compared to control group

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
</tr>
</thead>
<tbody>
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<td>control</td>
<td>18</td>
<td>6</td>
<td>34.74864</td>
<td>539.2255</td>
</tr>
<tr>
<td>baseline</td>
<td>33</td>
<td>6</td>
<td>69.68962</td>
<td>1439.637</td>
</tr>
<tr>
<td>1 week</td>
<td>33</td>
<td>6</td>
<td>48.67912</td>
<td>1062.731</td>
</tr>
<tr>
<td>1 month</td>
<td>19</td>
<td>6</td>
<td>42.55371</td>
<td>148.3707</td>
</tr>
<tr>
<td>3 months</td>
<td>7</td>
<td>6</td>
<td>46.11482</td>
<td>302.9825</td>
</tr>
<tr>
<td>6 months</td>
<td>4</td>
<td>6</td>
<td>41.19837</td>
<td>112.0606</td>
</tr>
<tr>
<td>12 months</td>
<td>3</td>
<td>6</td>
<td>33.73412</td>
<td>54.76244</td>
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</table>

<table>
<thead>
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<th>Source of Variation</th>
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<th>df</th>
<th>MS</th>
<th>F</th>
<th>Source of Variation</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>19247.41</td>
<td>6</td>
<td>3207.901</td>
<td>3.746876</td>
<td>0.001977</td>
<td>2.182082</td>
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<tr>
<td>Within Groups</td>
<td>94176.89</td>
<td>110</td>
<td>856.1536</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>113424.3</td>
<td>116</td>
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</table>
CHAPTER 8. CONCLUSIVE DISCUSSIONS AND EVALUATIONS

8. 1 DISCUSSIONS

As the above-mentioned results show, the statistic processing and analysis of the results is based on the existence of some quite homogenous groups, which is an important premise in the correct, comparative interpretation of the research data. As regards the demographic data, we need to mention a few aspects. This study was applied exclusively on male population, because of the profile of the department where the sample was established. In addition, there is a preponderance of the urban area for the group that also benefited from systemic therapy and this aspect could be explained by the particularities regarding the location of the Alcoholics Rehabilitation Club, which are mainly organized in the city, where, for now, patients from the rural area have a more reduces access possibility.

The severity of the alcohol dependence was evaluated with the help of the AUDIT scale for all the patients included in the study at the beginning of the research, before the division of the patients into the two treatment groups. The AUDIT scale evaluates the behavior and the issues associated to alcoholism, as well as to the harmful alcohol consumption. The application of this scale showed high total scores, indicating a high severity of the dependence. The calculation of the total scores average values, after the distribution by groups, showed close average values (around 30 for both groups), without significant differences from a statistic point of view. This aspect indicates correct research premises, seen that the study groups are homogenous and the alcoholism gravity level is high for both groups of patients. In fact, this aspect is also supported by scientific data, which prove that the high scores of this scale predict the severity of alcoholism (Hasin et al.2011).

One of the main factors of the alcoholism therapy efficiency is the abstinence index. In fact, any therapy for alcohol dependence has as a goal the maintenance of a period of abstinence as long as possible. This indicator was also used within the research hereby in order to compare the efficiency of systemic therapy associated with the standard therapy in comparison with the simple standard therapy. The statistical analysis shows that the patients under combined treatment (systemic therapy and standard therapy) had a better evolution from the point of view of abstinence than those that were under standard therapy only. Evaluated on a 12-month period, the abstinence in case of patients under combined therapy was higher than in case of the patients under standard therapy only, the differences between the two groups being of statistic signification. Thus, for the first group, I obtained an average period of almost 7 months, 2 months extra than in the case of the group under standard treatment. Let us not ignore the fact that a substantial percentage of the patients that entered under combined therapy were cases of severe dependence and, even more important, with a long-standing consumption history, being patients whose prognostic was rather unfavorable as regards the alcohol issue. This aspect proves obvious benefits from the abstinence point of view when the classic and systemic therapies are associated in cases of alcohol dependence. These data are supported by other studies showing benefits of systemic therapy and from this point of view some studies indicate an abstinence rate up to 80% after two and five years, associated with an increase of the quality of life from the point of view of the individual, marital, family, social and professional life (Branko et.al. 1992).

The OCDS scale was applied for each study stage. During the first three months, the statistical comparative analysis between the two treatment groups indicated lower scores of the scale
within the group that benefited from systemic therapy in comparison with the patients that benefited from medication only. During the next three months, the ratio is inverted: the patients from the standard therapy group have lower scores on the OCDS scale in comparison with the patients who benefited from combined therapy. There are no statistically significant differences for each study visit. The results of our study do not show significant benefits of the systemic therapy as regards the wish, obsessions and compulsions to consume alcohol, reflected with the help of the OCDS scale. It is possible for the systemic therapy either to influence abstinence by other mechanisms, either to influence the ideation to consume alcohol after a longer period than that comprised by this study. In addition, the loss of a significant number of patients during the study could influence the average score of this scale for the groups of patients. Subsequent studies meant to clear the impact of systemic therapy on the OCDS scale scores.

The quality of life increase is another index of beneficial change and progress in the treatment of alcohol dependence (Chirita et al. 2002). If the abstinence index is rather connected to the behavior associated to the consumption, the quality of life is rather a global change marker regarding not only the renunciation but also beneficial changes in the personal, familial and social life of the individual. This index suggests a modification of the patient’s general behavior, a progress, a personal development and a spiritual growth and maturation. When evaluating the efficiency of systemic therapy, the use of this change index is the most appropriate as this therapy aims to the improvement of the patient’s personal life, maturation and progress. The quality of life index was realized in dynamics, starting from the baseline moment, meaning before the time patients received any form of therapy and monitored in time, after 3, 6, 9 and 12 months. The results analyzed for a period up to six months indicate an increase starting with the first month of treatment for both groups, and increase that continues in the third and sixth month as well. For the patients who benefited from systemic therapy as well, starting with the first month of treatment and continuing during the other months, I noticed a higher increase of the quality of life scores in comparison with the group that received standard medication only. These differences were significant from a statistic point of view (p<0.05) reported to each visit. During the first six months of treatment for the patients that also received systemic therapy, the quality of life increase expressed by the increase of the scores of the QOL 16 scale was vertiginous, of about 30 points per scale. After the ninth month, the increase continued, but it did not have the same importance. The differences from the standard therapy group also maintained, having a statistical significance (p<0.05). The quality of life increase in dependent patients who attend the Clubs could be explained by the abstinence from alcohol, social reinsertion, reintegration and familial consolidation or individual change. The results of the study are comparable to the data presented in literature, which show a quality of life increase in patients who benefited from systemic therapy (Lempp, 1996). Correlated to the high abstinence index, the high quality of life level supports the clear benefits brought by the systemic therapy in patients that are alcohol dependents.

We can certainly claim that the systemic therapy associated with standard therapy brings more value regarding the improvement of the targeted functioning parameters from the quality of life quiz and the maintenance of abstinence in time.

The oxidative stress was evaluated in abstinent patients immediately after they stopped from consuming alcohol (baseline), after one week of treatment, one month of treatment, three months of treatment, six months of treatment and twelve months of treatment. The results were compared to those from the control group and followed in dynamics. The oxidative status was evaluated by dosing the superoxide dismutase (SOD) and glutathione peroxidase (GX) enzymes,
as well as by evaluating the lipid peroxidation markers represented by the malondialdehyde (MDA).

At the baseline moment, the activity level of the SOD enzyme was three times lower in patients in comparison with the control group, with an F(1,87)=11, p=0.001. Practically, in alcohol consumer patients we observe a reduced antioxidant activity, a diminished capacity of the organism to face the oxidative attack. Next, the analysis of the other enzyme in the antioxidant system, represented by the GPX, shows similar results. The average values of the enzymatic activities of the GPX for the two groups of patients, at the baseline moment, show a double value in the control group in comparison with the patients with alcoholism. Decreases of these enzymes during the consumption period were reported by other studies as well (Wu et al.2006).

As regards the level of oxidative stress reflected by the increase of the malondialdehyde, I revealed a high level of lipid peroxidation product at the baseline moment in patients with alcoholism (M=69) in comparison with the control patients (M=34). The results are of high statistical significance, F(1.50)=12, p<0.01. Practically, we have complementary results at the baseline moment regarding the antioxidant enzymatic activity and the level of lipid peroxidation. This aspect suggests that the alcohol ingestion leads to a pro-oxidant status with an increase of the harmful oxidative reactions and an overwhelmed antioxidant system, unable to cope with the oxidant requests. The obtained results correspond to the results reported by other authors as well (Huang et al, 2009, Kumar, 2007).

The evolution of the antioxidant activity of the SOD enzyme during the 12-month period of abstinence is interesting. Thus, during the first week we deal with a doubling of the enzymatic activity in patients, as opposed to the baseline moment, in comparison with the witness group (p<0.01), and after one month it will decrease to an average value of 0.6, which is also maintained six months later. After six months of abstinence, the SOD level begins to increase again and twelve months later it will reach almost the same level as the control group (the observed differences are not significant from a statistic point of view). It seems that once with the alcohol clearance from the system, the activity of the antioxidant system begins to increase. Still, about one year is needed for the system to function at a level that is similar to the persons who do not consume alcohol. The SOD is the first and most important enzyme standing in the way of oxidative attack (Albano, 2006). We expect its activity to mostly influence the level of oxidative stress and to have the greatest reaction to the pro-oxidant stimuli.

As regards the other enzyme dosed within this study, the GPX, the results are similar to the results obtained by the analysis of the SOD enzyme. Thus, immediately after stopping the alcohol consumption, there is a minimum enzymatic level, which progressively increases during the study in order to reach a close control level (and still, it does not reach the control level after twelve months!). Still, the differences between the control and the group of patients regarding the GPX activity are not as important as in the case of the SOD enzyme. This aspect supports the idea according to which the GPX is not as reactive as the SOD in case of alcohol consumption. Still, the decrease of the enzymatic activity mediated by alcohol is obvious and even more persistent than in the case of the SOD enzyme because the 12-month evaluation shows that after less than one year it does not reach the same value as in the case of the non-consumer patients.

Concordantly with the low level of antioxidant capacity represented by the two above-mentioned enzymes, I observed an increase of the MDA compound. The MDA is a resultant of the oxidative destruction reactions, indicating a pro-oxidant status that suggests either a low antioxidant activity or an accelerated pro-oxidant activity that overwhelms the natural
antioxidant capacity of the system. Generally, the studies showed that the alcohol abuse, as we can also observe within the study, determine an important increase of the MDA level (Nielsen et al. 1997). Therefore, at the baseline moment, the MDA concentration is double in consumer patients in comparison with the non-consumer patients. During the 12-month period, I observed a progressive diminishing of the MDA level, which reaches an inferior level in comparison with the control group, at the end of the study.

8.2. CONCLUSIONS

From the above presented data, we can obviously claim the supplementary benefit brought by the systemic therapy to patients and to their families with connected alcohol issues. The statistical analysis of the administered tests, as well as the registration of the abstinence period bring an extra weight in supporting the efficiency of this therapeutic method.

Thus, from the results and discussions of this study we can conclude the following:

1. The association of the systemic method with the standard therapy leads to the increase of the abstinence period in patients that are alcohol dependents. Evaluated for a 12-month period, the abstinence in case of patients under combined therapy was greater than in patients who received only standard therapy, the differences between the two groups being of statistical significance. Thus, for the first group we obtained an average value of almost seven months, two months longer than in case of the group under standard treatment.

2. The systemic method supplementary improves the quality of life in patients with alcohol dependence when associated with standard therapy.

3. The improvement of the quality of life takes place even from the beginning of the therapy, starting from the first month of systemic therapy associated with standard therapy – a 30 points increase during the first six months.

4. The positive effects of systemic therapy over life quality are also maintained in the long term (after 12 months).

5. The systemic method brings long-term benefits, proved by the increase of the scores of quality of life scale in time.

6. The association of the systemic method with standard therapy brings slight benefits as regards the compulsive wish to consume alcohol during the first three months of treatment.

7. The systemic method proved a benefic role in the therapeutic management of the post-hospital phase for patients with alcohol dependence when associated with standard therapy.

8. During the first three months, on the OCDS scale, the comparative statistical analysis between the two treatment groups indicated lower scores of the scale within the group that benefited from systemic therapy, in comparison with the patients who only benefited from medication. During the next three months, the ratio is inverted.

9. By this study, we found lower percentages of smokers (a general percentage of 65%) within the general population, with a slightly higher percentage (almost 70%) in the standard treatment group.

10. In case of patients who followed the systemic therapy, the percentage of persons suffering from a form of affective disorder was double in comparison with patients who only followed
standard drug treatment. The presence of depression in case of an alcoholic could influence the answer to therapy by diminishing motivation and loosing hope.

11. The alcohol dependence frequently develops in persons who suffer from personality disorders and the presence of a personality disorder in patients suffering from alcoholism is frequent. It is important to mention that within the group that received only medication the percentage of patients suffering from personality disorder was three times greater than the percentage of patients who also benefited from systemic assistance.

12. The management of the behavior disorders need an effort of the team made by assistant physician, social worker, clinical psychologist, the patient’s family and the patient.

13. There is a low antioxidant capacity represented by the reduction of the antioxidant activity of the SOD and GPX enzymes in patients suffering from ethanol dependence. The average values of the enzymatic activities of the GPX within the two groups of patients, at the baseline moment, show a double value in the control group, in comparison with patients with alcoholism. The SOD level after one month decreases to an average value of 0.6, a value that is also maintained after six months. After six months of abstinence the SOD level begins to increase again, reaching almost the same level as in case of the control group at twelve months.

14. After having stopped the alcohol consumption, a slow increase of the system’s enzymatic activity appears, reaching at the level of the control population after twelve months.

15. In case of alcohol consumers there is a high level of oxidative stress, revealed by the increase of the MDA concentration. At the baseline moment, the MDA concentration is double in consumer patients in comparison with the non-consumer patients.

16. The alcohol abstinence determines a gradual diminishing of the MDA level and therefore, of the oxidative stress, at the end of the study the MDA reaches a level that is inferior to that of the control group.

The analysis of the obtained results conforms the working hypotheses formulated at the beginning of the study.

In synthesis, this study brings a strong evidence level to support the idea according to which the systemic, multifamily approach of the alcohol-correlated and complex issues brings more value to the use of standard drug therapy, both as regards the obtaining an maintenance of abstinence for an average and long period of time, as well as the improvement of the quality of life of these patients. Also, the abstinence from alcohol leads to an improvement of the oxidative stress parameters.

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