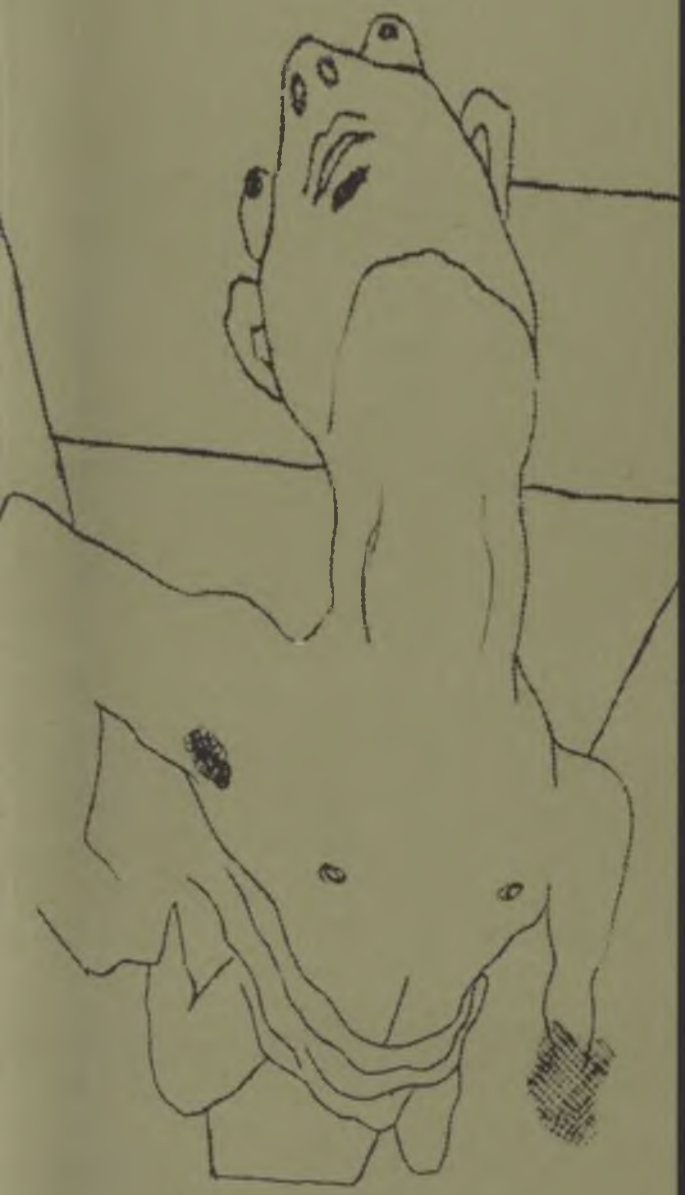
PHARMACODEPENDENCES

mechanisms, clinical aspects, treatment



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Pharmacodependences – mechanisms, clinical aspects, treatment

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FOREWORD

The monograph „Pharmacodependencies-from molecular mechanisms to clinical therapeutics" is dealing with an issue of great theoretic and clinical interests, of dependence created by use and drug abuse of substances with toxic properties.

Written by prestigious team of specialists, this book is caring the imprint of clinical and experimental experience of the authors, fulfilled by valuable screenings of new data in the literature about pharmacodependencies in general and psychic dependence in special.

The 22 chapters from this book contain a variety of biomedical aspects of alchool, nicotine, benzodiazepine, opiate and antidepressant dependencies, beginning with predisposed genetic and environmental factors and ending with diagnostic and treatment possibilities.

About the consequences of alcohol abuse there are brought proving facts for the existance of genetic markers in alcoholism and about possibilities of treating alcohol dependency with new medicines. One of these seems to be acamprosate presented by colleagues from Cluj. Morphine addictions treated from the point of reactivity changes at the opiate receptors' level producing dysforia and also about involvement of muscarinic receptors (with nitric oxide participation) at the mechanism of withdrawal syndrome emergence. Not less interesting are experimental data about magnesium influence in morphine addiction. A special attention is accorded to benzodiazepine dependence, with less known molecular bases. There are stressed altrastructural changes of benzodiazepine receptors determined by decreasing their GABA-ergic component. In case of nicotine dependence it is underlined the antinicotinic properties of naltrexone and antidepressant substances.

A number of 6 chapters are dedicated to drug addictions as acute or chronic phenomena. As examples are given neurotoxic symptoms produced by alcohol, opiates or cocaine, stressing the mechanism af action and treatment. Interesting legislative, deontological and educational information fulfill pharmacological data.

The book is ending with some chapters emphasizing some social economic and family implications of chemical dependencies in general and ethylism in special.

On general, the book puts at the disposal of physicians and of all interested in complex problems of pharmacodependencies, an interesting and worthy material of scintific information about the actual situation in theoretical and practical knowledge of toxic substances use and overuse.

I congratulate the editors (prof. dr. Mihai Nechifor and prof. dr. Petre Boisteanu) and collaborators of this worthy editorial work and I wish them new such useful realizations in scientific knowledge and public health.

Acad. Prof. Dr. I. Haulica

INTRODUCTION

Pharmacodependence at an increasing number of substances and on a larger area of this negative phenomenon is one of the greatest problem of mankind at the XXI century border.

Yet known from Antiquity, pharmacodependence become in the last years a social, medical, juridical, economic and finally a general human problem. In the beginning of 90', about 37% from USA population used at least once marijuana, cocaine or other drugs and 40% from hospital inpatients had (from National Institute on Alcohol Abuse and Alcoholism Report) diseases linked directly or indirectly on ethanol chronic consumption. In USA, 6% from adults are considered alcohol–dependents. Smoking (nicotine dependence being certitude) is also extremely widespread. About one–third from Romanian adult population is smoking. There are synthesized and permanently introduced in use new addictive substances or combinations. There are realized chemical modifications of pre–existent structures (changes which improve addictive properties or induce new user sensations). An example is "ecstasy", considered to be the drug "of new generation". Diversification of substances used as medicines put the issue of using an increasing number of medicines for non–medical purposes. The most suggestive example is benzodiazepines. Emerged on market in 1961 and considered one of the most efficient sedative–tranquilizers, hypnotic, anxiolytic and anti–seizures drug, they have become larger and larger used for non medical use. 4% from adult population in developed countries used benzodiazepines in different life stages for non medical purpose (directly bound to addictive properties of benzodiazepines.

A balanced prescription and one which regard medicine particularities and all patients characteristics represents an absolute necessity for all physicians. It is important that medicines release in pharmacy to be more careful for medicines with addictive potential.

An important problem is that pharmacodependence is a brake and sometimes a barrier for the use of some pharmacodynamic properties of substance. An example is cannabinoid use in therapy, possible medicines in some diseases but with proved addictive potential.

The more and more complete and complex discovery of molecular mechanisms involved in pharmacodependences is a way for understanding the action of these substances in human brain and on the other hand open large perspectives for pharmacodependence treatment and prophylaxis (with a heavy economical cost–over 500 billion $/yr worldwide). Discovery of reward systems in human brain and identification of pathways that allow a physiologic and not pathologic stimulation of these systems is an essential issue.

We consider that the problem of physiology, pathology and pharmacology of pleasure and reward request much more attention in contemporary medicine.

Not at last, there were performed many attempts in the last years to clarify terminology in use, but until now it wasn't realize a consensus in this direction. There are used terms like:

– **Drug abuse** – regards especially from a social, psychological and behavioral drug intake with addictive proprieties.

– **Addiction** – defined as a sum of physical and psychological dependence or as a compulsive disorder characteristic in using substances which produce pleasure and in appearance of withdrawal syndrome at ceasing.

– **Physical dependence** – adaptation of molecular (neuronal) mechanisms at a substance chronic consumption and withdrawal syndrome appearance at ceasing the intake.

Pharmacodependence term is more used because is much more medical and biological than drug abuse and because splitting physical dependence by psychologic dependence is often hard to do. In accordance with American Psychiatric Association data from "Diagnostic and Statistical Manual of Mental Disorder (3rd Edition revised – DSM III R) and with data sustained by Crabtree and Richardson, 1996, criteria for diagnose pharmacodependence at a substance are:

1. Frequent preoccupation with seeking or taking the substance
2. Often takes the substance in larger amounts or over a longer period than intended
3. Tolerance, as defined by either of the following:
   - a need for markedly increased amounts of the substance to achieve intoxication or desired effect
   - markedly diminished effect with continued use of the same amount of the substance
4. The characteristic withdrawal syndrome for the substance
5. The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms
6. There is a persistent desire or unsuccessful efforts to cut down or control substance use
7. A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain–smoking), or recover from its effects
8. Important social, occupational, or recreational activities are given up or reduced because of substance use
9. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine–induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

(after "Diagnostic and Statistical Manual of Mental Disorder" (3rd Edition Revised – DSM III R) and Crabtree and Richardson,1996)

Substance Dependence is defined as a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12–month period.

Without being unanimously accepted, these criteria offer a general frame for pharmacodependence.

This book contents in great measure papers presented during the ***1st National Conference of Pharmacodependences*** held in Cîmpulung Moldovenesc, Romania between 6–9 October 1999, a moment when ***Romanian Society for Pharmaco-dependences Study*** was concretized. We share the idea that only by efforts of a large number of specialists from all areas and bringing in mind at the society level the risk of pharmacodependences, we might stop this plague.

Iasi, December 2000

Prof. dr. Mihai Nechifor
President of ***Romanian Society for Pharmacodependences Study***

INDIVIDUAL VULNERABILITY AND ENZYMATIC GENETIC MARKERS IN ALCOHOLISM

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Man has classically divided matters from the environment into harmless and dangerous products, respectively: foodstuffs and poisons. Thus, some substances physiologically exist in the human organism, but they proved to be liable to produce serious acute and chronic intoxications in case of excessive administration (2). It is also the case of the ethyl alcohol, responsible for the scourge of our society – alcoholism. The human body contains small quantities of ethyl alcohol, originating in the alimentary canal. The concentration of this alcohol in blood does not surpass 2–3 mg ‰.

The ethyl alcohol is rapidly absorbed from the alimentary tube, through the buccal, gastric and intestinal mucous membrane. It spreads quickly in the tissues, where it undergoes a metabolic process. The greatest part of the absorbed alcohol concentrates in the brain, while the rest, in other organs such as the lungs, the spleen, the kidneys. The alcohol amount concentrated in the liver is hard to be estimated since it is in this organ that the bio–transformation of the alcohol takes place.

The rate of hepatic metabolizing of the alcohol for a healthy adult is of 10g/h (3). The ethylic alcohol does not accumulate in the organism, but it disappears in a rapid way, almost steadily, from the moment of its appearance in the tissues. The most part of the absorbed alcohol (90–95%) is metabolized and only small quantities (5–10%) are eliminated as such through the urine (2–4%) and through the expired air (3–7%).

The elimination of the alcohol cannot be considerably accelerated by the increase of diuresis or hyperventilation.

The bio–transformation of the alcohol is produced at the level of hepatic microsomes, by the influence of alcohol dehydrogenase (ADH), the enzyme having as co–factor nicotinamide adenine–di–nucleotide (NAD). The ethanol is transformed into acetaldehyde concomitantly with the transformation of NAD into NADH. Further, the acetaldehyde is transformed into acetate at the level of the mitochondria by means of the enzyme acetaldehyde–de–hydrogenase (ALDH) whose co–factor is also NADH. The acetate enters the Krebs cycle, where it is degraded up to CO_2 in H_2O. The forming of NADH during the bio–transformation of the ethylic alcohol would have – in the opinion of some authors – an important role in the determination of the toxic effects of the alcohol. Apart from this metabolic way, the ethyl alcohol is also degraded by two other secondary ways: one mediated by microsomal oxydase (together with NADPH) and another mediated by catalase together with hydrogen peroxide. Following both secondary ways, the alcohol is transformed into acetaldehyde.

The treatment of the addiction to alcohol by using disulfiram is based on the property of this medicine to stop the oxidation of the acetaldehyde to acetate, resulting in an accumulation of acetaldehyde in the body and the emergence of toxic phenomena immediately after the ingestion of small amounts of alcohol (3).

Complex bio–chemical and genetic studies of the two enzymes, alcohol–de–hydrogenase 2 (ADH–2) and aldehyde–dehydrogenase (ALDH–2), involved in the metabolizing of alcohol, allowed for the definition of several hypotheses regarding the reactivity of the human body to alcohol, so different from an organism to another.

The measurement of the genetic liability in case of alcoholism could be useful in the identification and prevention of alcoholism, but up to now there has been no identification of genes responsible for the development of this disease among all the ethnic groups (4).

A team of Japanese researchers determined the genotypes of the above–mentioned enzymes in a batch of alcoholic patients as compared to a witness batch and calculated the relative risk of alcoholism. Each of the two enzymes have three genotypes: ADH–2, the usual form (1X/1X); the atypical form (1/2) and the atypical form (2/2); ALDH–2: the active form (1/1); the inactive form (1/2) and the inactive form (2/2). The results emphasized several important conclusions:

1. The elimination of the alcohol can be slowed down much more for the persons with the "usual form" of ADH–2 than for those having an "atypical form" of ADH–2. That is why, maybe, the maintenance of a high alcohol concentration in blood favours the development of alcoholism.
2. The forming and rapid elimination of acetaldehyde are due to the usual form of ADH–2 and ALDH–2–active, consequently resulting in low levels of acetaldehyde in blood – a phenomenon which reduces to a minimum the adverse effects due to the alcohol ingestion.
3. Homozygotes ALDH–2X2, irrespectively of the genotype ADH–2, are not prone to develop alcoholism because they undergo a "flushing response" syndrome.
4. The relative risk (odds ratio) of alcoholism was maximal for the homozygotes with active form of ALDH–2 (1X/1X) and usual form of ADH (1/1) and correlated with short survivals.

These surveys, correlated with others, which established that the European race develops only the active form of ALDH–2 and the usual form of ADH–2, lays stress on the special attention that should be paid to this disease, also due to the high "sensitivity" of our racw as compared to the Asian one, which seems to be biologically protected (homozygotes with the active form of ALDH–2(2X/2X) and the atypical form of ADH–2).

The socio–cultural and material factors play an important role in the habit of alcohol consuming and the possible problems caused by alcohol. That is why th alterations of these factors can influence the risk of alcoholism, besides the existence of some genetic combinations favouring the two mentioned enzymes. The genetic aspects regarding alcoholism make up just one of the numerous markers of vulnerability – a concept which tends to explain in the best way the etiopathology of mental diseases. In 1987 Perris and a team of collaborators elaborated a comprehensive concept of vulnerability.

It suggested that an approach of the study of mental disorders and their adequate cure should be based on a complex theoretical framework taking into consideration the interaction of the cultural, social, biological and psychological variables in the development of the individual liability for psychopathological behaviour (1).

We consider possible the particularization of Perris' vulnerability pattern in case of alcoholism too and especially of addiction to alcohol.Otherwise, since 1960, in his work entitled "Alcoholism – a disease concept", Julinek underlined as a fundamental idea, that some people possess a specific vulnerability to the abuse of alcohol, an idea substantiated to some extent by the results of the genetic research mentioned in the first part of the work.

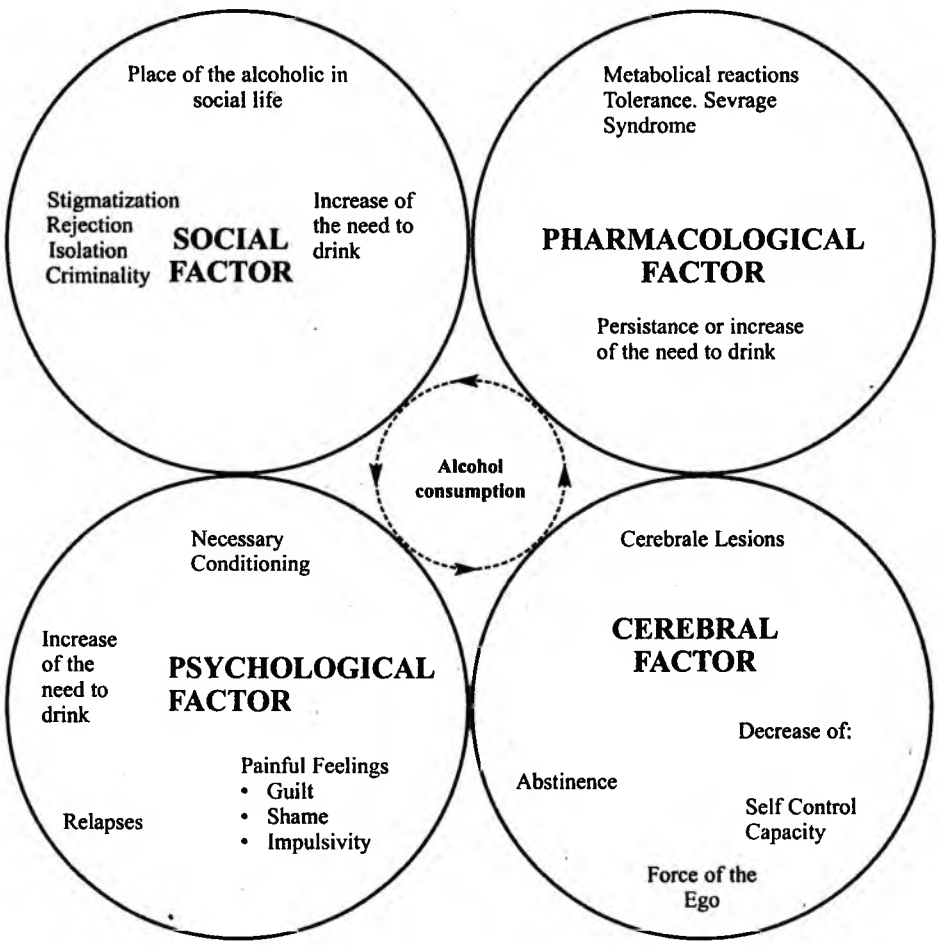
By comparing Perris' pattern with the "scheme of the four vicious circles" proposed in 1979 by W.K.Van Dijk, one can notice numerous common elements. We expose below both schemes accompanied by several comments on the content.

Perris' Pattern

ETIOPATHOGENIC BACKGROUND	CULTURE	TREATMENT, EVOLUTION AND RESOLUTION
Biological Variants ↑ ↓		Biological Variants ↓ ↑
Psychological Variables ↑ ↓	Life Events ↑ ↓	Psychological ↓ ↑
Social Variables	← INDIVIDUAL ←	Social Variables ↓
	→ VULNERABILITY →	Psychopathological Disturbance ↓
		Evolution and Resolution

TIME

Scheme of the Vicious Circles – W. K. Van Dijk



In Perris' pattern one can notice that to the factors of different fields (biological, psychological, social) supposed to determine the appearance as well as the evolution, treatment and predictability of mental disturbances are added a cultural perspective and a chronological dimension. The arrows on the scheme indicate the continuous dialectic interaction between the potential causal factors and the individual and its environment, alongside with the therapeutical factors. So, the vulnerability is not regarded as a statical trait but as a state which is modelled alongside the life cycle.

In the scheme made by W.K.Van Dijk the "permanent" factors of the addiction to alcohol are:

• social, pharmacological, psychological and of cerebral origin. One can notice the dynamic and sustained character of these factors, perfectly superposed over those regarding vulnerability.

The "pharmacological" vicious circle implies the progressive development of the tolerance and psychic dependence through complex bio–chemical mechanisms, then, the addiction to alcohol maintains and accentuates in its turn pharmacological disturbances (5).

The "cerebral" vicious circle refers both to the potential organic character of alcoholism (cerebral esions of different etiologies) and to the weakening of the Ego (term used with defensive significance of the personality) responsible for a bad "control" of the abstinence and of the motivations of the alcohol consumption (6).

The "psychological" vicious circle refers to the feelings of guilt, shame and impulsivity whose only possible remedy could be the alcohol consumption itself that generated them. This leads to a process which, in point of behaviour, could be named necessary conditioning. The prolonged alcohol consumption determines a regression of the instinctual and affective factors and a weakening of the Ego.

The "social" vicious circle implies social and family conflicts induced by alcoholism, which will determine themselves behavioural disturbances, environmental conflicts, job problems. These will generate stigmatization and rejection effects with the positioning of the alcoholist at the periphery of the society and will determine – on the side of the latter – the increase of the need to drink, thus closing the circle (5).

The immediate utility of this scheme seems to be an interruption of the circles in any point, followed by an "apparent recovery". In fact, the eradication of this scourge could be utopically achieved just by a cumulation of forces at all levels. A hardly attainable object! That is why we consider that the prevention of alcoholism by any means (therapeutical, psychological, cultural, legal) especially among the population with high risk (determined by a complex screening) would give much better results.

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ROLE OF LIFE EVENTS IN DEPRESSION IN ALCOHOLIC MEN

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Introduction

The relation between **alcoholism** and **depression** is one of the most studied problems in psychiatry. For many decades, clinical observation has demonstrated the association between the two disorders. Subsequent scientifically documented researches have demonstrated the existence of a multidimensional relation between the two nosological entities, relation that includes genetic, biochemical and psychological aspects. "Spectrum" depressive disease (5), partial similar changes of some neurotransmitters: serotonin, noradrenaline and dopamine (4), and the existence of common personality features with a less predisposing value (2, 7) summarize the interrelation of these two disorders.

Depressive symptoms are currently found in several nosological entities, from neurotic disorders: adaptation disorders (short depressive reaction – F43.20; prolonged depressive reaction – F43.21, and mixed anxious and depressive reaction – F43.22), to affective disorders (bipolar affective disorder, current depressive episode – F31.3–F31.6; depressive episode – F32; recurrent depressive disorder – F33 and dysthymia – F34.1) and, finally, organic psychic disorders (organic depressive disorder – F06.32). Depressive symptoms also occur with an increased frequency in chronic alcoholism.

The finding of the implication of life events in the determinism of psychic disorders has underlain the long–time term of psychogeny. Adaptation disorders are considered by definition a direct cause of psychotraumatizing events. Researches concerning the etiology of affective disorders have demonstrated an excess of life events in the months preceding the onset of a depressive episode of neurotic or psychotic intensity (3). Also, the risk to develop a depressive episode has been found to be six times higher in the six months following the experience of particularly dangerous or threatening life events (6).

Objective

This study aimed to determine the incidence of depressive conditions among men with alcohol dependence syndrome. It also attempted to determine to what extent life events play a role in the occurrence of depressive symptoms in alcoholic men, as well as to show the peculiarities of

depression in alcoholic men related to age, from the point of view of the vulnerability to stress of these patients.

Method

The study belongs to the category of prospective studies. The group of patients includes 44 cases selected from patients admitted to the Psychiatric Clinic of Cluj–Napoca.

The selection criteria of the group included in the study were the following:

- diagnosis of alcohol dependence syndrome (F10.2) according to ICD–10 diagnostic criteria
- absence of a withdrawal syndrome complicated by seizures (F10.31) or of a withdrawal syndrome with delirium (F10.4)
- absence of other psychotic disorders associated with alcoholism, i.e. psychotic disorders during or just after alcohol use (F10.5), amnesia syndrome (F10.6) and residual psychotic disorders or late onset psychotic disorders (F10.7)

The age of the patients included in the study ranged between 21 and 57 years. Most of the selected patients belonged to the 5th age decade (40–49 years; over 40%), while the fewest cases were in the 3rd decade (20–29 years; less than 12%). The distribution of the group by age decades is shown in ***Table no. 1.***

Table no. 1. Distribution by age groups

Age decade	Number of cases	%
20-29 years	5	11.4
30-39 years	10	22.8
40-49 years	19	43.1
50-59 years	10	22.7
Total	**44**	**100**

The patients included in the study were given questionnaires for the evaluation of alcohol use (Michigan Alcoholic Screening Test – MAST) and depression (Beck Depression Inventory, 21–item variant – BDI–21). The level of life events (Social Readjustment Rating Scale – SRRS) was also assessed (1). These questionnaires were applied after the withdrawal syndrome was overcome. During this period the patients did not receive antidepressive treatment or antiepileptic thymomodulators, they only received benzodiazepines (Diazepam 30 mg/day, i.m.), B–group vitamins and glucose (33% or 10% vials, administered parenterally)

The findings were introduced in a database created using EpiInfo program ver.6. Statistical calculation was made using Student t test, Pearson correlation coefficient (r) and significance thresholds (p).

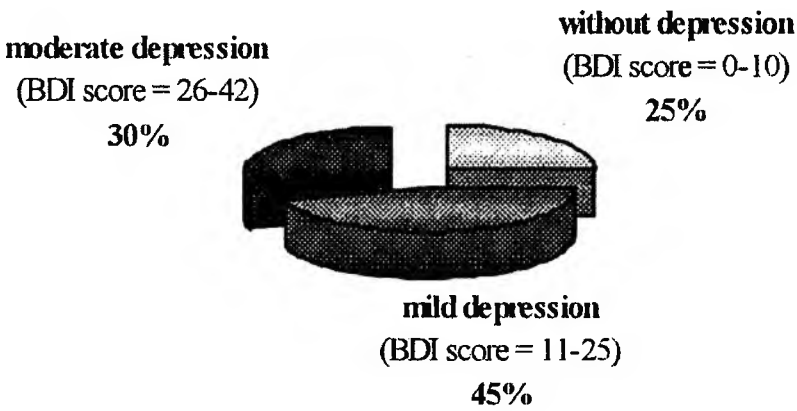
Results

All the patients included in the study had scores over 20 points for MAST questionnaire, which suggests a high degree of abusive chronic alcohol use in these patients (the 5 point value was considered as a "limit score"). The mean of the scores obtained for MAST was approximately 31 points.

The proportion of the cases with more than 10 points for BDI – showing a degree of depression – was 3/4 (75%), the rest of the patients having a normal condition (without depression). There were no cases with severe depression (BDI score over 24 points). Most of the patients from the studied group (45.5%) had a mild depression (BDI score=10–15 points). A moderate depression was found in more than 1/4 of the studied cases (29.5%).

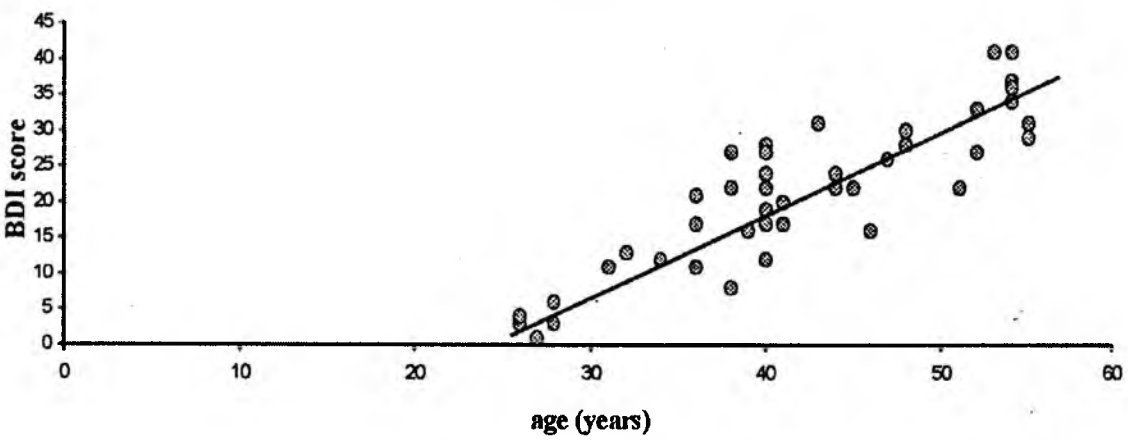
The distribution of the total number of cases according to the degree of depression evaluated through BDI score is shown in ***graphic no. 1.***

Graphic no.1: Incidence and degree of depression in men with alcohol dependence syndrome.



By analyzing the studied cases according to age, both the proportion and the degree of depression were found to increase with age. The calculation of the correlation coefficient r between BDI scores and the patients' age showed the existence of a close direct correlation between the two variables (r=0.46; p=0.01).

Graphic no.2: Correlation between BDI score and patients' age for the total number of cases.



In ***graphic no. 2***, the linear grouping of the point cloud having as coordinates age and BDI score can be observed, which illustrates the presence of a direct correlation between these two variables.

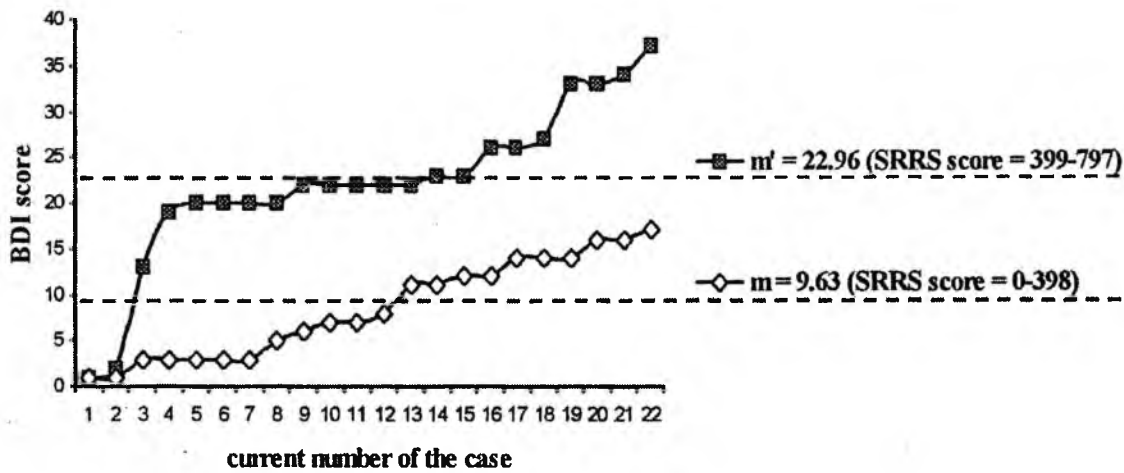
No significant relation was found between the scores obtained for MAST and those obtained for BDI (r=0.23; p>0.1). This demonstrates the absence of a direct correlation between the presence and the degree of depression, and the severity of alcohol dependence syndrome. Thus, in the determinism of depression occurring on the background of alcohol dependence syndrome, a

multitude of factors are involved. So, the relation between alcoholism and depression is more complex than a simple linear relation.

In order to evaluate the influence of life events in depression in alcoholic men, the total of the cases included in the study were divided in two groups depending on the level of life events. The limit score obtained for SRRS was calculated as a mean of the minimum and maximum scores obtained (minimum SRRS score = 0; maximum SRRS score = 797). Calculated in this way, the limit score (SRRS limit score = 398.5) determined the division of the total group in two groups with an equal number of patients (N = 22 cases with SRRS score = 0–398 and N' = 22 cases with SRRS score = 399–797). The calculation of the mean score obtained with BDI for these two subgroups resulted in different values: m = 9.63 and m' = 22.96. In order to establish the degree of statistic significance of the difference between the two means, the t test was applied, and the t value = 3.02 was obtained, corresponding to a significance threshold $p < 0.01$. This result demonstrates the fact that between the two groups of patients (one with a low level and the other with a high level of life events) there are statistically significant differences between the scores obtained for BDI–scores reflecting the presence and the degree of depression. From a statistical point of view, this finding allows us to affirm that BDI score represents a variable dependent on SRRS score considered as an independent variable – or: the presence and the degree of depression in alcoholic men depends on the level of life events of these patients.

Graphic no. 3 comparatively shows the BDI scores – consequently the degree of depression – for each of the two groups established depending on the level of life events – evaluated by SRRS scores.

Graphic no.3: BDI scores of the cases with low and high SRRS scores.



In order to evaluate the influence of age on the vulnerability to stress in the patients studied – the extent to which life events are involved in the determinism of depression – the studied group was divided in two age groups:

– young adults – age ranging between 20 and 39 years

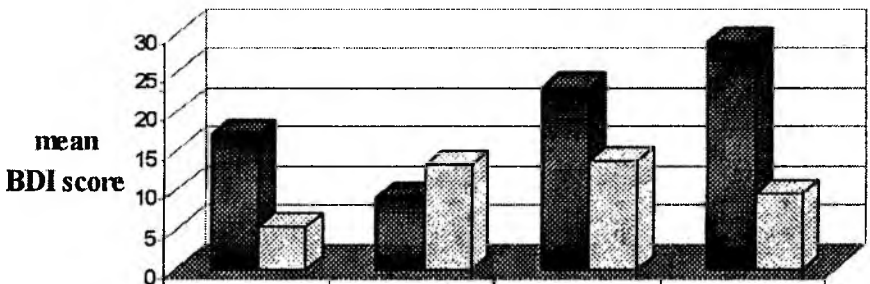
– adults – age ranging between 40 and 59 years

Their role in the determinism of depression increases with the patients' age.

Then, the BDI scores of the patients with low SRRS scores were compared with those of the patients with high SRRS scores, by calculating the t criterion. It was shown that for the first age group (20–39 years), there were no statistically significant differences between the means of the BDI scores in the cases with a low and high level of life events ($t = 1.02$; $p > 0.05$). In the case

of the patients included in the second age group (40–59 years), the calculation of the t criterion revealed the existence of statistically significant differences between the means of the BDI scores obtained in the cases with both low and high SRRS scores ($t = 2.83$; $p < 0.02$). These results prove that the role of life events in the determinism of depression in alcoholic men increases with age, or the men with alcohol dependence syndrome have a vulnerability to stress for depression that increases with age.

Graphic no.4: The mean BDI score for the cases with low and high SRRS scores for each age decade.



	20-29 years	30-39 years	40-49 years	50-59 years
mean BDI score (SRRS>398.5)	17	9	23.1	28.87
mean BDI score (SRRS<398.5)	5.25	13.11	13.75	9.5

In ***graphic no. 4***, the mean of the BDI scores in the cases with a low and high level of life events is presented for each age decade.

It may be noted that the maximum difference between the means of the BDI scores corresponds to the 6th age decade (50–59 years). Also, for the 4th decade the BDI mean of the cases with a low level of life events is somewhat higher than that found in the patients with high SRRS scores. This is most likely due to an insufficient number of cases. Anyway, this difference is small enough to influence the results obtained in the evaluation of the total group of patients which, as it has been mentioned, shows the implication of life events in the determinism of depressive symptoms in alcoholic men.

Conclusions:

1. *The incidence of depression in alcoholic men is high, increasing with the patients' age.* In spite of this, the majority of the alcoholics have a mild depression.
2. *The depression of alcoholics has at least in part a reactive character, the implication of life events being obvious in its determinism.* Life events seem to play in the occurrence of depressive symptoms in alcoholic patients a role whose importance increases with age.

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BIOLOGICAL MARKERS FOR PREDISPOSITION TO ALCOHOLISM

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Alcohol metabolic markers

Of a great interest are the two enzymes: alcohol dehydrogenase (ADH) and aldehyde–dehydrogenase (ALDH). Further studies concern CAT (catalaza) and P_{450} cytochrome. Genetic polymorphism of ADH and ALDH could explain a low risk for alcohol–related disorders. There are at least 8 ADH isoenzymes and 4 ALDH isoenzymes, each of a different activity. (1, 30) An atypical ALDH2 could explain the easy intoxication in some cases (40%). Asian person (in fact a "flush effect" due to a high level of acetaldehyde during the intoxication). An up–adjustment of the ADH (AH 2/1 and ADH 3/2) results in fast metabolism with high level of acetaldehyde. (1, 9, 30, 31)

The P_{450} II E1 cytochrome is a part of the MEOS (a microsomal alcohol metabolic system). There are two allele: C1 and C2. The C2 allele could have an increased function as an alcohol metabolizing enzyme. (11)

Some studies have shawn that catalase could be a biological marker for alcohol dependence. (13, 14) This enzyme catalyzes the conversion of alcohol into acetaldehyde with hydrogen peroxide consumption. Lieber al col. have considered this metabolic pathway as important as the microsomal system (MEOS).

In our study 59 paticuts were assessed (alcoholic and normal, women and men). Determination of the catalase levels was done on equal percentages of patients in the 2 groups. The mean catalase level was of 3 different ranges in the alcoholic groups:

– 36,8% normal levels;
– 16,2% higher levels;
– 47% lower levels.

The lower levels corresponded closely with the severity al alcohol related disorder. The percentage of 36,8% of lower levels of catalase activity could explain a certain degree of low vulnerability to alcohol–dependence in some person (20% of all).

The 2 other ranges of values could suggest a specific manner of reaction of the catalase pathway to the alcohol ingestion. The lower levels indicate a poor ability of the cell to protect it self against alcoholic aggression; on the other hand the higher levels could indicate the initial phase of a protection process. A high percentage of abnormal values in our study suggests the reliability of the catalase enzyme as a biochemical marker in alcoholism (not specific to alcohol dependence, as recommended in the literature, because of the lack of more sensitive methods in our study). At least one assignment is certain: the catalase is very important in protecting in cell against free radicals

released from alcohol metabolism by diminishing the oxidative stress. High levels of catalase are suggestive for a tendency to crave and a risk to develop an alcohol related disorder. (19)

Neurobiological addiction markers

D2– dopamine receptor

There is large amount of dopamine receptors both in the CNS and in the peripheral tissues. The D1 like receptors are responsible for vasodilatation in the kidney, intestine, heart or brain areas. The D2 receptors inhibit the neurotransmission in the sympathetic ganglia, the release of the noradrenalin and the release of the prolactine. Dopaminergic mechanisms seem to be involved in the alcohol addiction. A lot of studies report data about genetic polymorphism of D2 receptors associated with the heritability of alcohol related disorders. (6, 15, 22) Some studies report the association between A1 and B1 allele of D2 receptors and alcoholism. Noble has shown a high prevalence of E1 allele among alcoholics. All these studies have not been consistently replicated. Another D4 receptor allele seems to be associated with the severity degree in alcoholism. The A4 allele of D4 receptor gene could be involved in alcohol dependence (this gene, similar to D2 gene has a lower degree of polymorphism than D2 receptor gene. (24, 7, 8, 10, 29)

Some studies have shown the association between D3 and alcoholism but they have not confirmed. There is a study showing an association between the dopamine carrier gene (allele no.7) and the alcoholism. (18)

The MAO enzyme

This enzyme is abundant in most tissues, especially in the nervous tissue. There are two subtypes of MAO: A and B involved in maintaining a certain level of nore pinephrine at the synapse. The MAO genes are located on the X chromosome.

There is an association between the MAO gene regulation and a low enzymatic level in the alcoholics (there is an association between the early onset of alcoholism and an anomalous MAO gene in some persons). (33)

The MAOA and MAOB genes occupy proximate loci in the X chromosome. The mechanisms of their involvement in the etiology of alcohol dependence, their relationship with other etiological factors (behavioral, genetic, etc.) are to be discovered.

Serotonin

The serotonergic mechanisms have been studied on a plateled model. The platelets have serotonergic membrane receptors similar to those found in the brain tissue. (4)

There is a specific decrease in the uptake of serotonin in a group of abstinent alcoholics in a comparative study, thus indicating a low level of serotonin uptake as a possible etiological factor of alcoholism. These findings are more plausible considering the increased serotonergic activity during the alcohol ingestion in the nonalcoholic subjects.

Platelet serotonin receptors affinity in alcohol dependent patients (with recent withdrawal or long abstinence) is significantly increased. This finding suggests the lower affinity for serotonin as a possible marker in alcohol dependence. More research is to be carried out to find out whether these are of genetic origin or are a consequence of a prolonged alcohol intake.

A significant decrease in number of imipramine platelet receptors would be in favor of the former hypothesis. (2)

Triptophanhydroxylase, an enzyme involved in the serotonin metabolism, could be a marker for behavioral disorders including alcoholism.

Serotonergic neurotransmission seems to be an interesting research area being involved both in alcohol dependence and in depression, two frequently associated disorders.

GABA like plasmatic activity

Alpha aminobutyric acid is a major inhibitory neurotransmitter in the CNS. The GABA receptors have binding sites for benzodiazepines and barbiturate. The GABA ergic system is impaired by system is impaired by alcohol intake. The genes probably contribute to the level of GABA ergic activity, a mechanism considered to be a genetic marker for alcoholism.

Other markers

The CSF level of 3 methoxy–4–hydroxyphenylglycol (MHPG) is significantly correlated with alcohol level in the blood. The MHPG level is the CSF could be a genetic marker for alcoholism and a sign of alcohol intoxication. (32)

Imunological markers

Blood groups

Some studies have shown an association between alcoholism and blood groups.

The ABO system

There is no association between alcohol dependence and the ABO system though there is a high incidence of A group among the alcoholics suffering of cirrhosis and of group among those suffering of pancreatitis. (12)

The MNSs system

The MNSs system is determined by two pairs of allele: M and on one side, S and on the other side. The homozygous recessive genotype "ss" would be a protection factor against alcoholism. Pirollet have found differed frequencies of MNSs phenotype in alcoholics vs. general population (the N phenotype is more frequent in alcoholics than in general population, 30,8% and 18%, respectively). Other studies deny any genetic linkage between alcoholism and the MNSs system. (26, 21)

Other systems

Some studies have shown an association between D gene in Rhesus system and alcoholism or between Lewis system and the some disorder but these studies have not been replicated. (12)

HLA system

There are few studies concerning an association between the HLA system and the alcohol dependance.

Other markers

Enzymes

Adenylatcyclasa

This enzyme is involved in signal transduction and catalyze the production of cyclic AMP from ATP. The G proteins: Gs and Gi stimulate or inhibit the activity of this enzyme. The activity of the adenylylciclase is impaired in alcoholics by an anomalous Gi protein. (34, 36)

Further studies are to be done to get more information about the nature of this anomaly.

The level of adenylyciclase activity after dopamine activation is not immediately modified (in an animal experiment the first modification is observed after 8 hours of withdrawal; at 24 hours adenylylciclase activity is significantly decreased, the normal values being observed after 7 dais). The modified function of dopamine receptors could be the biochemical mechanism of the alcohol withdrawal syndrome.

The sensitivity of dopamine receptor fot its ligand is regulated by the state of the receptors phosphorylation. A low level of activating protein (a second messenger) in the cellmembrane is associated with a low adenylylciclase activity – this mechanism found in alcohol withdrawal.

The effects of alcohol on the second messenger systems (especially the c–AMP) are not the same at the different brain areas. Thus after alcohol administration the c–AMP level is decreasing by 54% in the cortex, 59% in the cerebellum (after 12 hours from intake). At the pons area the activity decreasing is at 54% after 3 hours. The decreasing of c–AMP levels is not explained only by the alcohol effect on adenylylciclase activity. The adaptation of the adenylylciclase/c–AMP system is not necessarily involved in alcohol dependence but could be a biochemical mechanism of the withdrawal syndrome.

D–esterase

Some authors suggested a possible relationship between an "alcoholism gene" and the locus for D esterase on the 13th chromosome. (35)

Glyoxalase

There is a study suggesting that people having a GLO1 phenotype would have a predisposition for alcoholism (a marker for alcohol seeking behavior).

Gammaglutamyltransferase (GGT)

GGT is involved in transmembranar transport of ammoniac's and peptides, in glutathion metabolism and in renal acid–base metabolism.

This enzyme's level values facilitates a discrimination between heavy and occasionally drinkers, the severity assessment of alcoholic hepatitis and the state alcoholic withdrawal.

In our study 33% of the subjects is the control lot had high values of GGT level, with normal values after 8 hours from alcohol stimulation. This finding suggests an inappropriate alcohol metabolism due do genetic factors, offering a useful help for preventing persons with family histories of alcohol abuse from becoming alcohol addicts. (20)

Endocrine markers

A blunted response in serum THS after TRH stimulation is common amount the alcoholics and the subjects with family histories of alcohol abuse. (5) This anomalous response could be a biological marker for alcoholism but amore subtle explanation of this impairment is to be found.

Persons with family histories of alcohol abuse have a lower level of ACTH after alcohol intake (1,1 ml/kg body m.) than those in the placebo lot. Similar results were found for cortisol plasmatic levels.

In some persons with family histories of alcohol abuse there is a less important in crease of the prolactine level after alcohol intake. (16)

Electrophysiological markers

The P300 wave

The P300 wave amplitude (evoked potentials) is influenced a by genetic factors an is reported to be of low amplitude and delayed in alcoholics during the sobriety period. A low amplitude and an increase latency period are not specific markers for alcoholism but they are associated in some degree with cognitive and psychological factors of alcohol dependence. There is a certain involvement of dopaminergic system in the P300 genesis. (25, 27, 23)

Electroencephalographical patterns

There are studies in this field. Some authors have found a high alpha wave in young nonalcoholic subjects with family histories of alcohol abuse but in other studies a high beta wave was found.

The further studies will discover markers for alcohol predisposition or will provide new evidences for the old ones. (3, 28)

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THE ROLE OF THE MUSCARINIC RECEPTORS AND OF THE NITRIC OXID IN THE MORPHINIC WITHDRAWAL

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In the last decade, important changes occurred in the so complex field of toxicomania that was consciously or unconsciously avoided. Part of them have medical connotations and were determined by the AIDS phenomenon which complicated the clinical reality of the drug addicts, and the others have social dimensions placing the drug addict at the periphery of the social life.

The opioids have euphoric effect on human beings and strongly generate the pleasure on animals. This is more evident when the effect is quicker at the beginning, especially when the opioids are injected or inhaled. The opioids, more than any other category of drugs, can induce physical dependence, having as a result an aggressive withdrawal syndrome, when the level of the main opoid decreases. This aggressive syndrome has an important role in the perpetuation of opioid consumption and the relapse at a short period of time after the withdrawal.

The opioids and the opioid receptors

The discovery of the multiple opioid stereospecific receptors and of the endogen ligands of these receptors facilitated the understanding of the effect of the morphine–like drugs. These discoveries required the redefining of the term "opioid"; from now on it is defined, like any other exogen substance which is specifically bound to some subspecies of the opioid receptors and produces an agonist effect upon them.

According to J.H. Jaffe, the term "opiate" defines the natural alkaloids derived from opium: morphine, codeine, tebaine, papaverine, and nosca pine and the term opioid defines both the synthesis products (pentazocine, metadone, butorfanole, petidine, fentanyl) and semisynthetic derivatives: heroine, apomorphine, buprenorfine. Some opioid substances with a pharmacological profile different from that of morphine (typically agonistic) can be differently bound to the various subtypes of receptors in comparison with the morphine bounding way and can improve the abstinence syndrome of the morphine.The substances that can be bound to any type of receptor without determining any effect are called antagonist opioids.

At the beginning of the researches in this field the following types of receptors have been described:

– miu receptors, to which classic opioids such as morphine are connected and actuated;
– kappa receptors, on which nalbufine and butorfanol actuates;

– delta receptors, endogen pentapeptide met–enkefaline as well as some synthetic peptide are preferentially bound;
– sigma receptors are activated by benzomorfan, a substance which has an excita ting and hallucinating effect on dogs, inducing pain–killer in a lower degree or at all.

The development of more specific ligands triggered the identification of sub types of receptors miu, kappa and delta.

Miu receptors are responsible for the majority of morphinomimetic effects, out of which the most important are the pain–killer and the respiratory depression; the other effects are: hypotermia, euphoria, miosis, bradycardia and the capacity of inducing physical dependence. Two types of this receptor have been identified:
– miu 1 receptors are the mediators of the pain–killer effect and their endogen ligands are the opioid peptides;
– miu 2 receptors are the mediators of the respiratory depression and their specific ligands have not been identified yet.

The kappa receptors are responsible of a pain–killer activity, without any effect on the respiratory function; their endogene ligands are the dinorfine s. Two subtypes have been identified: kappa 1 and kappa 2.

The old conception according to which kappa receptors are responsible for spinal pain–killer and miu receptors are responsible for supraspinal painkiller should reviewed. The activity of the two typed of receptors (miu and kappa) induce the pain–killer effect, but the subjective kappa effects are different: sedative and a disphoria effect. This difference could explain the lack of the potential auto–administration in comparison with the antagonists as compared to the antagonists.

The receptors kappa as well as the sigma ones have psychotomimetics effects causing hallutinations and dellirous ideation. Another physiologic role mediated by these kappa receptors is represented by the adjusting of the release of vasopresine by the retro–hypophysis.

Receptors delta also controlls nociceptia, but are involved in a smaller degree in the pharmacological activity of the exogene opioids. Their specific endogene ligands are the enkefalines. While receptors miu and kappa can be found under the form of "complex–receptors", receptors delta are integrated in a molecular complex with receptors miu, influencing in this way the depressive respiratory effect.

Receptors sigma have not been very well identified; they are different from the other receptors by the fact that their activity is not antagonized by naloxon. That is why, for a long period of time they were considered as opioid receptors. These receptors show a preferential affinity for some dextrogyr compounds (benzomorfan); the different effects that have been attributed to them, psihotomimatic and cardiovasculare are now under discussion again.

Effects of the stimulation of the opioid receptors

Miu	pain-killer respiratory depression hypothermia bradicardia euphoria miosis physical dependence
kappa	pain-killer sedation miosis
Delta	pain-killer respiratory depression
Sigma	tachycardia tachypnea midriasis hallucinations disphoria

The activity of the agonist opioids miu are primarily induced upon the receptors in the nervous system in CNS, in the vegetative nervous system and in a smaller proportion upon the receptors of the white sanguine cells. This activity of the agonist opioids miu includes: supraspinale pain–killer, respiratory depression, euphoria, the incapacity of anticipating the danger, drowsiness, decreasing of the capacity of concentration, endocrinous modifications regulated by hipotalamus and the increase of the tonus of the muscles of the gastro–intestinal tract. The miu agonists also induce tolerance and neuro–adaptive modifications in CNS having as a result the occurrence of the withdrawal phenomenon when the consumption of the agonist was interrupted.

The majority of opioids which determine abuse and dependence are typical agonist miu; they have a pharmacological profile similar to that of morphine being different only in pharmacokinetic or metabolism terms.

The tolerance and the physical dependence are characteristic for each type of receptor. So, when the tolerance occurred to an agonist miu, such as morphine, we can notice a cross tolerance with other miu agonists. When the tolerance is developed to a selective miu agonist, there is not a crossed tolerance with miu agonists. More than that, the physical dependence induced by the agonists kappa has distinct characteristics, and the withdrawal syndrome determined by them presents different sings and symptoms.

All types of opioid receptors are connected by G proteins, either by the secondary messenger system or directly by the ionic channels. Receptors miu and delta are connected by proteine G1 to adenilat–cyclase or to the potasium channels.

Mechanism involved in obtaining the dependence to opiacees

Dopamine is the most important neurotransmitter which mediates the installation of the dependence of substance by stimulating the mechanisms of reward. The dopaminergic, mezolimbic and mezocortical ways proved to be involved in the induction of reward. These ways constitute the dopaminergic projections from the level of the ventral tegmentale aria (VTA) to the limbic level (nucleus accumbens, striat olfactiv bulbus and tonsil) and at the cortical level (frontal cortex).

The opioids have afinity for receptors miu, delta and kappa; receptors miu and in a smaller proportion receptors delta mediates the euphoric properties of the opiates. A great number of these receptors can be found in the limbic region and in the cortical one, in a similar way with the dopaminergic projections of the VAT.

The stimulation of receptors miu and delta decreases the activity of adenilat–cyclase (via G protein) with a consecutive decrease of AMPc intracellular and with a release of GABA from the GABA interneurons.The belated effect of this fact induces the diminution of the stimulation of the GABA receptors located on the dopaminergic neurons, increasing the excitability of these neurons and secundary, increasing the release of DA. The exact mechanism of inducing the euphoria is not clearly known yet, but, practically, all substances having potential capacities to induce dependence stimulates the dopaminergic, mezolimbic and mezocortical ways. Tolerance requires the use of progressive higher doses in order to obtain the desired effect. This tolerance is not uniformly developed for all the actions of the opioid drugs. In this way we can have high levels of tolerance for some actions of opioids such as the pain–killer, sedative and depressive respiratory effect (which requires a 100 increase of the dose in order to obtain the initial effect) while a less evident tolerance is developed to constipation and miosis.

Physical dependence is a modification of the biological system induced by substance, manifested by a particular clinical expression withdrawal syndrome, when the drug is eliminated from the organism or removed from its receptors.

Mechanisms involved in the acute intoxication with opioids

During the acute intoxication with opiates, the opioid receptors located at the level of the noradrenergic projections in locus cerules (LC) in the majority of the cerebral regions are stimulated, intracellular modifications appearing in a consecutive way: decreasing of the activity of the adenilat–cyclaze (AC)CAMP and potassium.

These modifications induce a decrease of the rate of neurons discharge in LC.

Mechanisms involved in the opioids withdrawal

Chronic consumption of opioids determines a regulation at a high functional level of the activity of adenilat–ciclaze (AD) with a semnificative reduction of the potassium conductivity. These modifications lead to the increase of the rate of neurons discharge NA (noradrenergic) to normal condition as long as the opiate is consumed. When this consumption is interrupted and the opioid receptors are not stimulated, because of the up–regulation process of AC, a powerful increase of the rate of noradrenergic neurons discharge is exercited leading to a state of NA hyperexcitability, characteristic to the withdrawal symptom. Clonidine and lofexidine are agonist adrenergic alfa 2 which decrease the release of NA at sinaptic level; They were used with relative success in the attenuation of the hyperadrenergic symptoms characteristic to the opioid withdrawal.

The neuroadaptive modifications induced by the administration of opioids take place in the cells containing opioid receptors and start to become obvious after several doses. For example, if 18 mg of morphine are administrated to non drug addict persons, and in a period of 24 hours 10 –30 mg of naloxone are administrated to them, the naloxone could precipitate the occurrence of a mild agonist withdrawal syndrome. Simptomatology of withdrawal can be reduced by any opioid occupying the same receptor because of the phenomenon of cross dependence.

The mechanism of tolerance physical dependence. The tolerance and physical dependence of opioids is developed in parallel and the withdrawal symptom tends to be a clinical manifestation in the oposite direction to the effects produced by the drug (mirror image). Out of the mechanisms proposed we specify the following:

– modifications in the genic expression of the endogen opioids;
– alterations of the intracellular concentration of ionic calcium;
– variations of the number of receptors and of the their bounding affinity;
– modifications in the coupling mechanisms of the receptors to the ionic channels or to the secondary messengers;
– alarm in the neuron command;
– increase in the concentration of endogene antagonist peptides;

These mechanisms are not reciprocally excluded, they are complementary. The opioids drugs can alterate the expression of the genes which codify the opioid neurotransmitters. In this way, the cronic administration of morphine determines a down–regulation of the proenkefaline expression in the striat neurons, while the administration of an antagonist opioid causes the up–regulation of the proenkefaline expression. Chronic administration of antagonists produces also the up–regulation of the opioid receptors, having as a consequence the appearance of a higher answer to the administration of an agonist opioid.

Other researches have been focalized upon G protein (guanine–nucleotide binding protein) which is used as a transducer between the activation of the receptor and the ionic channels or the secondary messengers. The acute administration of the opioids or determines an inhibition of the adenil–cyclaze and a decrease of AMPc. The modifications induced by opioids in the concentration or the activity of proteine G could be the mechanism by means of which the chronic use of opioids modify the rate of CAMPc synthesis. When the opioid is removed, a higher rate of AMPc is obtained

leading to high transitory levels of AMPc. It was determined that some aspects of withdrawal are attributed to these high levels of CAMP.

The alterations of the concentration of the intracellular calcium can also induce modifications of G protein. It was stipulated that the chronic administration of opioids produces the activation of endogenous antiopioide peptides.

The chronic treatment with opioids induces a hypersensitivity of some neurotransmitters circuits including the following systems: dopaminergic, noradrenergic, cholinergic and serotoninergic. Opioids inhibit the activity of the adrenergic neurons in locus coeruleus.

Locus coeruleus (LC) is the most important noradrenergic nucleus in the brain. The activation of this area and the increase of the secondary noradrenergic activity in other areas of the brain and of the marrow would be responsible for the manifestations of the opioid withdrawal.

It is known now that these modifications are partially mediated by an up–regulation of the AMP ways cyclically induced by the chronic exposure to opiacees. So, the chronic administration of opiates increases the level of adenilat–cyclaze and proteinkinaze (PKA) in LC, and the readministration of opioid prevents the development of withdrawal phenomenology because the drug operates on these AMP ways cyclically activated, having as a result a "pseudo normal" activation of the neurons in LC. After the removal of the drug, the presence of opiate is no longer opposed to the hyperactivated AMPc ways, contributing in this way to the "real activation" of the LC neurons during the withdrawal (Nestler 1996).

That is why the preclinic and clinic studies stressed this noradrenergic hyper activity and certain medicine were used in the treatment of withdrawal, decreasing this adrenergic activity. In this respect, Clonidine is efficient in the diminution of certain objective symptoms of withdrawal, but it is not so efficient in the prevention of the objective symptoms accompanying the opioid withdrawal. Clonide operates by stimulating the adrenergic receptors in LC, producing in this way an inhibition of the noradrenaline discharge. It is logic that the vegetative symptoms are highly ameliorated by Clonidine during detoxification.

Recent studies on rats demonstrated that the microinjection with naloxon at LC level on animals dependent on morphine does not provoke the same symptoms as the systemic injection with nalaxone.

It comes out that the LC activity during withdrawal depends on the LC intrinsic factors, namely the increase of the glutaminergic neurotransmission at the level of the marrow nuclei (spinal nuclei) (Akaoka 1991). The factors leading to this activity are unknown for the moment.

The spinal ways are important in the apparition of the withdrawal symptoms, both after the local injection (medular) and the systemic injection with naloxon of the dependent rats.

The central cholinergic neurons mediate many of these symptoms. Further on it will be demonstrated that the muscarinic cholinergic system at the marrow level initiate many of the vegetative and comportamental symptoms of the morphine withdrawal.

Study on the selective antagonists of the muscarinic receptors in the diminution of opioid dependence. Pirenzepine (selective antagonist of M1 receptors) and metoctramine (M2 selective antagonist) were used in intraperitoneal (ip) or intratecal (it) injection. The withdrawal symptoms precipitated by naloxone on the rats dependent on morphine were blocked (cancelled) by metroctamine (ip) or pirenzepine (it). It leads to the conclusion that the M2 muscarininc subtype of peripheral receptors mediate the process of dependence on rats, and the M1 subtype mediates at the level of marrow.

The inactivation of the A proteinkinaze in the marrow during the opioid withdrawal was also studied, reaching the following conclusion:

- the level of noradrenaline in the marrow is low during the naloxone precipitated withdrawal, and the content of cyclic AMP is high under the same conditions;
- the PKA activity at the marrow level is low at the rats dependent on opoids, but is high during the withdrawal precipitated by naloxone (the naloxone is modifying the PKA activity).

Based on the following factors, it is considered that the muscarinic cholinergic neurons seem to influence the withdrawal symptoms:

– the inhibition degree of these symptoms produced by coliculine (an inhibitor of proteinphosphase) was equivalent to that produced by intratecal injection with pirenzepine (antagonist of muscarinic receptors).
– during the withdrawal a high quantity of acetylcholine is released; it activates protein phosphase.

Conclusion: the inactivation of PKA at marrow level mediates the opioid withdrawal.

Holland demonstrated in 1976 and Swain in 1993 that the muscarinic system plays a major role in the mediation of the opioid abstinence syndrome in rats and rhesus monkeys. Their preliminary studies demonstrated that scopolamine, a muscarinic antagonist can not only decrease the antinociceptive tolerance induced by morphine, but also to block the appearance of withdrawal induced by naloxone, facilitating in this way the morphine release (Yang 1994).

The efficiency of scopolamine (gr A) in the heroine detoxification was also studied in comparison with the control group on metadone (gr C) or clonidine (gr.B).

The results of this study demonstrated that number of the withdrawal symptoms was lower in group A than in group B, and the scopolamine detoxifiation was as efficient as the metadone detoxification during the first 5 days of treatment, differences appearing during the next 5 days of study.

The positive tests of urine at the end of the study (after 10 days) were reduced in group A (scopolamine) in comparison with group B (Clonidine), and the acceptance of naloxone in 50 mg dose/per day was higher in group A than in group B. The proportion of those who left the study on different causes was: 2% in group A (scopolamine), 10% in group B (clonidine) and 30% in group C (metadone). The analyze of craving, measured by drug inventory craving points out craving scores reduced in group A than in group B and C at the end of the treatment.

The secondary effects of scopolamine were higher that those of metadone and similar to those of clonidine. These effects are: dryness of the mouth, drowsiness, tachycardia and they are dose dependent.

In conclusion, scopolamine prooved to be as efficient as metadone in heroin detoxification. The abstinence syndrome of different degrees of severity was strongly ameliorated by scopolamine. The most important advantage of scopolamine is represented by its incapacity to induce dependence. So, it can be stated that scopolamine has a curative effect proved in the treatment of opiates dependence.

DIAGNOSIS AND THERAPEUTICS CRITERIA FOR BENZODIAZEPINES DEPENDENCE

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Many cases of high–dose benzodiazepines (B.Z.D.) use are described in substance abuse patients. Typically, these patients present a difficult management picture because of a questionable dose/duration history or mixed anxiolytic/hypnotic abuse.

Drug abuses are common (6% lifetime prevalence in US), often unrecognized, and poorly understood. There is great variability in degree of drug use from patient to patient; multiple drug use is common. Abuse occurs if patient uses drugs in a dangerous, self–defeating, self–destructive way, has difficulty controlling his use even though the use is sporadic, and has impaired social and/or occupational functioning because of that use, all within a 1–year period. Drug dependence requires the presence of tolerance, withdrawal, and/or continuos, compulsive use over a 1–year period. Patients may be classified by the type of drug abused (see below) or by the pattern and reason for abuse. Some recognized patterns of use (abuse) include:

– Recreational use – Patient takes drugs for "fun" and is not physically or psychologically dependent upon them. He may also take them "just to be part of group" or because it is countercultural requirement. This often fades into compulsive use, with time.

– Iatrogenic addiction – Patient addicted "by mistake". Patient (and physician) may not recognize the addiction. Many of these patients are convinced that they must have the drug to function (eg. To sleep, to interact with others) and may go to great lengths to talk their physicians into prescribing medication.

– The chronic drug addict – These patients usually abuse "street" drugs. Many have underlying depressions. Many have antisocial personalities. Some take drugs in a effort to self–medicate a chronic psychiatric disorder (eg, major depression, schizophrenia).

Benzodiazepines abuse

This condition results from the pathological use of more of this class of drugs for more 1 month. These patients frequently can not abstain from use, once started – a psychological addiction. Abuse of sedative–hypnotics is common and, unlike other substances of abuse, there are two distinct populations and patterns of abuse.

1. Males and females in their teens or 20s who obtain these drug illegally and use them (as well as many kinds) for "fun" and to get "high" or to block things out and "get away the hassle".
2. Middle–aged females who are frequently chronically anxious or depressed and who obtain legal prescriptions from (one or more) physicians for complaints of anxiety and insomnia, gradually increase the dosage themselves in a effort to cope, and often become physiologically addicted.

Although these patients are common, they are disproportionately frequently seen by physicians because they ultimately have to "doctor shop" to obtain drugs.

The assessment of liability in humans relies on two predictive models: self administration of B.Z.D. by experimental subjects who have a history of drug abuse and subjective responses that correlate with high abuse potential.

The predictive models in humans clearly establish that B.Z.D. occupy an intermediate position on the spectrum of abuse liability of sedative– hypnotics.

Recent work investigating patient characteristics that influence abuse liability shows that alcoholic persons and their sons. When given a single dose of alprazolam or diazepam have greater increases on abuse potential scales than do nonalcoholic controls without a family history of alcoholism.

Diagnostic criteria for the dependence syndrome: D.S.M. III–R

There are nine symptoms of dependence; not all of them have to be present for dependence diagnosis:

1. The person using a psychoactive (B.Z.D.) substance, noted that he used it in a larger quantity or a larger period than he initially intend.
2. The person admitted his excessive consume, his intention of decrease or control this consume, and his failure in doing that (as long as substance is available). In other cass, the person desire to decrease or control the consume, but he does not really do anything for that.
3. A long period of time is lost to obtain the substance (from a few hours by day till the whole day).
4. The person may have symptoms of intoxication or abstinence when he was to fulfill the obligation that his major role involve them (job, school, home). Sometimes, the person could be intoxicated or abstinent. When is dangerous for his corporal integrity (driving, using equipment).
5. Important social, professional or recreative activities are abandoned or diminished because using substance.
6. Various social, psychological and somatic problems might appear because of excessive and lasting use of the substance. This problems are exacerbate using away the substance. The person keep on using substance although he had one or more of this problems (and he admitted that the use exacerbate them).
7. A significant tolerance and important diminished effect may appear by using the same dose of substance. The person will increase the dose, to obtain the effect he want to.
8. In case of continuous use of B.Z.D., the withdrawal symptoms occur, when the person reduced, or stopped the dosed.
9. After the annoying withdrawal symptoms, the person use substance to relieve or avoid that. That involve to use substance the whole day, sooner after wakening.

Criteria for B.Z.D. dependence: D.S.M.–R.

Easy: A few or even no symptoms besides those who are necessary for diagnosis.
The symptoms determine an easy deterioration of professional activity, usual social activity or relationship.

Moderate: The symptoms causes a functional impaired, between "easy" and "severe"

Severe: More symptoms beside those who are necessary for diagnosis; the symptomatology are seriously interfere with professional and social activity and with relationship.

In partial recovery: during the last six months if was a low consume of substance, the person presenting just a few dependence symptoms.

In complete recovery: during the last six months there is not consume of substance, or exist, but without dependence simptomatology.

Diagnosis criteria for B.Z.D. dependence: D.S.M. IV.

The fourth edition of Diagnostic and Statistical Manual of Mental Disorders (D.S.M. IV.) defines abuses as a "maladaptative pattern of substance use manifested by recurrent and significant adverse consequences related to repeated use".

According to D.S.M.–IV. Substance dependence is "a cluster of cognitive, behavioral and physiological symptoms indicating that the individual continues use of the substance despite significant substance–related problems". There is a pattern of repeated self–administration that usually results in tolerance, withdrawal and compulsive drug–taking behavior. The term "physiological dependence" represents a pathological state brought about by repeated administration of a drug and that leads to the appearance of characteristic and specific group of symptoms, term an "abstinence syndrome" (discontinuance syndrome), when the drug is discontinued or in the case of certain drug significantly reduces.

Signs and symptoms of B.Z.D. discontinuation syndrome

– The following signs and symptoms may be seen when B.Z.D. therapy is discontinued.They reflect the return of the original anxiety symptoms (recurrence), worsening of the original anxiety symptoms (rebound), or emergence of new symptoms(withdrawal).
– Disturbances of mood and cognition: anxiety, apprehension, dysforia, pessimism, irritabilits, obsessive rumination, paranoid ideation, anorexia which has developed gradually over past 24 hours (1–3 days with the longer acting B.Z.D.).
– Disturbances of sleep: insomnia, altered sleep–wake cycle, day time drowness.
– Physical signs and symptoms: tachycardia, elevated blood pressure, hyperreflexia, muscle tension, agitation–motor restlessness, tremor, myoclonus, muscle and joint pain,weakness, nausea and vomiting, coryza, diaphoresis, ataxia, tinnitus, grand mal seizures (typically after 2–5 days), but occasionally status epilepticus, hyperpyrexia, coma.
– Perceptual disturbances: hyperacusis, depersonalization, blurred vision, illusions, hallucinations and formication (sense of insects crawling on the skin).

Diagnosis criteria for B.Z.D. dependence involve at least three of next characteristics (in the same period, for 12 months):

1. Specific withdrawal symptomatology.
2. A significant tolerance: increased doses are necessary (at least more than 50%) to obtain the effect; or a diminished effect as long as the person use the same dose.
3. A persistant desire, or one or more failure in stopping (or control) this abuse.
4. The substance is used often in a larger quantity or a larger period than the person initially intend to.
5. A great part of time is lost for obtain the substance.
6. Important social, profesional, or recreative activities are abandoned or diminished because consume.
7. The person keep using the substance, although he knows having a social, psychological or somatic problems (persistant or reccurent) caused or exacerbated by this use.

Diagnosis criteria for benzodiazepines dependence: I.C.D. 10

F.13. Mental and behavioral disorders caused by sedatives and hypnotics.

Dependence syndrome (F.1x2): represents a group of physiologic, behavioral and cognitive phenomenons in which the use of a class of substances gets a higher priority for a person, compared with another behaviors that was more important before.

The essential feature of dependence syndrome is desire (intense often, irresistible sometimes) for consume a drug (that can have or have not medical prescription).

It has been proved that the reuse of a substance after an abstinence period caused a quickly reappearance of another manifestation of the syndrome that appear to non–dependence persons.

Diagnosis criteria:

A certain diagnosis of dependence can established just if three (or more) of next characteristics has been treated or noticed to a patient for a period, in the previous year:

a. An intense or compulsive desire to use the substance.
b. Difficulties in the control of the behavior relating to the consume, the consumed quantity.
c. The withdrawal psychological state (when the consume of the substance is decreased or stopped), or the use of the same substance (or similar) for avoiding withdrawal symptoms.
d. The presence of the tolerance, so that are necessary increased doses of substance for obtain the same effect that the lower doses initially produce.
e. Markedly diminished interests or pleasure in the consumes favour, for obtain and administration the substance, or for recover the effects of the substance.
f. Persistent use of substance, despite of negative effects like: depression caused by the high ingestion of drug, cognitive alteration; we have to know if patient realised the nature and noxiousness of consume.

The dependence syndrome may be for a specific substance (e.g. diazepam), or for a class of substances (e.g. B.Z.D.).

The diagnosis of the dependence syndrome might be detail by using the second character of code:

F.1x.20: Abstinent in present.
F.1x.21: Abstinent in present, but in a protected medium (hospital, prison, therapeutic community).
F.1x.22: In present: in continuously clinical supervise– or substitute regimen (controlled dependence).
F.1x.23: Abstinent in present but treated with adversive or blocking drugs.
F.1x.24: Using substances in present (active dependence).
F.1x.25: Continuously using.
F.1x.26: Periodic using.

The withdrawal syndrome

Represents all symptoms (grouped in classes of variable severity) that occur after a relative or absolute interruption of a psycho–active substance consume, after a repeated and prolonged consume and/or in high doses of substance (e.g. B.Z.D.), depending by type of B.Z.D. and doses/day.

Withdrawal syndrome is one of the indicators of dependence syndrome. The usual characteristics of the withdrawal at B.Z.D. are: anxiety, depression, sleep disorder. Typical, the patient tell the symptoms of withdrawal are removed by ingestion of substance.

Therapeutics criteria for benzodiazepines dependence

Withdrawal syndromes that occur with discontinuation of B.Z.D. require pharmacologic management for patient comfort and sometimes, for prevention of potentially serious medical consequences. These symptoms have been described for older anxiolytic/ hypnotics.

Several clinical scenarios requiring management of B.Z.D. withdrawal exist. These include the substance abuse patient without a primary psychiatric illness using high doses of a single B.Z.D. or multiple anxiolytic/hypnotics and the generalized anxiety or panic disorder patient receiving therapeutic or high doses of a B.Z.D. Different strategies are necessary to manage these clinical situations.

Low–dose withdrawal and rebound symptoms:presentation:

Symptoms associated with low–dose withdrawal include: nausea, vomiting, irritability, tremor, incoordination, insomnia, restlessness, blurred vision, sweating, anorexia, and/or weakness as well as anxiety. Depersonalisation, heightened perception, especially to light and sound, and illusions are also commonly reported. Many of these symptoms have also been reported in unmedicated anxiety patients.

Tolerance test

There are several methods of determining the degree of dependence (and thus the probable severity and length of withdrawal). One method is given below. It can be used regardless of the particular sedative–hypnotic drug of abuse.

1. Hospitalize the patient for the test possible.
2. Administer test to patient who is comfortable or only mildly anxious (not to patient who is intoxicated or presently withdrawing– test would be invalid).
3. Give 200 mg. Pentobarbital orally.
4. At 1 hour, evaluate the patient. If he is:
   a. asleep but arousable–patient has no tolerance.
   b. Grossly ataxic, coarse tremor, and nystagmus–daily tolerance is 400–500 mg. of pentobarbital.
   c. Mildly ataxic, mild nystagmus–daily tolerance is 800 mg.
   d. Asymptomatic or has continuing signs of mild withdrawal–daily tolerance is 1000mg., or more. Wait 3–4 hours, then give an oral dose of 300 mg. of pentobarbital. Failure to become symptomatic at this larger dose suggests a daily tolerance of more than 1600mg.

Guidelines for treatment of benzodiazepines discontinuance syndrome

1. Evaluate and treat concomitant medical psychiatric conditions.
2. Obtain drug history and urine and blood sample for drug and ethanol assay.
3. Determine required of B.Z.D. for stabilization, as guided history, clinical presentation, drug–ethanol assay, and in some cases, challenge dose.
4. Detoxification from supratherapeutic doses: hospitalize, reduce dosage further by 10 to 25% every few days if tolerated, use adjunctive medication if necessary (carbamazepine, clonidine, and sedative antidepressants).
5. Detoxification from therapeutic doses: initiate 10 to 25% percent dose reduction and evaluate response, psychological intervention, most patient taking therapeutic doses will have uncomplicated discontinuation.

Benzodiazepine withdrawal schedule rating scale

For each of the following items must circle the numbers which best described the everity of each symptoms or sign.

1. Observe behavior for restlessness and agitation.
   0=none; 1=normal activity; 2=restless; 3=moderate; 4=paces back & forth, unable to sit still
2. Ask patient to extend arms with fingers apart, observe tremor:
   0=no tremor; 1=not visible, can be felt in fingers; 3=moderate with arms extended; 4=severe, with arms not extended.
3. Observe for sweating, feel palms
   0=no tremor; 1=not visible, can be felt in fingers; 2=visible but mild; 3=moderate with arms extended; 4=severe, with arms not extended.

   For each of following items, must estimated by number the severity of the problem based on scale below
4. Do you feel irritable?
   0=not at all. 1. 2. 3. 4=very much so.
5. Do you feel fatigued?
   0=not at all. 1. 2. 3. 4=very much so
6. Do you feel tense?
   0=not at all. 1. 2. 3. 4=very much so.
7. Do you feel you have difficulties concentrating?
   0=no difficulty. 1. 2. 3. 4=unable to concentrate.
8. Do you have loss of appetite?
   0=no loss. 1. 2. 3. 4=no appetite, unable to eat.
9. Have you any numbness or burning sensation on your face, hands or feet?
   0=no numbness. 1. 2. 3. 4=intense burning or numbness.
10. Do you feel your heart racing (palpitations)?
    0=not at all. 1. 2. 3. 4=constant racing.
11. Does you head feel full or achy?
    0=not at all. 1. 2. 3. 4=severe headache.
12. Do you feel muscle aches or stiffness?
    0=not at all. 1. 2. 3. 4=severe stiffness or pain.
13. Do you feel anxious, nervous, or jittery?
    0=not at all. 1. 2. 3. 4=very much so.
14. Do you feel upset?
    0=not at all. 1. 2. 3. 4=very much so.
15. How restful was your sleep last night?
    0=very restful. 1. 2. 3. 4=not at all.
16. Do you feel weak?
    0=not at all. 1. 2. 3. 4=very much so.
17. Do you think you had enough sleep last night?
    0=yes, very much. 1. 2. 3. 4=not at all.
18. Are you fearful?
    0=not at all. 1. 2. 3. 4=very much so.
19. Do you have any disturbances (sensitivity to light, blurred vision)?
    0=not at all. 1. 2. 3. 4=very sensitive to light, blurred vision.
20. Have you been worrying about possible misfortunes lately?
    0=not at all. 1. 2. 3. 4=very much so.
21. How many hours of sleep do you think you had last night?
22. How many minutes do you think it took you to fall asleep last night?

Rickels (1990) contrasted the effect of abrupt discontinuation of therapeutic doses of short half–life (SHL) B.Z.D s to long half–life (LHL) B.Z.D. B.Z.D. intake was three weeks prior to randomization to either the placebo substitution group or the B.Z.D. continuation control group. It was discovered that the only difference between the SHL B.Z.D. s (lorazepam and alprazolam) and the LHL B.Z.D. s (diazepam and clorazepate) was that the adrenergic symptom cluster (nervousness, agitation, nausea, diaphoresis) was demonstrated greater severity for SHL B.Z.D. Severity of withdrawal was also related to higher B.Z.D. doses, neuroticism and dependency personality traits, less education, and more anxiety and depressive symptoms.

It is recommended patients who have received manufacturer–recommended doses of B.Z.D. on a daily basis for greater than one month should not have the drug abruptly discontinued. Because severe withdrawal symptoms are not expected, gradual tapering of B.Z.D. on an outpatient basis should be attempted.

If the patient is receiving a long–acting B.Z.D., the patient can remain on the originally prescribed drug. The weekly rate is determined by dividing the total daily dose of B.Z.D. by five and rounding the number to a dose attainable with available dosage forms. Each week the dose would be reduced by the tapering dose calculated above.

If the patient is receiving a short– acting B.Z.D. consideration is given to slowly tapering

The dose with the prescribed B.Z.D. using a similar schedule described above for long–acting B.Z.D. s or substituting a cross–tolerant, long–acting B.Z.D. The rationale for the substitution method is the observation of less severe withdrawal symptoms with long–acting compounds. Though, theoretically, any long–acting B.Z.D. could be used, diazepam has been the most reported to be useful.

Non–benzodiazepine Management. Non–B.Z.D. agents have been suggested for management of B.Z.D. withdrawal. The rationale stems from the desire to remove the patient from the reinforcing pharmacologic effects of B.Z.D. Two– weeks of propranolol, in doses of 60–120 mg./day, reduced the severity, but not the incidence of withdrawal symptoms in one study.

Clonidine, an a 2–adrenergic agonist, 0,3 to 0,6 mg./day, po. For up to 3 months has been atilized to treat several cases of low–dose B.Z.D. withdrawal with mixed results.

Carbamazepine has been reported to be of value as an adjunctive agent in B.Z.D. withdrawal in both an report and an open study. Schweizer evaluated the effect of carbamazepine on B.Z.D. low dose (15–25 mg./day or equivalent) withdrawal severity and outcome in controlled trial of 40 patients who had a history of difficulty discontinuing long–term use of the drugs. There was only a trend to suggest that the carbamazepine reduced the severity of withdrawal symptoms. The authors concluded that crbamazepine was most useful in facilitating the withdrawal process taking more than 20 mg./day of diazepam because this group had such a poor outcome on follow–up.

Antidepressants as an adjunct treatment in management of B.Z.D. withdrawal desrves further research. Several patients were successfully withdrawn from a B.Z.D. while receiving only antidepressants. Both tricyclic antidepressant (TCA) and monoamine oxidase inhibitors (MAOI) are effective antipanic drugs. Studies suggests TCA and MAOI can be as useful in treating generalized anxiety disorder as B.Z.D.

In conclusion, while identification and treatment of the dependent person are necessary in order to avoid symptomatic withdrawal, the patient may be unable or unwilling to give an accurate account of drug intake. Also mixed anxiolytic/hypnotic abuse would indicate tolerance testing to determine a tolerant B.Z.D. dose.

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THE BENZODIAZEPINE AND THE IATROGENIC–INDUCED DEPENDENCE RISK

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Medicine, the oldest science in the World, was born together with the man. Nevertheless in the animals kingdom me can notice a therapeutic activity (wounds deaning, herbs feeding of sick individuals) so that we can state that medicine appeared previously to the birth of the human being. Unlike the other living creatures, in which the curing is instinctive, in the man (rationale being), this is conscious and motivated by the pain and the threatening death. Although the human being is enough strong and immune in the fight for survive, he has been the target of the diseases since the ancient times, because of the difficult condition of life. This is the origin for the focus on psyche–specific diseases drugs.

The psychotropic substances appeared mast of then near the half of the XX century. If we are talking about the anxiolytics, the first drug was Meprobamate – which was synthesized in 1951 by Ludwig and Piech. Later the weapons increased strongly in number through the benzodiazepines.

Until the 1960 the anxiety disorders and the insomnia were approached onlu the barbiturates. The benzodiazepines discover gave the occasion for the replacement of the first products in the therapy of the majority of the sleep disorders, the anxiety, epilepsy, muscular spasm etc. This was possible because the barbiturates gave rise to intoxication's, dependence and withdrawal syndromes.

Although the benzodiazepines are commonly called "anxiolytics", their action in much more complex. Blaha and Brukmann (1983) prefer to talk about the antinociceptive (protective) effect of the tranquilizers. This action has three aspects: the psychovegetative balance, the protection of the sleep and the mood mitigation–trough the management of the anxiety. The anxiolytics, administration leads to a favorable subjective state, a state of quiet and sometimes even to a little elation. Under such circumstances the patient will look again for the some state giving rise to the dependence with a great psychological contribution the physician.

When using the tranquilizers must be very cautious considering Tue aspects:

I. Pharmacodynamics

II. Clinical aspect

I. The Pharmacodynamical Side

This is a physiological, biochemical, chemical or physical phenomenon which results from the contact of the drug with the organism (the reactive substrate). At last, this action is the positive – change (stimulation) or negative – change (inhibition) of certain physiological functions and/or

the diminishing of some disorders of these funtions. The drugs don't create new functions in the organism but they only accelerate or brake the processes of physiological regulation.

For a certain pharmacodynamic action we can describe several aspects:
– the direction – stimulation/inhibition;
– the speed of the effects (the latency period) which dependes on – the way of administration; the structure;
– the intensity of the pharmacodynamical action which is related to the – substance – receptor bind; intrinsec activity of the organism;
– the time of the effects;
– the place of action of the drugs;
– the mechanism of action.

These pharmacodynamical aspects have to be known by the physicians when they make medical prescriptions.

II. The Clinical Side

When giving tranquilizers we have to bear in mind the conditions which demand the necessity of these drugs. The anxiety is a mood which has several and different aspects:

1. The first kind of this state is the psychological one response with a normal motivation in a certain situation. Here we have in mind the fear, the restlessness or, generally speaking, the specific human suffering whose appearance, although unwashed, is adequate and common. The abandonment of the congruence between the state and the context with a switch to a false spiritual life, to a drug–induced "cloudless" condition can represent sometimes a runaway from the individual responsibility and from the "dignified bearing" of the normal human confricts. (Predescu, 1968)

This physiological anxiety is short, slow with rapid onset and finish and it doesn't interfere with the psychic balance. It has no negative influence on the familial or socio–professional activities. The psychic tension has a well–known stimulating role when a certain problem must be solved. These phenomena are particular and normal for every personality.

2. The pathological anxiety is the condition when we meet a diminish of the coping individual capacity. This type of anxiety de regulates the optimal functioning of intra–psychical processes and it interferes negatively with the familial, social and professional adaptabily. The pathological anxiety has a sudden onset and finish but it asks the therapy with tranquilizers because of the intense, hardly beaved and unpleasant fear with leads to the panic attack, irritability, autonomous symptoms (elevation of blood pressure, tachycardia, tachypneea, gastro–intestinal troubles). In our country, the morbidity through anxiety is 15–200% of the whole population.

Consequently, the clinical assessment of each case is very important in practice.

The tranquilizers are the most used drugs in unpsychotic disorders and outside hospitals. They prepare the way for psychotherapy, they prevent the chronicization and even the change of the functional disorders in organic diseases, they diminish the anxiety and the pathological intra–psychic tension and can be used in connection with other drugs.

In the non–psychiatric medical practice, the tranquilizers are the mast frequently prescribed withered succeeding in breaking the vicious pathological circle of most of the "psychosomatic" diseases. Although the benzodiazepines are called minor tranquilizers, they have in the some time hypnotic–like properties, too. Besides the tranquilizing action this group of drugs facilitates the sleep–industion, they have anti–emetic, anticonvulsivant, mio–relaxing, antihistaminic and antiparkinsonic effects as well as the potentization of the action of other nervous depressants.

The individual tolerance is generally good, but in elders, in liver, kidney problems, `n myasthenia gravis, in glaucoma, in barbiturates intoxication's etc., we have to be cautious.

Table no. 1 Selective indication of the benzodiazepines

Indications for the therapy in hospitals (preferences)

a. Anxiety in certain depression (with the anti–depressants);
b. Delirium tremens (only in the acute therapy);
c. Psychomotor restlessness;
d. Hallucinogenic – induced disorders, some withdrawal syndromes;
e. Sleep–disorders;
f. Pre–medication in anesthesiology;
g. Tetanus;
h. Status epileptics;
e. Some forms of seizures;
j. Non–epileptic convulsion (fever, eclampsy)

Indications for the therapy outside hospitals:

a. Falling asleep disorders;
b. Muscular spasms (central and rheumatism originated);
c. Some forms of seizures (generally associated with the classical anti–convulsivant).

Both the physicians and the drug–abusers consider that the benzodiazepines would not have tolerance and/or withdrawal phenomena which is not true.

The main risk is the self–administration of these drugs and this is dangerous for the mental and physical health of the population. It can lead to severe accidents: suicidal attempts or, when over–taking the term of use, unpredictable health problems, with fatal end.

Consequently we have to waje a very precise estimation of the anxiety when prescription the benzodiazepines are not necessary leaving the possibility for the organism to adapt itself or we can approach the problem by psychotherapy.

In the case of the phatological anxiety, the anxiolytics must be given after a separation of the free anxiety, whish can't be related to a certain trigger–factor, and the situational anxiety, caused by a stress. In the last case we have to distinguish: first the acute from, whish includes the traumatic anxiety (e.g. after a traffic injury) and the phobias anxiety or the panic attack anxiety; second, the chronic from whish is generalized, has a longer duration and we can native physical and somatic symptoms which are common to the other types of anxiety.

The type of personality must also be considered in prescribing the benzodiazepines. Her, some authors described a neurotic, "toxico–manic" structure which can be met frequently in two types of patients:

– the impulsive, in which the toxicomanic tendencies have no control and which rorrespond to the psychiatric notion of "psychopathies";
– the compulsives, which fight for their drives control and which are self–guilting for their repeated failure, belonging to the neurotic type.

With other words, after clinical observation, one could notice that the extraverted and physically–active persons responded little to the anxidytics because these drugs depressed their dynamics. We can meet a better response to the anxiolytics in the introvertited person. We have to understand the detached attitude of certain physician which consider the anxiolytic as a "placebo" for the anxiety.

When over–taking the therapeutic doses, the use of the benzodiazepines can lead to the anxiolytic–interaction syndrome; here one can speak about the benzodiaspeine–drunkeness, which appears in the case of short–action drugs. After on over–dose of short–action benzodiazepines–usually above 20/50 therapeutic doses, the intoxication leads to come.

The long–term abuse of benzodiazepines can produce the augmentation of the tolerance for the ingested substance. When the administration is suddenly interrupted we can notice the withdrawal syndrome. Most of such cases appear for: Diazepam, Larozepam, Temazepam, Alprazolam, Nitrazepam.

Concerning the benzodiazepines withdrawal syndrome, several authors performed researches taking in attentions different drugs like: Clordiasepaxide (Librium), (L.E. Hollister and colab., 1961), Diazepam, Lorazepam, Temazepam, Alprazilam (Goodman and Gilmore, 1975, K. Rikels, 1981, J. Marks, 1978).

Based on the similitude between the alcohol, the barbiturates and the benzodiazepines withdrawal syndromes, most of the authors made a description of the psychiatric symptoms which can appear generally in this type of disorder. The following are possible:

– confusional psychosyndromes;
– mood disorders – elation, disphoria;
– delusional disorders (short episodes);
– anxious–neurotic–like syndromes;
– personality disorders induces by the metabolic changes after the chronic abuse of the benzodiazepines;
– suicide.

Clinical aspects of the withdrawal for:

Alcohol	**Barbiturates**	**Benzodiazepines**
Anxiety	Anxiety	Anxiety
Restlessness	Restlessness	Restlessness
Agitation	Agitation	Agitation
Depression	Depression	
Faintness	Faintness	Faintness
Itch	Disorientation	Memory impairment
Confusion	Confusion	Depersonalization
Hyperreflectivity	Hyperreflectivity	Derealization
Insomnia	Insomnia	Insomnia
Anorexia	Anorexia	Anorexia
Nausea	Nausea	Nausea
Vomiting	Vomiting	Vomiting
Perspiration	Perspiration	Perspiration
Trembling	Trembling	Trembling
Dizziness	Dizziness	Dizziness
Headache	Headache	Headache
Talkativeness	Talkativeness	Talkativeness
Muscle pains	Muscle pains	Muscle pains
Fever	Fever .	Numbness
	Paraesthesia	
	Photophobia	
Perception	Perception	Perception
Impairment	Impairment	Impairment
Visual	Visual	Hyperaudition
Auditive	Hyperaudition	Tactile
Tactile	Olphactive	
Delusions	Delusions	Delusions
Visual	Visual	Visual
Auditive	Auditive	Auditive
Tachycardin	Seizure	Paranoia
Palpitation	Incoordination	
Nistagmes	Symptoms of false influenza	
	Seizure	
	Seizures	

The authors were motivated in the choice of the field by the observation of the huge importance of the stress in nowadays life and of the intensity reached by the anxiety following this stress. This abuse is met very frequently in our country, too, with the some motivation.

Several statistical studies were performed in different countries referring to the benzodiazepines abuse. Here are some of them: it is estimated that in the last 30 years the benzodiazepines has the first world place as medical prescriptions and use; more that 500 million people received a people received a therapy with benzodiazepines.

The ratio female/male in using benzodiazepines is 1/3. In the United Kingdom, between 1985 and 1992 a quarter of a million people took such drugs at last one year. In Australia the abuse of benzodiazepine is on the third place after the use of alcohol and cannabis.

Consequently for a correct prescription of benzodiazepines and for a favorable response, some authors tried to delineate several condition needed to be respected which depend on the physician attitude, the patient personality traits, the social traits etc.

In the following table we can see all these aspects (Richels, 1983).

The predictions of the favorable response in the benzodiazepine therapy (after Rickels, 1983)

a. The physician qualities:
- relational warm;
- favorable perception of the patient (and not as a "difficult patient");
- positive attitude;
- favorable opinion concerning the outcome.

b. The patients personality characteristics:
- verbal intelligence;
- therapy compliance;
- realistic expectations regarding the therapy;
- the strength of the Ego;
- low verbal hostility.

c. Nevrotic psychopathology:
- high somatization;
- high anxiety;
- low depression;
- mild obsessions and compulsions;
- low interpersonal sensitivity.

d. Social traits:
- education;
- high occupational level;
- high socio–economic status;
- good marital stability.

e. Orientation concerning the therapy:
- understand of the psychogenic causality;
- waiting of a medical prescription.

f. Previous therapy characteristics:
- less chromic disorder less approached previously;
- superior response at the previous psychiatric drugs therapy;
- trigger–stress.

We consider it is necessary to formulate some statements regarding the benzodiazepine prescription in order to avoid the iatrogenic risk. We think it is important to be very cautions in pre-

scribing these drugs on long periods–only in very justified situations, in patients with no toxicomanic history. When the patients augment the doses as their own chaise, it is better to interrupt the therapy. Ward (1980) underlines that the psychologic dependence on benzodiazepines is not due to an inner "dependence capacity" of these drugs but, rather, because of the individual sensitivity and the environment conditions.

On the other side, it is very the that, after Morrison, 1974 (quoted by Ward, 1980), "there is nothing really in the useless human suffering". So the benzodiazepines prescriptions problem and the anxiolyse problem generally can be reduced to a precise definition of the pathologic anxiety – which requests the therapy with these drugs.

BENZODIAZEPINE DEPENDENCE

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Introduction

Anxiety states and sleep disorders are common problems and sedative–hypnotic drugs are among the most widely prescribed worldwide. The benzodiazepines have been used with a high frequency as anxiolytics and hypnotics for more than 30 years (2,18,21). After their introduction into clinical practice, in the early 1960`s, it soon became clear that an overdose of these compounds is safer and less likely to be abused in comparison with barbiturates. Step by step, BDZ replaced barbiturates in many cases of anxiety, insomnia, mild depression, other forms of unhappiness, alcohol withdrawal and various psychosomatic complaints (5,14,17). BDZ are of great interest and there are many reasons for anymore to believe this, mentioning only that: they are the most widely prescribed psychotropic drugs and their chronic use is expensive enough, it should sufficient for being attentive to this group of drugs. Shortly after their introduction, chronic treatment was shown to result in the induction of dependence. This is because it is difficult for people who have been taking BDZ for more than several months to stop taking them. There is a great number of BDZ, some of them are suggested to have a greater potential of dependence than others. However, even in the beginning, evidence of withdrawal problems was appearing. The dependence is both physical and psychological. There are studies and case reports on physical dependence on BDZ that indicate it to occur even at therapeutic doses and even a few hours after a single dose (8,22) in several species (rat, cat, dog, baboon). The idea that therapeutic doses might similarly produced withdrawal problems conduced to more complex studies in humans (17).

Tolerance, dependence, withdrawal

Tolerance – decreased responsiveness to a drug following repeated exposure – is a common feature of sedatives and hypnotics use. It may result in an increase in the dose needed to maintain symptomatic improvement or to promote sleep (11). Tolerance to the effects of a drug may be classified in two types: metabolic and functional tolerance (21).

Metabolic tolerance

In this type of tolerance, because of its pharmacokinetic changes, a drug tends to have different effects depending on its long or short term of administration. As an example, it can be describe enzyme induction. When a drug is administered in a continued mode, the production of liver enzymes is stimulated and these enzymes metabolize the drug. The drug is metabolized more rapidly with the rise in the amount of enzymes, so, for the same effect, a higher dose of drug has to be administered. There are no evident data that BDZ are associated with metabolic tolerance (13).

Functional tolerance

In the case of BDZ the development of tolerance is associated in animals with down–regulation of the brain BDZ receptors. With long term usage, a drug modifies the threshold of organ system affected by its administration (8,14). These changes include alterations in the sensitivity of receptors and even modifications of target tissues themselves. As an important aspect of functional tolerance the withdrawal of a drug lies in a temporary increase in the sensitivity of the organ system concerned before return to normal function (4). Even in the situation of the maintenance of equivalent blood and tissue concentrations, behavioural tolerance means the lessened effects of a drug on behaviour after long term administration. Tolerance is evident for anticonvulsant and sedative effects but is less clear whether tolerance develops for hypnotic and anxyolitic effects (11). Tolerance in the case of BDZ is less marked than it is with barbiturates and other sedative hypnotics drugs.

Dependence

For maintaining the pharmacological drug `s effect, classical tolerance is normally followed by escalation in dosage. This escalation in dosage may be inferred from clinical observation with dependence. Dependence is the imperious need to continue the intake of a drug. Dependence may be psychological and for physical and sometimes separating these may be difficult (8,11,17)

Speaking about BDZ, in the case of this group of drugs, both types of dependence co–exist. The psychological component may be initially a simple neurotic behaviour difficult to differentiate from those of old coffee–drinkers or cigarette smokers. When the use of BDZ becomes compulsive, more serious complications develop, including physiologic dependence and tolerance. Physiologic (physical) dependence can be defined as an altered physiologic state that requires a continuous administration of a BDZ to prevent the appearance of an abstinence or a withdrawal syndrome. There are two major types of physical dependence: a high–dose one, the dependence of barbiturate type and a low dose dependence that may occur with therapeutic doses (17).

Withdrawal

Withdrawal is a state of altered function due to cessation of drug administration, a result of tolerance and/or dependence development. The abstinence syndrome often leads to chronic use, as patients are unable to resist at the unpleasant manifestations of BZD withdrawal.

Withdrawal of BDZ, appeared after cessation of treatment and after reductions of doses and is characterized by a variety of signs and symptoms. Some of them are typical of anxiety, but the others appear to be characteristic for BDZ withdrawal (ataxia, transient psychotic state, epileptic seizures, increased sexual arousal). The severity of withdrawal symptoms differs between different BDZ and depends also on the magnitude of the dose used immediately prior to cessation of administration. In the case of high doses of BDZ, the abrupt cessation leads to serious withdrawal signs. Differences in the severity of abstinence symptoms between different BDZ relate to half–life of the drug: when this parameter is long the drug is eliminated slowly; the result is a gradual withdrawal with few physical symptoms. The intake of drugs with very short half–lives (mainly for hypnotic effect) may produce an abstinence syndrome even between doses (8,11,17,19,22).

The signs and symptoms of withdrawal at BDZ differ with the reactivity of patients too; current studies suggest that 20–25% (some data indicate up to 50%) of patients are at risk of having significant sensitivity to the withdrawal of BDZ (8,10). Abuse and physiologic dependence occurring with BDZ are probably less frequent than with barbiturates, the BDZ withdrawal consists of a multitude of signs and symptoms; (craving, aggressive feelings, depression, hallucinations, paranoid ideas, poor sleep, restlessness, seizures, confusional state, abnormal taste, nausea, gastrointestinal cramps, muscle pains, flu–like symptoms) (8,11) .

It is clear that the abruptness of onset of withdrawal syndromes as well as their sevetity is a function of the half life of the drug. Those with half lives between 8 and 24 hours produce a rapidly evolving and severe abstinence syndrome. BDZ with longer half–lives (48–96 hours) produce a slower withdrawal, which is less severe but longer in duration. If the half–life is longer than 96 hours it usually appears a built–in tapering – of action that reduces the possibility of withdrawal reactions. BDZ with very short half–life (24 hours) generally cannot be taken frequently enough to obtain high plasmatic concentrations, so they are less frequently associated with abstinence manifestations (13,21).

There are individual differences among abstinence syndrome between different people as well between different BDZ, as mentioned before (10,17).

Dependence mechanisms

Mechanisms of BDZ tolerance, dependence and withdrawal are incompletely understood. The differential rate of tolerance development indicates that, in the appearance of this phenomenon, different mechanisms are implicated (including increased noradrenergic function) (7,11). In the humans the chronic administration of BDZ does not modify the number of BDZ receptors or their affinity (only at a toxic level). It has been recently demonstrated that the efficacy alteration in the BDZ/$GABA_A$ receptor complex may underlay tolerance and withdrawal (1,9,12,16). In low or therapeutic doses and even a few hours after a single dose, some of BDZ are able to produce functional shift (withdrawal shift) of BDZ receptors toward the inverse–agonist binding conformation. At the level of $GABA_A$ receptors, the actions of GABA and muscimol is greatly reduced. A discontinuity in the BDZ intake allows endogenous inverse agonists to interact with the hypersensitive receptors (14). Inverse agonists (beta–carbolines, endozepines) act as negative allosteric modulators of GABA receptor function (3,20). Their interaction with BDZ receptors can produce anxiety and seizures.

Prevention and treatment of BDZ dependence

For avoiding withdrawal syndrome at BDZ, the usual method is the intermittent administration of a long half–life BDZ for periods no longer than 4 weeks and the gradual reduction of doses. A special care needs to be taken in these patients who have already been addicted to other agents (e.g. alcohol,opiates). In this situation, the dosage should be steadily scaled down to avoid substituting one kind of dependence for another. The result of this using is more selective administration of BDZ and, further more, an important reduction in a total dose of medication.

Another serious problem is the reducing of BDZ dosage in those who have been taking them for longer than 4 months (6). In this case, the pharmacological dependence should be considered. The methods that can be carried out are: gradual reduction of doses; substitution of BDZ with non–addictive drugs; simultaneous reduction of doses and introduction of non–pharmacological treatments of anxiety. These methods mentioned before should be chosen after a detailed analysis of the particularities of the used BDZ and of the reactivity of those who was taken the drugs (10,17,19).

A very important issue is to find some compounds that are able to alleviate or suppress BDZ withdrawal. There are observations concerning the possible efficacy of $alfa_2$ agonists, carba-

mazepine, centrally–acting beta–blockers and $5HT_3$ antagonists in this situation (13,15). The results do not indicate one of them to be particularly effective.

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NICOTINISM BETWEEN TOXITUDE AND TOXICOMANIA

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The use of tobacco, widely practiced (inhaled, chewed, snuffed) is differently perceived and considered – from the socially allowed habit, outside addiction (toxitude) to the voluntary chronic intoxication, by means of smoking, extremely harmful for the individual and the rest of the society (toxicomania).

The noxiousness of the nicotine, a weak base, among other 200 alkaloids of tobacco, very fast absorbed by membranes because of its lipophilia, emphasized for over a century (according to J.N. Langley & W.L. Dickinson, 1890), is the subject matter of a great interest and at the same time controversy. If in the 4th decade of the 20th century (according to 1) Ch. Laubry accused it of coronarian pathology, at the same period, Tassinari praised it for antimicrobial qualities, and Ch. Richet (Nobel prize for medicine in 1913 and author of "Treatise on Metapsychics" – 1922) – addicted to the substance–denied any harmful character, while another famous smoker, S. Freud, scotomized the object of the addiction.

After the first world war, consecutivily with the cigarette smoking pandemizing, the issue evolved to such extent that could not be oculted anymore.

Appetence and dependence

Each of the nine categories of substances included in the WHO classification (acc. 9) concerning drugs, encourages preoccupation with appetence, tolerance and dependence. It seems that the arguments of the theory centres on indivdual, thesis which regards addicton as a real behaviour pathology following the interaction between a vulnerable phenotype and a toxic substance prevailed in the dispute with the exogenous theory focussed on the substance. The biological characterstics of some subjects would be accountable for a "pathological" response to the drug, which would support the transition from a "non–pathological" utilization to the genuine toxicomania. Non– smokers, particularly those who had never smoked, seem to have a different physical build compared to smokers, concerning the nicotine cholinergic receptors; they would not become smokers as they would not respond appetently to nicotine (acc. 6).

The probability that a substance determins the setting up of psychic and physical subjection to the drug depends on the lapse of time between administration and central stimulation. Nicotinism by smoking is the most addictive because nicotine is thus absorbed faster in the pulmonary circulatory system (4).

As the first administrations are not under the sway of the addiction compulsion, and during the toxitude state the consequence on psychism and on social relationships are not dramatic, society considers smokers rather as wrongdoers than as sick people. However, the coordinates undergo

considerable changes after the exercise chronisizing, daily dose increase and somatical determnation occurrence.

If psychoanalysis perceives behind the drug need, the search of subordination, an effect of desire, a self erotic and masochistic behaviour and some clinicians (Rado & Rosenfeld cited by (8) bring toxicomania closer to the manic–depressive disorders, the biological pattern in psychiatry increasingly relevantly to areas,circuits and neuromediation.

Addiction equalizes "another state" of the organism, a biocomportamental disorders, affecting both the brain (acc. Volkow, who in "addiction cerebral areas" mentions changes of the metabolic activity and of receptor density) and the critic behaviour and the social context. Conditioning plays an important part in addiction, as the use circumstances strenghtens the dependences. Nicotine self–administration by smoking also allows self–titration as the smoker is able to control his dose by means of inhaling number, volume, length and depth (4); the dilution of the smoke inspired from the ambient proves to be of great importance, too.

The substances sensible to addiction increas the production or prevent the degradation of cerebral dopamine. According to J.P. Changeux, an acetyl–cholinic receptor subunit (beta–2) is incriminated in nicotine dependence when nicotine is fixed on these receptors, a stimulation of dopamine release occurs. Although they are only 0,3% of the brain cells, the dopaminergic neurons take part in every dependence behaviour, of some interest bring "the satsfaction areas" (nucleus accumbens with afferences and efferences which involves the ventral tegmental area and the frontal cortex (acc. 4).

Cocaine supresses dopamine reception, increasing the quantity available at synapse level; alcohol and amphetamine increase dopamine secretion ("mood barometer").

Nicotine would do the same besides, another substance in tobacco smoke would affect the monoaminoxidase which degrades the recaptured dopamine. The complexity of the nicotine effect on neurotransmitters is also pointed out by the number and variety of nicotine cholinergic receptors, the interest in mood and cognitve performances during nicotine abstinence being worth mentioning (4) .

Vulnerability and compensatory exercise

The reactivity type at stressful stuations may be the estimation behaviour criterion of drug vulnerability. The indivdual with ample reactions, "high responders" (HR) would express the existence of a susceptible biological substrate (6): a neuronal system whose drug dopaminergic activation determines toxicomanogene properties and a hormonal system in which the glucochorticoids – dopaminergically favourizing – modulate in their turn the cerebral activity. The opposite category – "low responders" (LR), with a stress reduced reaction, would have an increased resistence to addiction.

HR subjects are closer to those with behaviour features grouped under TABP acronyme (Type A Behaviour Pattern–extremely talkative, with a high intensty and tonalty voice, wide gestures, ignoring interruptions and demonstrating a tendency to interrupt his collocutor– as the authors Rosenman & Friedman described), affiliation which would double the risk of cardiovascular accident, regardless the traditional risk factors. Among the coronarian cases we have studied, A type features could be seen at 73% of men and 53% of women, thus emphasizing the contribution of the essential character depending on sex psychology and endocrine constellation.

C. Durand's "compulsive" drug addicts would correspond to the neurotic group, while the "impulsive" ones would stand for the disarmonic ones –transgressive and looking for risk; in literature interesting is the registering (proved by images) according to which the impulssive addiction may correspond to orbito–frontal cortex and right striatum activity– cerebral areas affected in compulsive disorders (11).

Dopaminergic stimulative and inhibitory effects MAO (MAO–A and MAO–B) determined by nicotinism (3,4) are in accordance with J. Bergeret's conclusion, which points out the depression

importance in addiction development. The decreasing of cognitive performances during abstinence would be due both nicotinemia reduction and withdrawal phenomena.

Many reports certify the significantly negative relationship between Alzheimer and smoking. According with the nicotine receptor reduction in patients' neocortex and hipocamp, after hypodermic nicotine administration, the improvement of perceptual performances and visual attention, as well as the increasing of the nicotine receptors number by an up–regulation process were reported. As in the case of scopolamine (muscarinic antagonist), mecamilamina (nicotinic antagonist) reproduces experimentally Alzheimer disease; nicotine receptor stimulation would also protect against beta–amiloide noxiousness.

Epidemiological report pointing out the invers proportion between smokers and Parkinson cases is in acordance with the experimental observation concerning the stimulation by nicotine of dopamine release in substantia nigra and striated structures; moreover, literatures also notes the favourable effect of nicotine in Gilles de la Tourette syndrome (4).

The smokers who were given haloperidol have high nicotinemia; dopaminergic receptor blokade would decrease the drug sensibilty level, leading to the increase of nicotine self–administration aiming to maintain the degree of satisfaction (Le Huoezec).

Is suspected chromosome 15 involvement (nicotine receptor site) in attention deficiency and schizophrenia physiopathology. The great schizophrenic smokers would try to counteract the effect at the nicotine receptor level, which would lead to the anhedonia and negative symptomatology attenuation (4) .

Nicotine rapid elimination (half life = 2–3 Hours) determines the significant diminishing of plasmatic level at night (nocturnal abstinence), and as a consequence of receptor desensitezation, for smokers, the number of nicotine receptors is 50% greater than for non–smokers.

Some personality features may predispose to the searching either of the sedative effect or the stimulative one of nicotine. According to our clinical observation, the "impulsive" smoker (after Durand) presents the irresistible tendency of cancelling the nocturnal abstinence effect, lighting his morning cigarette methodically before breakfast the same kind of smoker tries to get rid of the uncomfortable mood during the hiperirritable periods, controlling nicotine titration mainly by increasing inhalation frequency. The compulsive–neurotical smokers control minutely their gestures, avoid "a jeun" self–administration and seek the stimulating effect in the meditative moods by increasing the volume and depth of inhalation.

Symbolic and gregarious

The tobacco burning in the sacred calumet and its inhalation by ritual smoking with a purifying tendency, changed altogether, along five centuries, among others in a public health issue.

In the anthropological approach of psychology (acc. to G. Bachelard), the figurative meaning of incandescence would suggest the wish of accelerating time, of renewel; the dreaming before the phlogistic image fascinates, "the pyre call" being an apprehension of catharsis and resurrection.

Although the disorders due to the improper substance usage are closely connected to individual factors (neurotransmission and neuromodulation particularities, mood and personality changes) the interdependence between pulsions, sensitiveness, mental elaborations and social relationships cannot be ignored.

The fact that the individual history influences the future reactions is experimentally proved by the discovery that after stress area of pregnant rat, the offspring is more susceptible to addiction. The phenomenon is confirmed by means of anamnestic data in human clinic; life experiences, particularly stress, seem to have an important role in toxicomania development (6,10).

The control of a strict abstinence would exert by prefrontal cortex–association area with governing potential (not always operative) on primary deep structures; it is also relevant that smok-

ers are tempted to light a cigarette when they come across situations usually associated to their addiction (e.g, after lunch, during a meditation effort etc.).

What is disturbing besides the feminezing on the large contingents of smokers (anxiety and agresivity development by assuming the social impact), is the dropping of the age of those "initiated "; incipiently, pubescents, teenagers and emotionally immature associate the use of this substance with the endeavour to be assimilated, through gesture and attitude contamination, by a behaviour prototype prased in the origine and/or the reference group (2,5,7).

The practice not only solitary of the exercise, element of a solidarity of a brotherly kind in a joined ritual, from the display to the offering of cigarette and the employment of accessories, as well as the abssence of incompatibilty reactions, may lead to repeated exposals and conditioning guaranted by neuromediation.

The activ nicotinism through cigarette smoking causes multiple problems besides that of the inadequate substance usage, favouring the occurrence of the coping capacity, of behaviour patterns in cardio–vascular comorbidity and of other pathological concomitance and conditioning, from hypoacustics (with a similar mechanism of coronarian "claudication") to carcinogenesis favoured by the lack of glutation–s–transferase.

The random economic and social elements, the outlooks regarding the entertaining and the initiated–gregarious usage provided with symbols bring in the foreground of the prophylaxis the concept of tobaccoindulgence – due to approval and carelessness.

The future therapies (e.g. in Alzheimer disease) might consider cocktails of colinesterase inhibitors + cholinergical agents mixture which would also include nicotine (with the specific contraindications however); the application of the latter does not descharged morbogenous smoking.

The methodical and detailed reporting on smoking practice in medical documents may offer the clinical reasoning relations for the diagnostical and therapeutical planning, having the meaning of a memento with the neuro–modulator potential.

The prophylactic character of theme inserting in the individual–group relationship (commercialls warning, differential insuarance bonuses, taxes) should be associates to a marked desuasive–educational tendency.

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THE INFLUENCE OF ANTIDEPRESSANT MEDICATION ON SMOKING

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Introduction

Molecular mechanisms involved in pharmacodependences represent an important field of biomedical contemporary research.(Nestler 1994). Synaptic transmission, neuromediators release and re–uptake and biological signal transduction at the neuronal level are certainly involved in pharmacodependences (Koob 1992, Nestler and al. 1993). Smoking is wider and wider world spread. From 1990 data of National Institute of Drug Abuse (NIDA), USA, about 77% from adult population have smoked for longer or shorter period of time and about 28% from population smoked with regularity. The nicotine pharmacodependence was undoubtedly proved. Smoking has many unwanted effects on human body. Decrease in smoked cigarettes number or ceased this habit is major medical and social goal.

The nicotine increases the synthesis and release of glutamate and aspartate from CNS neurons. Synaptic neurotransmission based on glutamate is enhanced. The enhanced release of glutamate under nicotine influence is doing by action on presynaptic receptors. After their stimulation is taken place an enhance of penetration of Ca^{2+} ions in presynaptic area and glutamate release. At the level of postsynaptic area, glutamate activates NMDA receptors and increase Ca^{2+} penetration in neuron by Ca^{2+} channels coupled with NMDA receptors. It is produced neuronal calmodulin activation, which stimulate NO–synthetase. Citalopram (high selective seratonine reuptake inhibitor0 reduce nicotin craving locomotor manifestatin induced by nicotine.

Patients and method

We have performed a prospective, randomized study about the influence of antidepressant medication on smoking habit in a number of 48 patients diagnosed with major depression admitted in "Socola" Psychiatric Hospital, Iasi during the 1999.

Patients were 38 males and 10 women with age between 22 and 60 years. We excluded from experiment patients with other pharmacodependencies or with other psychiatric diseases. Group characteristics are shown in Figure 1.

In order to confirm depression we used Hamilton scale. Tobacco dependence was investigated with Fagerstrom scale (shown in Table 1) at the admission in the group and at the end of antidepressant treatment. According with antidepressant medication received we divided the patients in these groups:

Group I got fluvoxamine (Floxyfral[R]), a selective serotonin reuptake inhibitor (SSRI);

Group II got tianeptine (Coaxil[R]) a selective serotonin – uptake enhancing drug with anxiolytic properties;

Group III got tricyclic antidepressants (TCAs)–imipramine (Tofranyl[R]), amitriptiline, doxepine

Group IV got tetracyclic antidepressants – mianserine (Tolvin[R]).

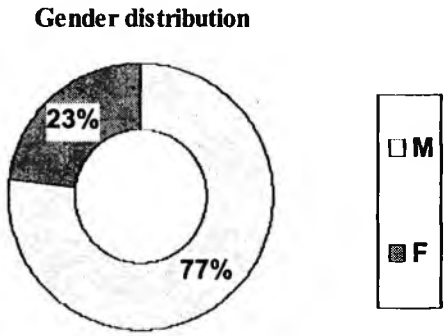
We have assessed the evolution of smoking habit at the beginning and at the end of antidepressant treatment with Fagerstrom test. Patients distribution according to substance administration is shown in Fig. 4.

Table 1. Tobacco Addiction Screening Form

(modified from the Fagerstrom Scoring System)

1	How soon after you awaken do you smoke your first cigarette?	<30min >30min
2	Do you find it difficult to refrain from smoking in places where it is forbidden (like church, libraries, movies, etc...)?	Yes No
3	Which cigarette would you most hate to give up?	1st Other
4	Do you still smoke if you are so ill that you are in the bed much of the day?	Yes No
5	Do you smoke more frequently during the first few hours after awakening than during the rest of the day?	Yes No
6	How many cigarettes per day do you smoke?	<16 17–26 >26
7	What is the tar content of your brand?	Low Med Hi
8	Do you inhale?	Yes No
*	Do you think that you are addicted to cigarettes?	Yes No
*	Do others think that you are addicted to cigarettes?	Yes No

If your score is 6 points or greater, there is a strong likelihood that you are addicted to cigarettes. The initial distribution of Fagerstrom score is shown in Fig.3.



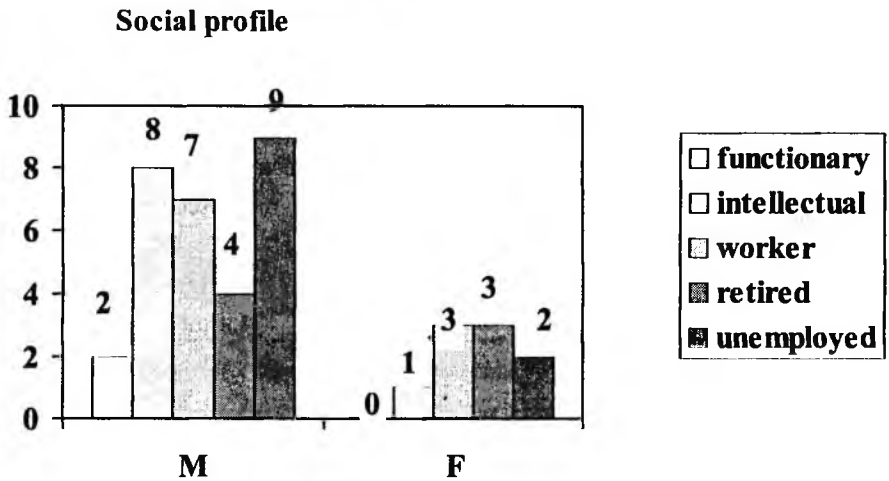


Fig. 1. Group characteristics

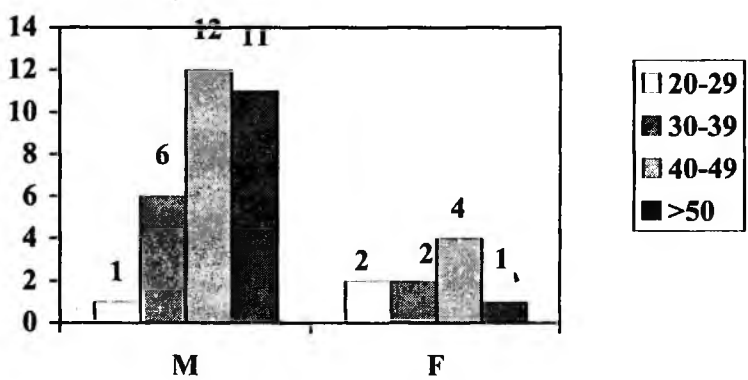


Fig. 2. Age distribution

Results

The results are shown in Fig. 5 and Fig. 6.

Depression treatment has known an important diversification in the last years. Beside trycyclic and tetracyclic antidepressants used for a longer time, nowadays there are used substances which inhibit serotonin re–uptake and also norepinephrine re–uptake. Tianeptin is used for decreasing ethanol intake in alcoholism. Data obtained shown that tianeptin is the most efficient in decreas-

ing Fagerstrom score and consequently the number of smoked cigarettes (according with Fagerstrom score in 65% of the group patients). Tetracyclic and tricyclic antidepressant didn't influence significantly the smoking habit in depressive patients and we couldn't set a correlation between antidepressive effect and changes in smoked cigarettes number.

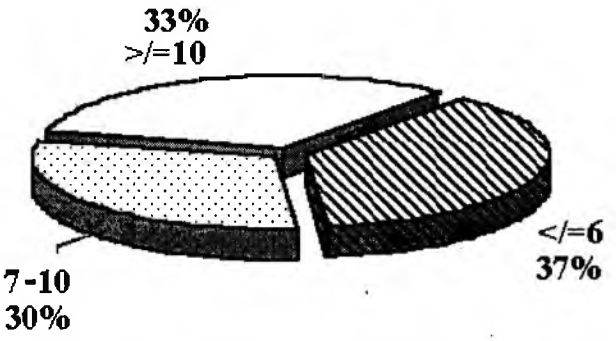


Fig. 3. Initial distribution of Fagerstrom score

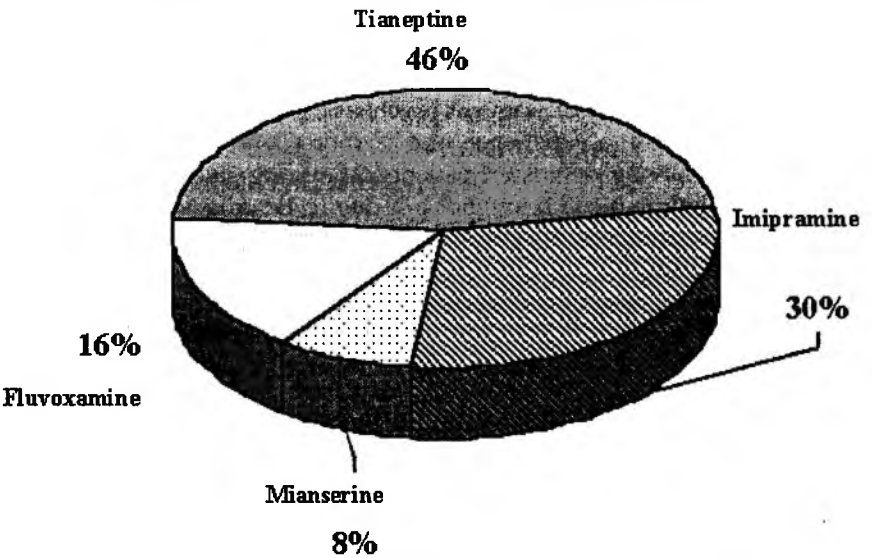


Fig. 4. Patients distribution on treatment groups

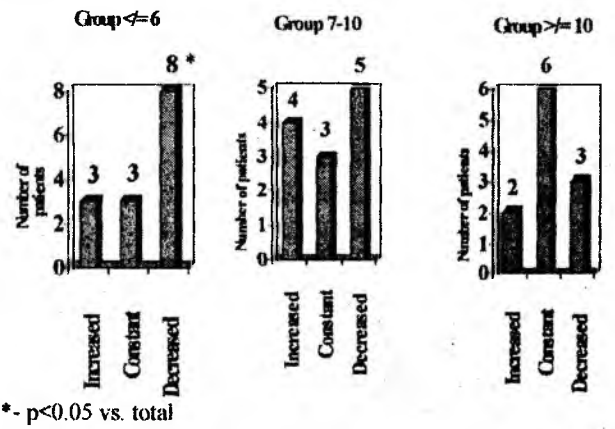


Fig. 5. Fagerstrom score evolution according to initial score

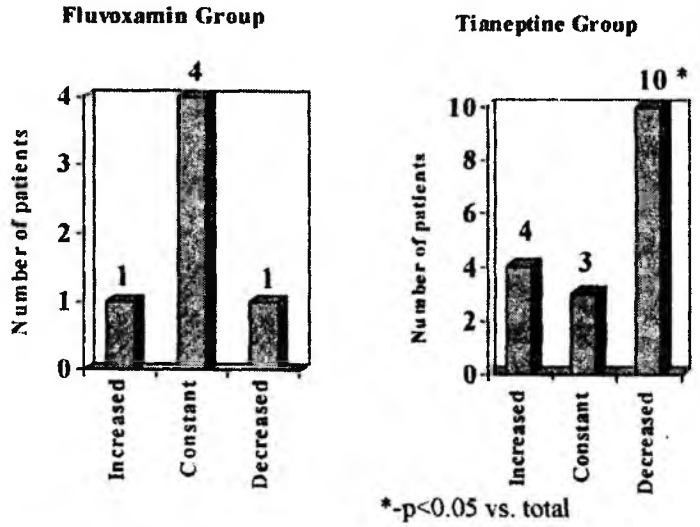


Fig. 6. Fagerstrom score evolution according to substance administrated

Discussion and conclusions

Depression is one of the most frequent psychiatric disease. Potter and Hollister 1998 evaluate that about 10% of population experience one or more depression episodes during life time. Smoking is frequently met among depressed patients. Managing smoking–depression and antidepressive drugs – smoking link is made a tougher job due to heterogeneity of depression and also because of antidepressive drugs diversity (Potter and Hollister 1998)

We may conclude that:

A. There is not a correlation between antidepressant effect and the influence on smoking;

B. Tianeptine has a significant decreasing effect on smoking habit during the treatment.

Our data plead for tianeptine use in a wider range for reducing tobacco dependence.

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ACAMPROSATE AND ALCOHOL DEPENDENCE

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Alcohol dependence is defined by increased tolerance of the effects of ethanol, impaired control over drinking and continued drinking despite harmful consequences. Alcoholism is treated by pharmacological, psychological and social interventions that reduce or eliminate the desire to drink and the devastating effects of alcohol. In alcohol withdrawal treatment focuses on two main different phases: detoxification and rehabilitation (20).

In acute withdrawal phase, detoxification ameliorates the clinical and biological manifestations of withdrawal. Short–acting benzodiazepines are the drugs of first choice. Carbamazepine is another drug which may be employed (8).

Rehabilitation helps the patient avoid future problems with alcohol. Most rehabilitative programs are psychological and almost all of them advocate complete alcohol abstinence (20). In maintaining this abstinence, two types of pharmacotherapy are available: aversive drugs and anticraving drugs. The latter group are relatively new and are represented by acamprosate and naltrexone, a partial opiate antagonist (8,10).

Acamprosate is a homotaurine analogue. Commercial product contains 33.3 mg calcium 300 mg acetyl–homotaurine and 33.3 mg calcium (26). Acamprosate has now been registered in most of EC countries. It has so far been launched as AOTAL^{R} and CAMPRAL^{R}. Sales of the product in Europe by 2000 are estimated at between $ 100 million and $ 200 million. In 1996, the US FDA has given go–ahead for clinical trials of acamprosate (25).

Pharmacokinetic properties

In humans, acamprosate is slowly absorbed from the gastrointestinal tract. There are large intra–individual variations of drug absorption when it is given by oral route; generally less than 10% of a dose of acamprosate is absorbed (26). Most of this fraction is absorbed within 4 hours after administration (8). Concurrent food intake more decreases the absorption. Peak blood levels are reached in approximately 4 hours (t_{max}). Elimination half–life ($t_{1/2}$) is 13 hours. Steady – state plasma concentrations are achieved after 7 days of therapy (26). Acamprosate does not bind to plasma proteins. It crosses the blood–brain barrier and penetrates in breast milk. Acamprosate is not metabolized prior to elimination and is primarily excreted by kidney. There is a linear correlation between creatinine clearance and total plasma clearance, renal clearance and plasmatic half life of acam-

prosate. As a consequence, the dose should be reduced in impaired renal function. Impaired hepatic function does not alter significantly pharmacokinetic parameters.

Effects and mechanism of action

Acamprosate does not affect blood ethanol levels (5,26). Acamprosate crosses the blood–brain barrier and influences various neurotransmission systems (2,12,16,21). Acamprosate is thought to have agonistic activity at $GABA_A$ receptors (5) and inhibitory activity at NMDA glutamatergic receptors (13). As a consequence, normalization of glutamatergic excitation (2,13,16,19) and gabaergic activity (8,20) occurs in alcohol withdrawal. But this explanation is very approximately.

Different parts of the brain have varying sensitivity to acamprosate.The drug increases GABA uptake in the hippocampus. In this area, alcohol does not affect GABA mechanisms. In the thalamus and striatum, acamprosate potentiates alcohol effects on GABA neurons. In the nucleus accumbens, it facilitates NMDA – receptor – mediated neurotransmission (2). This phenomenon is also observed in rat hyppocampal CA1 neurons (11). In the mentioned nucleus accumbens, acamprosate inhibits presynaptic $GABA_B$ receptors (23).

One of the most important action of acamprosate appears to be interaction with taurine, a sulphonated aminoacid, acting as neuromodulator in central nervous system (4,24). Acamprosate acutely increases the level of taurine in extracellular space in the nucleus accumbens and other area of the central nervous system (4,15).

Acamprosate inhibits voltage operated calcium channels and has weak blocking activity on opiate receptors (8). Summarising these data, it might be concluded that the major action of acamprosate is produced by directly inhibition of NMDA receptors and of voltage operated calcium channels and by indirectly effects related to taurine release.

Clinical utilization

The effect of acamprosate is targeted at the craving for alcohol (8). Reductions in craving are associated with longer abstinence (20).

Efficacy of acamprosate is appreciated by laboratory parameters (normalization of gamma–glutamyl transpeptidase and of carbohydrate–deficient transferrin; reduction in erythrocyte mean corpuscular volume) and by clinical indicators (improvement of tremor and of ankle jerk reflexes, reduction in symptoms of anxiety and depression) (1,22).

Outcome specific measures determined in the various acamprosate clinical studies differed (6,8,20), but can be summarized as:

– alcohol relapse rate (average time until first drink);
– cumulative abstinence rate(average number of days of continuos abstinence, in the respective trial);
– drinks per occasion;
– total drinks (alcohol consumption);
– total days with drinks;
– alcohol craving (scored by categorical or visual scales);
– drop–out rate.

Acamprosate has been shown to influence favourable many of these indicators. The therapeutic effect is dose dependent. The usual daily dose is 2–3 g in three divided doses, with meals (20,26). In the most of the European multicenter clinical trials, acamprosate demonstrated higher success rates compared to placebo (14,17). Acamprosate was more efficient than other currently used therapeutic modalities (9,18,22). Generally, twice as many patients given acamprosate as patients given placebo remained abstinent from alcohol during treatment periods (6,14). Acamprosate was

more efficient in long term clinical studies (> 1 year of continuous treatment). The clinical improvement remain stable with carry over of the effect after cessation of therapy for at least 1 year.

Side effects

Preclinical studies do not relevate mutagenic, carcinogenic, embryotoxic or teratogenic effects, nor adverse reaction on reproductive function in animals.

The most common adverse reactions are on gastrointestinal tract and cutaneous teritory. In humans the frequency of these side effects is low, with temperate intensity, being transitive. The percentage of withdrawal for undesired effects is similar in the acamprosate and placebo groups.

Digestive side effects are: diarrhea (7–20%, versus placebo 3–12%); less frequent occur nausea, vomiting and other gastrointestinal complains, such as abdominal pain. Pruritus is the most frequent dermatological effect. Sexual undesirable effects reported during acamprosate therapy consists of impotence, frigidity, altered libido (with similar occurrence in placebo group). These sexual dysfunctions appear with chronic alcoholism too. Acamprosate has no sedative properties. Abuse and dependence potential is practically absent (7).

In animal studies high doses produce calcium–like effects: calcification of soft tissues, nephrolitiasis and myocardial lesions. In humans, overdoses of acamprosate had a benign evolution with no hypercalcemia in any case. Until today, 5 clinical cases of acamprosate overdose have been reported (up to 43 g ingestion), with only diarrhea as a disturbing symptom.

Contraindications and precautions

Acamprosate is contraindicated in patients with hypersensitivity to drug, initial alcohol detoxification, in nephrolitiasis, impaired renal function (plasma creatinine > 120 μmoli/L) and in severe hepatic insufficiency (Childs–Pugh class C). No clinical data are available in elderly and children, pregnancy and lactation and in these situations the drug should be avoided (5, 8, 26).

Interactions

No significant pharmacokinetic and pharmacodynamic interactions have been observed between acamprosate and the following agents and drugs: ethanol, diazepam, disulfiram and imipramine (8, 26).

Conclusions

At date, acamprosate appears superior to other rehabilitative therapies. The drug may be preferred above other anticraving drugs because its long–term effectiveness after cessation (8). As not all patients will respond to acamprosate further studies need to be undertaken to identify those patients most likely to respond to this drug (3).

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THE INFLUENCE OF MAGNESIUM ON MORPHINE EXPERIMENTAL ADDICTION IN RAT

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Introduction

Mg^{2+} is the most important intracellular bivalent cation and play many functional roles in all tissues and cells. Mg plasmatic levels put this cation at the border between macro and trace elements. Mg deficit is linked to modifications in the turnover of various types of neurotransmitters: monoamines, amino acids, but also nitric oxide, neuropeptides, and cytokines (Itokawa and Durlach 1989, Birch 1993).

Neuronal hyperexcitability (NHE) due to Mg^{2+} deficiency mainly depends on modifications in the turnover of several neuromediators and neuromodulators. They associate an increased turnover of the monoamines: serotonin (5HT), catecholamines (dopamine and noradrenaline, mainly), and of excitatory amino acids (aspartic and glutamic acids, mainly) (Bac et al 1993) with a decreased turnover of inhibitory amino acids (GABA and taurine, mainly). There are known many pathological involvements of Mg^{2+} deficiency . An increased production of nitric oxide and of various inflammatory peptides – such as substance P, CGRP, and VIP – is observed in Mg–deficient rats. All these substances might directly intervene as neurotransmitters in the physiopathology of NHE due to Mg^{2+} deficiency; but NO could also mediate an increase in cGMP whereas inflammatory neuropeptides might stimulate production of inflammatory cytokines and of free radicals. During the progression of Mg^{2+} deficiency in a rodent model, dramatic increases of inflammatory cytokines were observed: interleukines 1 and 6 (IL1, IL6) and tumor necrosis factor (TNF). Increase of these various cytokines was neither concomitant nor constant, according to species and strains. Opioid peptide activity could be reduced since, in the complex mechanisms of opioid action, Mg at the physiological level may be most often an agonist of μ and kappa opiate receptors (Weglicki and Phillips 1992).

Magnezium deficiency results in three basic effects: disturbances in cellular Ca^{2+} distribution, decreased second messenger nucleotidic ratio, and increased susceptibility to peroxidation. Through membranous and postmembranous alterations, Mg^{2+} deficiency brings about a cellular Ca^{2+} load with subcellular distribution modifications. Magnezium deficiency reduces 3',5'–cyclic adenosine monophosphate (cAMP) concentration and increases 3',5'–cyclic guanosine monophosphate (cGMP) concentration, perhaps through inhibition of adenylate cyclase and activation of guanylate cyclase. Mg–deficient animals show an increased susceptibility to *in vivo* oxidative stress and the tissues of these

animals are more susceptible to *in vitro* peroxidation, affecting lipid particularly. Mg deficiency may increase formation of free radicals directly, but also indirectly through free–radical–triggered mechanisms. Protein oxidation in Mg^{2+}–deficient rat brains occurs early. These changes take place prior to any detectable tissue damage, dysfunction, or changes in cellular glutathione concentration. It was increasing magnesium therapeutical use (Durlach 1988, Gunther 1991, Fehlinger 1990, Gullestad et al. 1992).

Material and method

We tested the influence of Mg^{2+} on morphine experimental addiction in rats. We used 4 groups of 15 adult, male, Whistar rats each, weighing between 180–210 g, bread in the same laboratory conditions. For Magnezium administration we used Mg acexamate (chemical structure is shown in Fig 1.

Group **I** did not receive any substance (control group).

Group **II** got morphine in an administration schedule with progressive growing of the dose from 7mg/kg/zi to 50 mg/kg/zi (daily dose being split into 2 equal doses).

Group **III** got morphine on the same administration schedule but got also with an hour before morphine, magnesium acexamate (MgAcx), 100 mg/kg i.p. (in an unique dose).

Group **IV** got only MgAcx for 15 days.

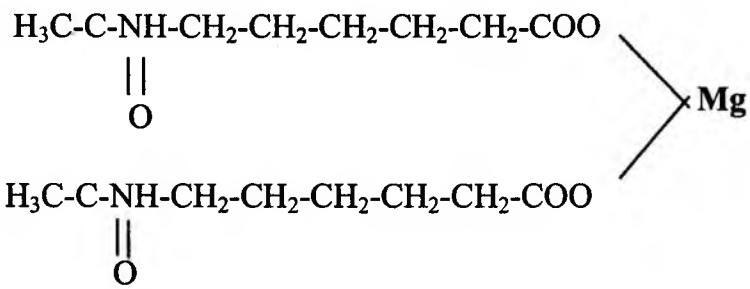

Fig. 1. Magnesium acexamate structure

At the end of 15 days, morphine and MgAcx administration were ceased.

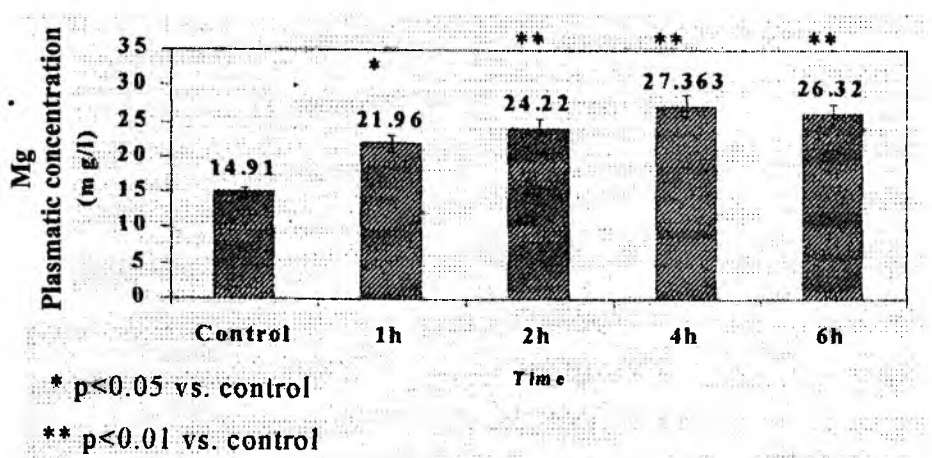

Fig. 2. Mg^{2+} plasmatic levels (after MgAcz 0.5 mEq/kg i.p.)

All animals got naloxon 1 mg/kg s.c. Than, for 3 days consecutively, were surveyed 15 minute (for each animal in each day) on clinical signs which reflect intensity of withdrawal syndrome: forced mastication, chills, explorers, body curving, aggressive positions, diarrhea, piloerections, toilets. 3 independent observatories carried out the follow up of animals. Plasmatic concentrations of magnesium were spectrophotometric determined from blood sample from retro orbitary plexus at 2,4,6, 12 hours after MgAcx administration. Data obtained was statistically interpreted.

Results

After MgAcx administration in mentioned doses, Mg^{2+} plasmatic concentrations raised (Fig. 2). Data obtained show an unequal influence of Mg^{2+} on tests performed in withdrawal syndrome in opiate dependent rats (Fig. 3 and Fig. 4). MgAcx associated with morphine decreased with more than 40% the number of explorations (toward group which got only morphine, $p<0.01$) and also frequency of forced mastication. Administrated alone MgAcx does not influence stereotypes.

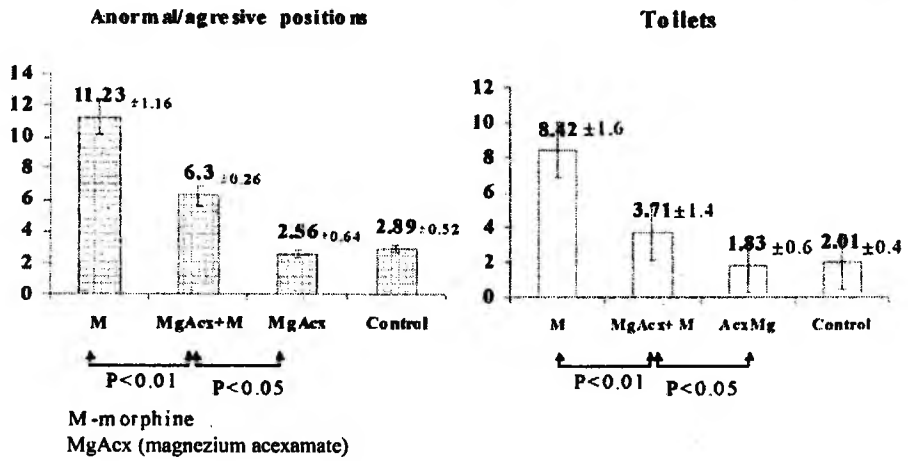

Fig. 3. The influence of MgAcx on intensity of withdrawal syndrome in rats morphine dependent

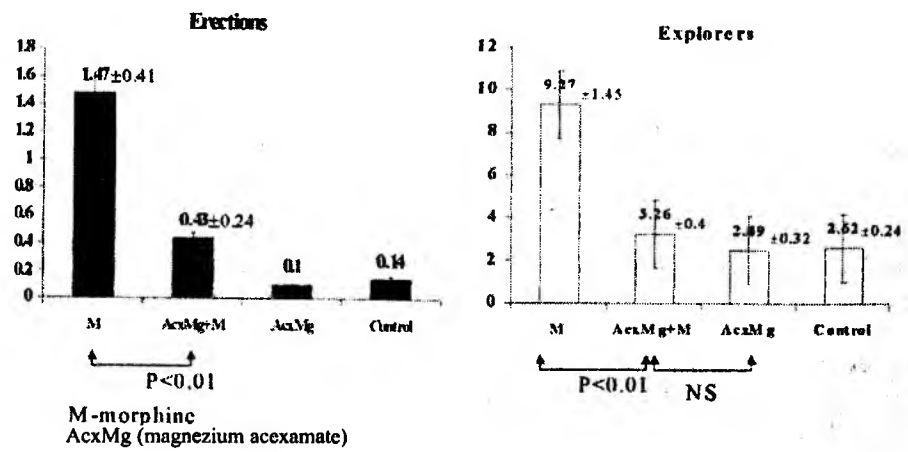

Fig. 4. The influence of MgAcx on intensity of withdrawal syndrome in rats morphine dependent

Our data are in accordance (in part) with Moller–Rerter et al 1997 which shown that i.v. Magnezium administration (4 mmol/h) for 24 h determines a decrease in withdrawal symptoms in patients with morphine pharmacodependence. Magnezium salts was also used in delirium tremens crises in dipsomanic patients (Karson et al, 1989).

Martel 1974 shown that magnesium deficit increases ethanol consumption in rats with ethylic experimental addiction and Mg intake decreases ethanol craving and intake in this animals. We consider that effect is due to Mg^{2+} ion and not to acexamic acid, this substance alone having no specific effects.

Conclusions

Mg^{2+} decreases the intensity of some symptoms from withdrawal syndrome and might decreased the intensity of morphine addiction. There is no explanation for differences observed in case of Mg intake on special manifestation of withdrawal syndrome. There might be involved (at least partially) special mechanisms of action for each one of these symptoms.

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PRESCRIBED DRUG, ADDICTIVE DRUG, DRUG ADDICTION

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The medical language uses technical terms coming from "classical" or "modern" languages. These terms have a precise meaning and an adequate spelling. In our medical language phonetic spelling is used.

Sometimes the technical terms undergo an "adaptation". In Romanian, terms should be taken from foreign languages by respecting the meaning of the word in the original language. Sometimes the terms are taken erroneously by certain "innovators". Such an example is represented by the term "drug", which in English has several meanings, among which that of remedy or medicine. Due to a superficial borrowing by some authors, "drug" becomes "drog" ("addictive drug") and the innovators in question use this inadequate form instead of the term "medicament" ("prescribed drug", "medicine") which is currently used in Romanian. The word "medicament", of Latin origin, is suitable for the Romanian language, which is a Latin language.

In the majority of the definitions of the literature, a medicine is a chemical substance which is used in adequate doses for preventive, diagnostic, curative (therapeutic) purposes in human or animal diseases, as well as in order to influence a condition or function of the organism (2–4, 6, 8–10, 13, 15, 16).

It should be mentioned that the Greek "pharmakon" corresponds to the Latin "medicamentum". In this sense pharmacology is the medicine science (6, 9).

In many languages the notion of prescribed drug is designated by usual terms. Among these, for example, are "drug" in English and "Arzneimittel" in German. As it may be noticed, the term "drug" is not used for "medicine" ("medicamentum")!

What is the meaning of the word "drog" and what is the explanation of the confusion in some authors who (inadequately) use this term instead of that of "medicament"? What is the connection between "drog" and "drug"?

1. The term "drog" comes from Dutch, from where it has been borrowed by other languages ("die Droge" – in German, "la drogue" – in French, etc.). The term is derived from the adjective "drooge" = "dry". In the course of time, the notion of "drog" has acquired several meanings. Earlier books and some dictionaries described under the heading of "drog" natural products, preservable through drying, representing raw material for medicines. These can be of mineral (kaolin), animal (organs, tissues), and vegetal origin (plants, plant parts). These drogs can be used as such or after pharmaceutical processing. The products in question act on the organism due to the chemical substances they contain, called active principles. The term of "drog" has the meaning mentioned above in recent works as well, however certain specifications appear such as "raw drug" or

"crude drug" – in English, or "Rohdrogen" – in German; in these cases the significance is that of raw material used for the preparation of officinal or magistral medicines (4, 8, 10).

Another significance of the term "drog" is that of a substance creating addiction. According to some opinions, in order to avoid the lack of precision, the term "drog" should only be used with the second meaning. Consequently, it is recommended to talk about drogs only in the case of abusively used substances that have an action on the nervous system: narcotic analgesics, euphoriants, stimulants. Among these we mention opioids (morphine, heroin, etc.), hashish (marijuana, cannabis), cocaine, alcohol, etc. (6, 9, 10).

2. The English word "drug" is used in the English literature with the following meanings: a) remedy, corresponding to the terms "pharmakon", "medicamentum", "Arzneimittel"; b) abusively used substance, when it is specified that "drug abuse" is involved (6, 13, 16).

In English there is a differentiation between "drugs", which are called "prescribed drugs" or sometimes "medicines", and "addictive drugs", which are used illegally, for non–medicinal purposes (3, 13, 16). This meaning is attributed to substances that are used abusively, for example poisonous or stupefying substances (2). Consequently, the term "drug" has several meanings in English, designating, according to the nature and use of the substance, either a medicine or a substance used abusively, for relishing purposes. The latter variant corresponds to the notion of "addictive drug", that is a substance which creates tolerance and addiction. Due to the ambiguity of the word "drug" in English, "drug dependence" designates both the dependence on a prescribed drug (pharmacodependence) and the dependence on stupefying substances ("addictive drug dependence") (2, 7, 12).

The prolonged abusive use of substances, including prescribed drugs, can lead to addiction (2, 3). Addiction defines the inclination of an individual to take a substance to which he/she becomes addicted. Consequently, "addiction" refers to the syndrome of dependence on the substance in question (6, 11).

In the course of prolonged abusive use of a substance or medicine, tolerance and psychological and physical dependence can occur (6, 14).

Tolerance represents the progressive diminution of the effect after the repeated administration of a medicine, the subsequent increase of the dose being necessary in order to obtain the initial effect. The term "tolerance" is sometimes used erroneously, for example for the way in which a medicine is coped with.

According to the mechanism through which it occurs, tolerance can be pharmacokinetic (dispositional), pharmacodynamic and acquired – one of its forms being behavioral tolerance (6).

It has been shown above that a medicine or a substance can determine physical dependence, condition due to the adaptation – through the resetting of homeostatic mechanisms – to repeated administration. The sudden discontinuation of the administration of the substance to which tolerance has been produced will lead to a disequilibrium that will determine the withdrawal syndrome.

Tolerance, physical dependence and withdrawal syndrome are biological phenomena that occur after the prolonged use of a medicine. These phenomena are not characteristic of medicine addiction, since they can occur even after the correct use of some prescribed drugs, according to medical prescriptions. Such a situation can appear in a hypertensive patient when propranolol (that has been administrated in adequate doses) is discontinued. In this case, the withdrawal syndrome is characterized by a rebound of blood pressure, at values that can exceed those prior to treatment (6).

Dependence on a medicine can be correctly defined as a condition of chronic intoxication, which is characterized by the compulsive need to use a substance or medicine ("compulsive drug use") (6, 9, 14).

In order to complete what we have shown above, we should mention that in the case of psychotropic substances, a psychological dependence can occur, accompanied by a physical dependence – more or less expressed – and prolonged abusive administration can lead to psychological disorders (6, 14).

The term of "addiction" currently undergoes a process of redefinition (6). Abuse and addiction are behavioral syndromes (6).

In order to avoid confusions, the use of the term "substance dependence syndrome" is recommended, which is characterized by tolerance, psychological and physical dependence (6, 14).

Table 1 includes the psychotropic substances that can create dependence.

Table 1. Psychotropic substances that can create dependence (6, 11)

• **Central nervous system depressants*:**
Ethyl alcohol, anxiolytics and hypnosedatives (benzodiazepines, meprobamate, barbiturates, methaqualone, glutethimide).
• **Central nervous system stimulants*:**
Cocaine, amphetamine, dexamphetamine, methamphetamine, methylphenidate, cathinone ("khat"), nicotine, caffeine, numerous anorexigens (e.g. mazindol)
• **Opioid analgesics ("narcotics")*:**
Heroin, dextropropoxifen, dextromoramide, buprenorphine, morphine, pethidine, metadone, phentanyl, etc., some antitussives (codeine, hydrocodone, pholcodine).
• **Cannabinoids:**
Marijuana (hashish)
• **Psychedelic agents:**
LSD, mescaline, psilocybin, psilocin, dimethyltryptamine, dimethoxyamphetamine, phencyclidine, (PCP, "angel dust"), methoxymethylenedioxyamphetamine (NMDA, "ecstasy").
• **Inhalants:**
Solvents (toluene, fluorocarbon, methanol, acetone), amyl nitrite, nitrogen protoxide

Note *Can determine tolerance and physical dependence

Psychotropic drugs can create psychological dependence due to pleasant positive effects (e.g. euphoria) or due to the removal under their action of negative unpleasant effects (e.g. anxiety, sadness, pain) (6, 9, 11).

Psychological dependence on opioids, barbiturates, benzodiazepines, alcohol, cocaine and amphetamine (6, 9, 14) develops easily.

The purpose of this article was to clarify some terms concerning the abusive use of remedies, terms which are sometimes used inadequately.

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PHARMACOLOGICAL TREATMENT OF ADDICTIONS

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I. General Treatment Principles

Individuals with substance use disorders are heterogeneous regarding a number of clinically important features:

- the number and type of substances used;
- the severity of the disorder and the degree of associated functional impairment;
- the associated general medical and psychiatric conditions;
- the patient's strengths (protective/resiliency factors) and vulnerabilities; and

Although the full spectrum of substance use disorders includes conditions that have a narrow impact on an individual's health and functioning, many patients have more severe conditions that broadly affect their health and functioning and that are long–term and/or relapsing in nature. Individuals with more severe conditions, which are less responsive to low–intensity treatments, are the focus of much of this guideline.

Treatment for individuals with substance use disorders may be thought of as occurring in phases:

- **assessment phase**, during which information on the aforementioned cross–sectional and longitudinal features, as well as other critical information, is obtained and integrated;
- **treatment/withdrawal,** as necessary; and
- **post withdrawal treatment.**

Depending on the clinical circumstances, the treatment strategy may emphasize the individual's need to remain drug free or it may entail substitution of one presumably safer drug (e.g., methadone) for another (e.g., heroin). Substance use disorders may affect many domains of an individual's functioning, and they frequently require multimodal treatment. Some components of treatment may be focused directly on the substance use, and others may be focused on the associated conditions that have contributed to or resulted from the substance use disorder.

The specific pharmacologic and psychosocial treatments for patients with substance use disorders are generally applied in the context of treatment programs that combine a number of different treatment modalities. It is uncommon for a single treatment to be effective when used in isolation.

A. Goals of Treatment

Long–range goals of treatment for patients with substance use disorders include reduction in the use and effects of abused substances, the achievement of abstinence, reduction in the frequency of relapses, and rehabilitation. For some patients, abstinence can never be achieved or can be achieved only after many years of either continuous or episodic treatment. However, even in the absence of complete abstinence, important reductions in morbidity and mortality can be achieved through reduction in the frequency and intensity of substance use and its associated sequels (American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, APA, 1994).

1. Abstinence or reduction in the use and effects of substances. The ideal outcome for patients with substance use disorders is total cessation of substance use. However, many patients are unable or unmotivated to reach this goal, particularly in the early phases of treatment. Such patients can still be helped to minimize the direct and indirect effects of substance use. Interventions discussed in this guideline may result in substantial reductions in the general medical, psychiatric, interpersonal, familial/parental, occupational, and other difficulties commonly associated with substance abuse or dependence. Reductions in the amount or frequency of substance use, substitution with a less risky substance, and reduction of high–risk behavior may also be achieved. Engagement of the patient in a long–term treatment that may eventually lead to further reductions in substance use and its associated morbidity is an important goal of early treatment.

Patients who achieve total abstinence from abused substances have the best long–term prognosis, and many experienced psychiatrists feel that since substance use by these patients may be accompanied by disinhibition, increased craving for other drugs, poor judgment, and an increased risk of relapse, patients should be abstinent from all potential drugs of abuse, including alcohol (Weiss et al. 1988; Rawson et al. 1986; Rounsaville et al. 1991).

Patients who agree to pursue a goal of achieving and maintaining abstinence should be advised about the possibility of relapse and participate in developing a treatment plan that includes methods for early detection of and intervention in episodes of relapse.

2. Improvement in psychological and social/adaptive functioning. Substance use disorders are associated with problems in psychological development and social adjustment, alienation from friends and family, impaired school or work performance, financial and legal problems, and deterioration of patients' general health (Wise, 1988). Substance dependence is associated with failure to develop age–appropriate interpersonal or coping skills or gradual atrophy of such skills (McLellan et al.,1992). A substantial minority of substance–dependent individuals lack the educational, social, or vocational skills necessary to succeed in our society. Treatment specifically directed toward repairing disrupted relationships, reducing impulsivity, developing social and vocational skills,

B. Pharmacotherapy

Pharmacotherapy for patients with substance use disorders may be used

1) to ameliorate the signs and symptoms of drug intoxication or withdrawal;
2) to decrease the effect of an abused substance and, more specifically, to decrease its subjective reinforcing effects;
3) to make the use of an abused substance aversive by a) inducing unpleasant consequences through a drug–drug interaction or b) coupling substance use with an unpleasant drug–induced condition;
4) to use an agonist substitution strategy to promote abstinence from a more dangerous illicit substance (e.g., the use of methadone for individuals with opioid use disorders); and
5) to treat comorbid psychiatric or general medical conditions (American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, APA, 1994).

1. Medications to treat intoxication or withdrawal states. Patients who develop tolerance to a particular drug also develop cross–tolerance to other drugs in the same pharmacologic class. As a result, one can take advantage of cross–tolerance in the treatment of withdrawal states by replacing the abused drug with a drug in the same general class but with a longer duration of action

and then slowly tapering the longer–acting drug in a way that allows time for the restoration of physiologic homeostasis. Examples include the use of methadone in the treatment of heroin withdrawal and benzodiazepines in the treatment of alcohol withdrawal (Miller and Hester, 1986; Jaffe, 1985; Liskow and Goodwin, 1987). Clonidine is an example of an agent that ameliorates abstinence–related symptoms in patients withdrawing from opioids but is not a competitive agonist (Liskow and Goodwin, 1987).

2. Medications to decrease the reinforcing effects of abused substances. A variety of medications have been used to block or otherwise counteract the physiologic and/or subjective reinforcing effects of abused substances. For example, the narcotic antagonist naltrexone blocks the subjective and physiologic effects of subsequently administered opioid drugs (e.g., heroin) (Jaffe and Ciraulo,1985; Kleber, 1994). Repetitive testing of antagonist–induced "blockade" of opioid effects theoretically leads to extinction of conditioned craving for opioids (Kleber, 1994).

Because of their strong affinity for and binding to opioid receptor sites, the narcotic antagonists also displace opioid agonists from neuronal and other receptors and can, therefore, be used to treat acute opioid intoxication. Abstinence symptoms precipitated by narcotic antagonists have also been used as a provocative test for the presence of opioid dependence (Galanter, 1993).

3. Medications that discourage the use of substances. The most prominent example within this category is disulfiram (Antabuse), a drug that inhibits the activity of aldehyde dehydrogenase, the enzyme that metabolizes acetaldehyde, the first metabolic breakdown product of alcohol. In the presence of disulfiram pretreatment, alcohol use results in the accumulation of toxic levels of acetaldehyde, accompanied by a host of unpleasant, potentially dangerous, and rarely lethal signs and symptoms (Meyer et al., 1979; Wikler, 1973).

Medications have also been used as part of a chemical aversion treatment in which conditioned stimuli signaling drug availability, or the abused substance itself, are coupled with drugs that produce highly unpleasant effects, such as succinylcholine, which interferes with respiratory function, or emetine, which induces vomiting. The use of aversive medications for this purpose has been tried with patients who have alcohol use disorders and or cocaine use disorders (Gragg, 1982) with some success, but it is not recommended outside of specialized treatment settings.

4. Agonist substitution therapy. The use of agonist medications may help some patients to reduce illicit drug use by reducing or eliminating symptoms of withdrawal and by decreasing craving for that particular class of substances. An example is the use of methadone or LAAM in the treatment of opioid–dependent patients.

II. Alcoholism: Treatment Principles

The relationship between alcohol dependence and abuse is variable. In one study (Beane and Beck, 1991), only 30% of male subjects with alcohol abuse at baseline met criteria for alcohol dependence 4 years later. The other 70% met criteria for either alcohol abuse or alcohol abuse in remission.

The long–term goals of treatment for patients with alcohol use disorders are identical to those for patients with any type of substance use disorder; These include abstinence (or reduction in use and effects), relapse prevention, and rehabilitation. There is some controversy in the literature, however, regarding the possible benefits of striving for a reduction in alcohol intake, as opposed to total abstinence, for those who are unlikely to achieve the latter. In a comprehensive review of the issue (Anker and Crowley, 1981), Rosenberg concluded that a lower severity of pretreatment alcohol dependence and the belief that controlled drinking is possible were associated with the achievement of controlled drinking after treatment. Interventions aimed at achieving moderate drinking have also been used with patients in the early stages of alcohol abuse (Conditions for the use of narcotic drugs, Code of Federal Regulations [CFR], April 1994; Helzer et al. 1991). Controlled drinking may be an acceptable outcome of treatment, for a select group of patients, when accompanied by substantial

improvements in morbidity and psychosocial functioning. For most patients with alcohol dependence or abuse, however, abstinence is the optimal goal.

Numerous studies have documented the efficacy of alcoholism treatment; approximately 70% of all patients manifest a reduction in the number of days of drinking and improved health status within 6 months (Ball and Ross, 1991). The majority of patients who are treated for alcohol use disorders have at least one relapse episode during the first year following treatment. However, there is now considerable evidence that most individuals with alcohol use disorders drink less frequently and consume less alcohol after receiving alcoholism treatment, compared to their pretreatment drinking behavior (McKay et al. 1993; Rosenberg, 1993; Baer et al., 1992; Kivlahan et al., 1990). For example, patients typically report drinking heavily on 75% of the days during a 3–month period before treatment. During posttreatment follow–ups patients are often abstinent on 70%–90% of the days, and they engage in heavy drinking on 5%–10% of the days (Zinberg et al., 1978).

Treatments for Dependence and Abuse of Alcohol

1. Naltrexone. Two independent double–blind, placebo–controlled studies (Walsh et al.,1991; O'Malley et al., 1992) have documented the efficacy of the narcotic antagonist naltrexone for the treatment of alcohol dependence. The study by O'Malley et al. (1992) showed that naltrexone in doses of 50 mg/day was superior to placebo in terms of reduced drinking and the resolution of alcohol–related problems. Patients who received both naltrexone and coping skills training were the most successful at avoiding full relapse. These studies suggest the potential utility of this agent, particularly when combined with other therapeutic approaches, in preventing relapse. The mechanism by which naltrexone exerts its therapeutic effects is not adequately known but may involve blocking the primary subjective effects of a first drink. Animal studies suggest that part of alcohol's reinforcing effects relate to release of endogenous opioids, which are then blocked by naltrexone (Eskelson et al., 1980;Wilkinson et al., 1986; Stine et al., 1992).

2. Disulfiram. Pretreatment with disulfiram establishes conditions in which the subsequent use of alcohol results in a toxic and highly aversive reaction. Disulfiram inhibits the activity of aldehyde dehydrogenase, the enzyme that metabolizes acetaldehyde, a major metabolite of alcohol. The usual therapeutic dose is 250 mg/day, although some patients achieve optimal benefit at either a higher or a lower dose (range, 125–500 mg/day). In the presence of disulfiram, alcohol consumption results in the accumulation of toxic levels of acetaldehyde, which in turn produce a host of unpleasant signs and symptoms, including a sensation of heat in the face and neck, headache, flushing, nausea, vomiting, hypotension, and anxiety. Chest pain, seizures, liver dysfunction, respiratory depression, cardiac arrhythmias, myocardial infarction, and death have also been reported. Understanding and explaining disulfiram's toxic, or lethal, effects to patients is a prerequisite for its use (Stine et al., 1992; Marchner, 1984; Peachey,1981), so it should never be used without the patient's knowledge and consent.

Controlled trials have not demonstrated any advantage of disulfiram over placebo in achieving total abstinence, in delaying relapse, or in improving employment status or social stability (Peachey, 1981; fox, 1968). However, some clinicians believe that this medication, when combined with other therapeutic interventions, has some benefit for selected individuals who remain employed and socially stable (Wikler, 1973; Fuller and Roth, 1979; Arana and Hyman, 1991). Treatment effectiveness is enhanced when compliance is encouraged through frequent behavioral monitoring (e.g., breath tests), group support for remaining abstinent (e.g., in group therapy or Alcoholics Anonimous) (Keso and Salaspuro, 1990), contingency contracting, or, where feasible, supervised administration of disulfiram. Patients who are intelligent, motivated, and not impulsive and whose drinking is often triggered by unanticipated internal or external cues that increase alcohol craving are the best candidates for disulfiram treatment. Poor candidates include patients who are impulsive,

have poor judgment, or are suffering from a comorbid psychiatric illness (e.g., schizophrenia, major depression) whose severity makes them unreliable or self–destructive (Meyer, 1991; Peachey, 1984).

Patients taking disulfiram must be advised to avoid all forms of ethanol (including, for example, that found in cough syrup). In addition, disulfiram interferes with the metabolism of many medications, including tricyclic antidepressants, so that care must be taken to avoid toxicity (Lister, 1988). Disulfiram can cause a variety of adverse effects; hepatotoxicity and neuropathies are rare but potentially severe. The medication should be avoided for patients with moderate to severe hepatic dysfunction, peripheral neuropathies, pregnancy, renal failure, or cardiac disease.

3. Acamprosate. Acamprosate (calcium acetyl–homotaurine) is a synthetic compound that crosses the blood–brain barrier and has a chemical structure similar to that of the naturally occurring amino acid neuromediators, homotaurine and l–aminobutyric acid (GABA). Acamprosate appears to act primarily by restoring normal n–methyl–d–aspartate (NMDA) receptor tone in the glutamate system, and has been shown to have a specific dose–dependent effect on decreasing voluntary alcohol intake in animals with no effects on food and water consumption. The safety and efficacy of acamprosate in alcohol–dependent outpatients is currently under evaluation in the United States. Acamprosate has been available by prescription since 1989 in France and more recently in most European and Latin American coutries as well as Australia, South Africa, and Hong Kong. More than 4 million people have been treated with acamprosate since it became commercially available. (Mason and Ownby, 2000)

4. Antidepressants. Although past evidence regarding the efficacy of tricyclic antidepressants for depression associated with alcohol use disorders is equivocal (Daley and Marlatt, 1992), two studies showed improved mood and reduced alcohol consumption in open and double–blind placebo–controlled trials with desipramine (Gerrein et al., 1973; Ciraulo et al., 1985;). Preliminary data indicate that selective serotonin reuptake inhibitors may significantly reduce problem drinking in nondepressed social drinkers (Fawcett et al., 1987) and in those with alcohol abuse or dependence (Dorus et al., 1989; Mason and Kocsis, 1991).

Management of withdrawal

The syndrome of mild to moderate alcohol withdrawal generally occurs within the first several hours after cessation or reduction of heavy, prolonged ingestion of alcohol; it includes such signs and symptoms as gastrointestinal distress, anxiety, irritability, elevated blood pressure, tachycardia, and autonomic hyperactivity. The syndrome of severe alcohol withdrawal especially occurs within the first several days after cessation or reduction of heavy, prolonged ingestion of alcohol; the syndrome includes such signs and symptoms as clouding of consciousness, difficulty in sustaining attention, disorientation, grand mal seizures, respiratory alkalosis, and fever.

Fewer than 5% of individuals with alcohol withdrawal develop severe symptoms, and fewer than 3% develop grand mal seizures (American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC, APA, 1994; Ciraulo and Shader: Clinical Manual of Chemical Dependence, 1991). In the past, the mortality rate for patients experiencing alcohol withdrawal delirium was as high as 20%, but currently it is closer to 1% because of improved diagnosis and medical treatment of such patients.

Thiamin should be given routinely to all patients receiving treatment for moderate to severe alcohol use disorders to treat or prevent common neurologic sequelae of chronic alcohol use (Tallaksen et al., 1992; Bond and Homewook, 1991).

Although pharmacotherapeutic agents are often used to ameliorate the signs and symptoms of alcohol withdrawal and to prevent a major abstinence syndrome, the relative importance of supportive and pharmacologic treatment for these patients is not well established (Shaw et al., 1981, Naranjo et al., 1983). Generalized support, reassurance, and frequent monitoring is sufficient treatment for approximately two–thirds of the patients with mild to moderate withdrawal symptoms

(Whitfield et al., 1978). In one case–controlled study (Shaw et al, 1981), 74% of hospitalized alcohol–dependent patients without serious comorbid general medical problems responded to supportive treatment for alcohol withdrawal. Patients in more severe withdrawal and those who developed hallucinations required pharmacologic treatment.

There are numerous reviews of the pharmacologic treatment of moderate to severe withdrawal (Femino and Lewis,1982; Rosenbloom, 1988; Victor, 1966). The pharmacotherapy is directed toward reducing CNS irritability and restoring physiologic homeostasis. This often requires use of fluids, benzodiazepines, and, in selected cases, other medications (Liskow, Goodwin, 1987). Most patients should be monitored by using breath and/or urine testing to ensure that they have not resumed alcohol use.

Many authors recommend use of benzodiazepines to control abstinence symptoms, which takes advantage of the cross–tolerance between alcohol and this class of drugs. A single oral loading dose of chlordiazepoxide, 200–400 mg, or diazepam, 20–40 mg or as needed, may be used. Orally administered chlordiazepoxide (50 mg every 2–4 hours), diazepam (10 mg every 2–4 hours), oxazepam (60 mg every 2 hours), and lorazepam (1 mg every 2 hours) are commonly used (Naranjo et al., 1983, Saitz et al., 1994). The total dose necessary to suppress CNS irritability and autonomic hyperactivity in the first 24 hours (i.e., the stabilization dose) is then given in four divided doses the following day, after which the dose can usually be tapered over 3–5 days, with monitoring for reemergence of symptoms (Bradley, 1992). For most patients, the equivalent of 600 mg/day of chlordiazepoxide is the maximum dose, and many patients require less; a few, however, may require substantially more (Woo and Greenblatt, 1979). Patients in severe withdrawal and those with a history of withdrawal–related symptoms may require up to 10 days before benzodiazepines are completely withdrawn. Benzodiazepine administration should be discontinued once detoxification is completed.

For patients with severe hepatic disease, the elderly, and patients with delirium, dementia, or other cognitive disorders, short–acting benzodiazepines such as oxazepam or lorazepam are preferred by some clinicians. These agents have the advantage of being metabolized and excreted principally through the kidneys and may be more suitable for patients with poor hepatic function; they also do not have active intermediary metabolites that may accumulate. Unlike the longer–acting preparations, they can also be administered intramuscularly or intravenously. Because of their brief half–lives, the short–acting benzodiazepines need to be given more frequently (Sellers and Naranjo, 1983; Seppala et al., 1982; Gessner,1979).

Beta blockers (e.g., propranolol, 10 mg p.o. every 6 hours) have been used to reduce signs of autonomic nervous system hyperactivity (e.g., tremor, tachycardia, elevated blood pressure, diaphoresis) and, at higher doses, arrhythmias (Gross, 1982; Zilm et al., 1975; Sellers et al., 1975). Atenolol has been used for a similar purpose, usually combined with benzodiazepines (Kraus et al., 1985), thus allowing use of lower doses of benzodiazepines and thereby reducing the sedation and cognitive impairment often associated with benzodiazepine use.

Clonidine, an –adrenergic agonist (0.5 mg p.o. b.i.d. or t.i.d.) has been shown to reduce tremor, heart rate, and blood pressure (Wilkins et al., 1983; Robinson et al.,1989).

However, the use of either ß blockers or clonidine alone for the treatment of alcohol withdrawal is not recommended, because of their lack of efficacy in preventing seizures.

Barbiturates (e.g., pentobarbital, phenobarbital, and secobarbital) may be useful in reducing withdrawal symptoms in patients refractory to benzodiazepines (Robinson et al.,1989).

For patients manifesting delirium, delusions, or hallucinations, neuroleptics may be used, particularly haloperidol (0.5–2.0 mg i.m. every 2 hours as needed), in most cases less than 10 mg per 24 hours, although some patients may require considerably more. In such cases, neuroleptics are an adjunct to the benzodiazepines, since the former are not effective for treating the underlying withdrawal state.

The use of anticonvulsants to prevent seizures in patients with alcohol withdrawal syndromes is controversial (Smith, 1989; Gorelick and Wilkins, 1986). For patients with a prior history of withdrawal–related seizures, benzodiazepines are generally effective for this purpose. For patients

with a history of non–withdrawal–related seizures, their anticonvulsant medication should be continued or restarted. Patients currently taking phenytoin should have their dose increased to a minimum of 300 mg/day (Greenblatt, Shader, 1975). Oral as well as intravenous loading doses of 10 mg/kg, not to exceed an administration rate of 50 mg/min, should be given to patients who have discontinued phenytoin during a drinking spree (Sandor et al., 1981). The prophylactic use of phenytoin to prevent seizures during alcohol withdrawal is not indicated (Shaw, 1982, Rothstein, 1973). Carbamazepine (600–800 mg/day for the first 48 hours, then tapered by 200 mg/day) has also been demonstrated to be effective in preventing withdrawal–related seizures, although its tendency to lower white blood cell counts in some patients may pose an added risk of infection (Sampliner and Iber FL, 1974; Wilbur and Kulik FA,1981; Poutanen, 1979; Malcolm et al, 1989; Chu, 1979). Intramuscular magnesium sulfate has also been used for preventing withdrawal seizures (Post et al., 1983). Opioid dependence is associated with a high death rate– approximately 10 per 1,000 per year among untreated persons. Death most often results from overdose, accidents, injuries, or other general medical complications. Accidents and injuries due to violence associated with buying or selling drugs are also common and in some areas account for more opioid–related deaths than overdose or HIV infection.

The long–term course of opioid use is quite heterogeneous. Although many untreated individuals with an untreated opioid use disorder are able to maintain a pattern of abuse without ever meeting the DSM–IV diagnostic criteria for dependence, many do become dependent; among such patients, relapse following a long period of abstinence (e.g., after incarceration) is common. The latter finding suggests the importance of environmental and peer–related factors, along with drug availability, in the development and maintenance of this disorder.

The goals of treatment for patients with opioid use disorders are similar to those for patients with other substance use disorders. Although some opioid–dependent patients are able to achieve abstinence from all opioid drugs, many require and benefit from opiate agonist maintenance (e.g., with methadone or LAAM).

Periodic monitoring of patients for the presence of opioids and other drugs in breath, blood, or urine is a necessary component of any treatment program. Maintenance of a therapeutic alliance is often difficult with opioid–dependent patients, particularly those with comorbid antisocial personality disorder. Many such patients require an initial period of treatment in a structured drug–free setting in which there is a high level of staff experience and expertise in confronting denial and setting limits. The use of coercive pressure to encourage the patient to remain in treatment (e.g., through the legal system) can also be a useful external support for patients with poor impulse control and high levels of ambivalence about abstaining from nonprescribed substances.

Terapeutic communities

Therapeutic communities have been shown to be effective in the treatment of patients with opioid dependence. Simpson and Sells (1990) reported that in a large–scale study with a 12–year follow–up, individuals with opioid dependence treated in therapeutic communities had the most favorable outcomes, even after age and demographic variables were controlled for. However, these data are tempered by the fact that only 15%–25% of those admitted voluntarily completed the program.

Long–term treatment with methadone or LAAM is generally provided through specialized outpatient programs that are licensed to dispense these substances.

Treatments for Dependence and Abuse

1. Agonist substitution therapy. For many patients with chronic relapsing opioid dependence the treatment of choice is maintenance on long–acting opioids. Of these, methadone is the most thoroughly studied and widely used treatment for opioid dependence. LAAM is a longer–acting preparation that can be administered less frequently than methadone (discussed later in this section). Buprenorphine is a partial opioid agonist that has shown promising results in the longer–term treat-

ment of opioid dependence, but additional research is needed. The current formulation of buprenorphine for the treatment of opioid dependence is sublingual; an oral form remains to be developed. Experiments are being conducted on a combination of buprenorphine and low doses of naloxone to determine whether it reduces the chances for diversion and abuse.

The primary goals of methadone (or LAAM) maintenance are:

a) to achieve a stable maintenance dose that reduces opioid craving and illicit opioid use and

b) to facilitate engagement of the patient in a comprehensive program designed to prevent dependence or abuse of other substances and promote rehabilitation.

Since maintenance on methadone leads to the development of physiologic dependence and perhaps other CNS adaptations, federal guidelines limit the use of this modality to patients with a prolonged (e.g., more than 1 year) history of opioid dependence including (with some carefully defined exceptions) demonstrated physiologic manifestations. For patients who meet these legal criteria, the choice of methadone maintenance treatment is a matter of patient preference, assessment of the patient's past response to treatment, the probability of achieving and maintaining abstinence with other treatment modalities, and the psychiatrist's assessment of the short– and long–term effects of continued use of illicit opioids on the patient's life adjustment and overall health status.

Methadone maintenance treatment has generally been shown to be effective in decreasing the psychosocial and general medical morbidity associated with opioid dependence, with overall improvements in health status, decreased mortality, decreased criminal activity, and improved social functioning. Several studies also support the usefulness of methadone maintenance in reducing the spread of HIV infection among patients who administer drugs by injection (Metzger, 1993).

No single dose of methadone is optimal for all patients. Some may benefit from maintenance on low doses (10–20 mg/day), while others require more than 100 mg/day to achieve maximum benefit. Although 40–60 mg/day of methadone is usually sufficient to block opioid withdrawal symptoms, higher doses (averaging 70–80 mg/day) are usually needed during maintenance treatment to block craving for opiates and associated drug use. In general, higher doses (i.e., 60 mg/day) are associated with better retention and outcome (Ball and Ross, 1991; Joe et al, 1991). If higher doses are used, monitoring of plasma methadone concentrations may be helpful, with the aim of maintaining minimum levels of 150–200 ng/ml (Schottenfeld and Kleber, 1995). Retention rates for patients in methadone maintenance programs exceed 60% at 6 months, with up to 90% reduction in illicit opioid use in the patients who remain in treatment (Hubbard et al,1989).

Key issues in methadone maintenance treatment include determining a dose sufficient to suppress opioid withdrawal and craving, deciding on the appropriate duration of treatment, and including this modality within a comprehensive rehabilitation program. Programs that stress rehabilitation and long–term methadone treatment have been associated with the availability of more general medical and psychiatric services (Joe, 1991; McLellan et al, 1992) and higher overall program quality (Ball and Ross, 1991). Majority of programs may fail to provide optimal treatment. In some studies, use of higher doses of methadone has been associated with better overall outcome (Joe et al, 1991); in others, high–dose methadone has been associated only with less heroin use (Ball and Ross, 1991). Behavioral monitoring, random urine testing to assess recent illicit drug use, and linking the results of urine tests to counseling and other contingencies also improve outcomes (McLellan et al, 1993, 1994).

LAAM is a long–acting preparation that also reduces craving for opioids. LAAM is usually prescribed in doses of 20–140 mg (average, 60 mg) (Ciraulo and Jaffe,1991). Some patients prefer LAAM to daily methadone since dosing can be as infrequent as three times per week (Tennant et al, 1986), thus allowing for fewer clinic visits and expanded integration into work or other rehabilitative activities. While treatment with LAAM has been shown to be comparable to methadone treatment with respect to reduction of opioid use (Tennant et al, 1986; Ling et al 1978; Zangwell et al,1986), retention rates are reportedly higher for patients treated with methadone at doses of 80–100 mg/day. In general, longer duration of LAAM treatment (i.e., 6 months) is associated with better outcome.

Precipitous discharge from maintenance programs and concurrent withdrawal of methadone are associated with a high rate of relapse to illicit opioid use (Des Jarlais et al,1981; McGlothin and Anglin, 1981). Voluntary termination of methadone maintenance also carries a high risk of relapse, even for patients who have responded well to treatment. Patients who choose to voluntarily discontinue maintenance treatment should receive supportive treatment during detoxification and aftercare services to aid in maintaining abstinence (Nurco et al, 1991). Patients who relapse repeatedly despite such support should be given the option of voluntary lifetime maintenance on methadone.

2. Opioid antagonist treatment. Maintenance on the opiate antagonist naltrexone is an alternative to methadone maintenance. The goal of treatment is to block the effects of the usual street doses of heroin or other opioids, thereby discouraging opioid use and facilitating extinction of classically conditioned drug craving (Wikler and Pescor, 1967). Because of its long duration of action (24 to 72 hours, depending on the dose), naltrexone can be administered three times per week (100 mg p.o. on Monday and Wednesday, 150 mg on Friday). Because it has no abuse potential, naltrexone can be an important adjunct in the treatment of patients with opioid use disorders (Gonzales and Brogden, 1988).

Adverse effects of naltrexone may include dysphoria, anxiety, and gastrointestinal distress. Like other opioid antagonists, naltrexone can precipitate severe withdrawal symptoms when administered to patients who are physiologically dependent on opioids. In general, naltrexone should be administered only to patients who have been withdrawn from opioids under medical supervision and have remained opioid free for at least 5 days after the use of heroin or other short–acting opioids, or 7 days after the last dose of methadone or other longer–acting opioids. Before naltrexone treatment is begun, a test dose of naloxone, 0.8 mg i.m., should be used to assess the degree of opioid dependence. The interval between completion of opioid detoxification and initiation of naltrexone treatment is a period of high risk for relapse. For this reason rapid opioid withdrawal, with use of clonidine and naltrexone, has been used to shorten the interval between detoxification and initiation of naltrexone maintenance (Kleber,1994; Brewer et al, 1988). Repeated naloxone doses have also been used with clonidine to shorten opioid detoxification.

Although naltrexone is extremely effective when taken as prescribed, its utility is often limited by lack of patient compliance and/or low treatment retention. Compliance is improved when drug administration is directly observed and supervised by a designated health care professional, responsible family member, or work supervisor (Meyer, 1979). Treatment retention is facilitated by family involvement in treatment planning and by the use of behavioral contingencies (i.e., reinforcement or punishment) (Anton et al, 1981). Higher rates of success with naltrexone have also been reported for court–mandated treatment and for physicians or other professionals who are at risk of losing their professional licenses if they do not comply with treatment (Washton et al, 1984).

Management of withdrawal

The treatment of opioid withdrawal is directed at safely ameliorating acute symptoms of withdrawal and facilitating entry into recovery and/or rehabilitation programs. Four pharmacologic strategies are in general use:

a) methadone substitution, with gradual methadone tapering;
b) abrupt discontinuation of opioids, with use of clonidine to suppress withdrawal symptoms;
c) clonidine–naltrexone detoxification, where withdrawal symptoms are precipitated by naltrexone and then suppressed by clonidine; and
d) buprenorphine substitution, followed by discontinuation (abrupt or gradual) of buprenorphine.
e) other medications

a. Methadone substitution. Methadone hydrochloride is highly effective in ameliorating the signs and symptoms of opioid withdrawal. While the use of narcotics to detoxify or maintain

patients with opioid dependence requires special licensing, this regulation is waived for inpatients with life–threatening general medical or psychiatric conditions.

The procedure for opioid detoxification with methadone involves stabilizing the patient on a daily dose of methadone that is determined by the patient's response (based on objective signs of withdrawal) to a dose of 10 mg every 2–4 hours as needed (Kleber,1989; 1981). During the first 24 hours, 10–40 mg will stabilize most patients and control abstinence symptoms. Once the stabilization dose is determined, the drug can be slowly tapered (e.g., by 5 mg/day). In inpatient settings, detoxification from heroin or other short–acting opioids can usually be completed within 7 days, but a more gradual tapering will result in a smoother clinical course. The detoxification of patients from longer–acting opioids (e.g., methadone) generally is done over a much longer period (federal regulations allow methadone detoxification in licensed facilities to last as long as 180 days). The benefits of slow tapering include greater patient comfort and more time in which to strengthen other therapeutic interventions. When the methadone dose drops below 20–30 mg/day, many patients begin to complain of renewed (but milder) abstinence symptoms. These may be ameliorated by the addition of clonidine (see the following section). Unless patients can be sufficiently motivated to complete the course of treatment, the dropout and relapse rates during this stage of methadone–assisted withdrawal are very high.

b. Clonidine–assisted detoxification. Clonidine is a nonopioid antihypertensive drug that has been used successfully to reduce symptoms of opioid withdrawal. It acts by stimulating midbrain 2–adrenergic receptors, thereby reducing the noradrenergic hyperactivity that accounts for many of the symptoms of opioid withdrawal. Clonidine suppresses nausea, vomiting, diarrhea, cramps, and sweating but does little to reduce the muscle aches, insomnia, and drug craving that often accompany opioid withdrawal. Some patients are extremely sensitive to clonidine and experience profound hypotension, even at low doses.

Protocols for clonidine detoxification have been described by Kleber (1994). On the first day of treatment, clonidine–aided detoxification involves 0.1 to 0.3 mg in three divided doses, which is usually sufficient to suppress signs of opioid withdrawal; inpatients can generally receive higher doses because of the greater availability of staff monitoring for hypotension and sedation. The dose is adjusted until withdrawal symptoms are reduced. If the patient's blood pressure falls below 90/60 mm Hg, the next dose should be withheld, after which tapering can be resumed while the patient is monitored for signs of withdrawal. In the case of short–acting opioids, such as heroin, clonidine–aided withdrawal usually takes 4–6 days, whereas withdrawal from methadone usually takes 10–14 days.

Clonidine has some advantages over methadone in that it does not produce opioid–like tolerance or physical dependence, it avoids the postmethadone rebound in withdrawal symptoms, and patients completing a course of clonidine–assisted withdrawal can be immediately given an opioid antagonist (e.g., naltrexone) if indicated. The disadvantages of clonidine include insomnia, sedation, and hypotension as side effects. In addition, clonidine will not ameliorate some symptoms of opioid withdrawal, such as insomnia and muscle pain, which may require additional treatments. Contraindications to the use of clonidine include acute or chronic cardiac disorders, renal or metabolic disease, and moderate to severe hypotension (Jasinski et al, 1985).

In general, clonidine–assisted detoxification is easier to carry out in inpatient settings, where it is possible to use higher doses to block withdrawal symptoms while monitoring side effects (e.g., hypotension). Clonidine–induced sedation is also less of a problem for inpatients. However, with experienced staff, outpatient detoxification with clonidine is a reasonable approach. Outpatients should not be given more than a 3–day supply of clonidine for unsupervised use, since treatment requires careful dose titration and clonidine overdoses can be life threatening (Gold et al, 1980).

While clonidine can be an effective alternative to methadone for treating opiate withdrawal, it does not substantially shorten the time required for withdrawal. In addition, the completion rate for clonidine–treated outpatients is relatively low and roughly comparable to that with methadone (Kleber et al, 1987; Vining et al, 1989).

c. Clonidine–naltrexone ultrarapid withdrawal. The combined use of clonidine and naltrexone has been demonstrated as safe and effective for rapidly withdrawing patients from heroin or methadone. Essentially, naltrexone–precipitated withdrawal is avoided by pretreating the patient with clonidine (Vining et al, 1988; Charney et al,1986). The technique is most useful for opioid–dependent patients who are in transition to narcotic antagonist treatment.

O'Connor et al. (1992) reported that 95% of patients successfully completed detoxification with clonidine and naltrexone on an outpatient basis. However, the limitations of this method of detoxification include the need to monitor patients for 8 hours on day 1 (because of the potential severity of naltrexone–induced withdrawal) and the need for careful blood pressure monitoring during the entire detoxification procedure.

d. Buprenorphine. Buprenorphine is a partial opioid agonist. At low doses (2–4 mg/day sublingually), the drug blocks the signs and symptoms of opioid withdrawal. Because it is only a partial agonist, high doses (i.e., 8 mg/day) do not produce as much respiratory depression or other agonist effects as do comparably high doses of pure agonists (e.g., morphine). Patients treated with low doses may be able to stop taking the drug abruptly and experience milder symptoms of opiate withdrawal than after taking heroin or methadone. In experimental studies (Mello and Mendelson,1980) buprenorphine has been shown to suppress heroin use in both inpatient and outpatient settings.

e. Other medications. There is considerable controversy, and few factual data, about the use of sedative–hypnotics or anxiolytics to treat the insomnia, anxiety, or muscle cramps associated with opioid withdrawal. Some psychiatrists maintain that the abuse potential of CNS depressants for these patients is too great and may also precipitate craving for opioids and relapse. Others feel that for carefully selected patients and with appropriate monitoring, use of benzodiazepines over a relatively brief period (i.e., 1–2 weeks) may be helpful in ameliorating the often–debilitating insomnia that can accompany opioid withdrawal (O'Connor,1992). Hydroxyzine, and sedating antidepressants (e.g., doxepin, amitriptyline, and trazodone) have also been used for this purpose. It should be noted that these medications may also be abused, although much less often than the benzodiazepines (Kleber, 1994).

IV. Cocaine–Related Disorders: Treatment Principles

Cocaine–related disorders are most commonly found in persons aged 18–30 and are almost equally distributed between males and females. In a 1991 study, 12% of the U.S. adult population reported using cocaine one or more times in their lifetimes. A community study conducted in the early 1980s indicated that about 0.2% of the adult population have had cocaine abuse at some time in their lives (American Psychiatric Association–Diagnostic and Statistical Manual of Mental Disorders,1994). It is likely that the prevalence of abuse is now higher since the overall use of cocaine has increased since that time.

Cocaine smoking is associated with a more rapid progression from use to dependence or abuse than is intranasal use (Gorelick, 1992). Dependence is commonly associated with a progressive tolerance to the desirable effects of cocaine, leading to increasing doses. With continuing use there is a diminution of pleasurable effects due to tolerance and an increase in dysphoric effects. Few data are available on the long–term course of cocaine–related disorders (American Psychiatric Association–Diagnostic and Statistical Manual of Mental Disorders,1994).

The goals of treatment for patients with cocaine use disorders are identical to those for patients with other forms of substance use disorders; these include abstinence, relapse prevention, and rehabilitation. Psychiatric management is an important component of a successful treatment plan.

Choice Of Treatment Setting

In general, the choice of a setting depends on the clinical characteristics of the patient, the preferences of the patient, the treatment needs, and the available alternatives. As in the treatment of all patients with substance–related disorders, the least restrictive setting that is likely to facilitate safe and effective treatment is preferred.

Several studies have indicated that most patients can be effectively treated for cocaine abuse in intensive outpatient programs (McKay et al.,1992; Alterman et al, 1994). Although in one non-randomized study (Budde et al,1992) a group of 149 inpatients fared better at 1–year follow–up than did patients treated in an outpatient setting, a randomized study (Alterman et al, 1994) revealed no difference in outcome after 3 and 6 months between patients assigned to inpatient and partial hospital care.

Pharmacologic Treatments for Dependence and Abuse

Although a number of studies have shown promising results with a variety of pharmacotherapeutic agents, no medication has been found to have clear–cut efficacy in the treatment of cocaine dependence (Gorelick, 1993; Kosten and McCance–Katz, 1995). Consequently, pharmacologic treatment is not ordinarily indicated as an initial treatment for many patients with cocaine dependence. However, patients with more severe forms of cocaine dependence or individuals who do not respond to psychosocial treatment may be candidates for a trial of pharmacotherapy. Thus far, desipramine and amantadine appear to have had the most positive (although mixed) results, although other medications may prove to be more successful.

1. Drugs to reduce symptoms of cocaine abstinence or craving. Over 20 different medications have been studied in the search for an effective pharmacologic treatment for cocaine dependence. Most of these studies have been hampered by methodological problems, including lack of adequate controls and consistent outcome measures (e.g., urine tests rather than self–reports), failure to standardize the type and "dose" of the accompanying psychosocial interventions, lack of clarity about the importance of craving in the maintenance of cocaine dependence, the role of craving in the natural course of untreated cocaine abstinence syndrome, and lack of agreement as to the exact meaning of the term "craving" (Gawin and Kleber, 1986; Weddington et al, 1990).

Desipramine to be more effective than either lithium or placebo in reducing cocaine use by outpatients without coexisting mood disorders. More recent reports (Arndt et al., 1989;Weddington et al.,1991; Kosten et al.,1992) have failed to confirm these positive findings, possibly because of differences in patient population and route of cocaine administration.

Initial studies of carbamazepine in the treatment of cocaine dependence yielded some favorable results (Halikas et al.,1991,Halikas et al.,1991), but subsequent double–blind, placebo–controlled studies failed to establish the efficacy of carbamazepine for these patients (Cornish et al.,1992; Montoya et al.,1994).

Other agents used in the treatment of cocaine dependence have included pergolide (Malcolm et al., 1991), L–dopa/carbidopa (Wolfsohn and Angrist, 1990), fluoxetine (Pollack and Rosenbaum, 1991), flupentixol (Gawin et al.,1989), bupropion (Margolin et al.,1991), amantadine (Kosten et al.,1991), and maprotiline (Brotman et al, 1988). All have shown some promise, but in relatively small, uncontrolled trials.

The mixed opioid agonist/antagonist buprenorphine has shown some promise in open trials in the treatment of patients dually dependent on cocaine and opioids (Kosten et al., 1989).

Future directions.

DA uptake inhibitors

These are drugs with mild psychomotor stimulant effects (e.g., DA uptake inhibitors), but with other effects that may block the positive effects of cocaine or enhance the negative effects of cocaine. (Acri et al. 1994)

Blockade of cocaine pharmacological effects by treatment with drugs with specific targets may alter acute cocaine effects. (Kosten and Nestler 1994)

- **Clozapine:** An atypical neuroleptic has been shown to inhibit cocaine–conditioned place preference. (Heidbreder and Shippenberg 1994)
- **SCH23390:** A D1 antagonist that has been shown to attenuate cocaine effects in an animal model. (Sepinwall et al. 1992)
- **Dextrophan and dextromethorphan:** NMDA antagonists that have shown some evidence for attenuation of cocaine effects in animal studies.

Management of withdrawal syndrom

Cessation of cocaine use does not always cause specific withdrawal symptoms, although anhedonia and drug craving are common. However, many people experience a characteristic withdrawal syndrome within a few hours to several days after the acute cessation of, or reduction in, heavy and prolonged cocaine use.

The clinical features and duration of the cocaine abstinence syndrome are still somewhat controversial and ill defined. An early uncontrolled outpatient study (Gawin and Kleber, 1986) characterized withdrawal as progressing through three phases: an acute "crash" phase, a period of more gradual withdrawal, and an extinction phase lasting 1 to 10 weeks. Acute withdrawal (crashing) is seen after periods of frequent high–dose use. Intense and unpleasant feelings of depression and fatigue, at times accompanied by suicidal ideation, have been described during this phase. More–recent inpatient studies (Weddington et al.,1990; Satel et al., 1991), however, have suggested that cessation of regular cocaine use is associated with relatively mild symptoms of depression, anxiety, anhedonia, sleep disturbance (i.e., insomnia or hypersomnia), increased appetite, and psychomotor retardation, which decrease steadily over several weeks.

Dopamine agonists, such as amantadine (200–400 mg/day), were initially thought to be effective in reducing symptoms of cocaine withdrawal, craving, and subsequent use (Cornish et al.,1992; Handelsman et al., 1988), but two more–recent studies (Weddington et al., 1991; Kosten, 1992) failed to confirm this finding. The management of withdrawal syndrom is an important problem and new tentatives to choose a therapeutic way.

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COGNITIVE – BEHAVIORAL THERAPY IN DRUG ADDICTION

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One of the most complete definition of the addiction is that of Donovan and Marlatt (1988), as a complex,progressive behavior pattern having biological, psychological, sociological and behavioral components. They see such a pattern differing from others by the individual's overwhelmingly pathological involvement in or attachment to it, subjective compulsion to continue it, and reduced ability to exert control over it.

Donovan and Marlatt list common denominators of addictive behaviors:

- The individual choosing to mentain the addictive involvement even when other, more gratifying sources of reinforcement are present.
- Dependence upon the behavior or experience, on either a physiological or psychological level, that may lead to withdrawal distress when the individual is prevented from engaging in the behavior.
- Increasing high need for a given experience or behavior representing a form of tolerance.
- Perceiving the need for the experience or a powerfully strong desire in the form of craving having both physiological and cognitive underpinnings, the strength of the craving being gauged by how willing the person is to sacrifice other sources of reward or wellbeing in life to continue to engage in the addictive behavior.
- The power of the addictive experience promoting a tendency for rapid reinstatement of the behavior pattern following a period of non–involvement with it.

Donovan and Marlatt's working definition of addictive behaviors is applicable to each of Orford's (1985) descriptions of the phenomenology of excessive drinking, gambling, drug taking, eating and sexuality, despite the seeming exclusiveness and diversity of these behaviors.

For the past several years cognitive therapy has been refined to help people addicted to alcohol, nicotine, cocaine, heroin, marijuana, and other psychoactive substances. The cognitive therapy of substance abuse is quite similar to cognitive therapy for other psychological problems, including depression, anxiety and personality disorders. Each places emphasis on collaboration.case conceptualization,structure, pacient education, and the application of standard cognitive–behavioral techniques. In addition, when working with substance abuse patients, cognitive therapists focus on the cognitive and behavioral sequences leadind to drug use, management of cravings, avoidance of high–risk situations, case management, mood regulation and lifestyle change.

In the cognitive–behavioral therapy of substance abuse, thoughts and beliefs are viewed as playing a major role in the mediation of addictive behaviors (actual drug use), negative emotions (anxiety,depression, anger), and physiological responses (including some withdrawal simptoms). Although strategies and interventions vary somewhat from individual to individual and from drug to drug, the basic conceptualisation of the patient in cognitive terms remains constant.

When timely and appropriate,cognitive therapists assess the development of their pacients beliefs about themselves, their early life experiences,exposure to drugs or alchool, the development

of drug–related beliefs, and their eventual reliance on drugs.An important assumption is that substance abuse is learned and can be modified by changing cognitive–behavioral processes.

All therapies of substance abuse has been substantially influenced by the Marlatt and Gordon's model (1985,1989), based itself on the model of behavior change imagened in 1983 by Prochaska and Di Clementi.

The central concept of this model is that the behavior change takes place through a series of discrete stages.

The precontemplation stage is the period prior to the individual recognising the need to change. The next stage in the change process is the contemplation stage where the person recognises the problem and considers doing something about it. It is possible for the individual to remain at this stage indefinitely if ambivalence to move on the next stage is not resolved. The active change stage is where the individual attempts to change behavior by his or her own efforts or by seeking outside help (treatment). The final stage is the maintenance stage where the individual struggles to maintain the changes made.

An important feature of this model is that it is a circular model of change as opposed to a linear one. This offers a more optimistic approach to behavior change. If the person relapsed, he or she could re–enter the cycle and go through the process again until the desired outcome was reached.

The implication of treatment matching is the most salient aspect of this model. Each phase may require a very specific therapeutic approach which may or may not be complementary to general counselling the client is receiving. For example if the client is in the precontemplation stage, the therapeutic approach most suitable would be "motivational interviewing", whereas a client centered type of counselling approach may not necessarily move the client on to doing something about his or her addiction.

Relapse prevention is clearly aimed at the maintenance phase in the model. It is also aimed at getting a person back into the cycle following a relapse. Re–entry could be back into any phase. Relapse prevention aims to facilitate the process.

Lapse or relapse?

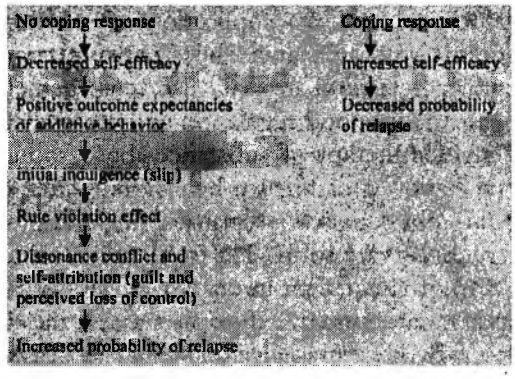
With the traditional definition of relapse, any "lapse" or "slip" is viewed as a switch which turns on a full blown relapse. This view of lapse = relapse takes away any potential for learning or corrective action. When the "lapse = relapse"view becomes firmly engraved in a persons belief system it invariably acts as a self–fulfilling prophecy,e.g. "one drink and a drunk".It does not leave any margin for error.

We consider the lapse not to be a relapse, but only a discrete violation of a self–imposed rule or a set of regulations governing the rate or pattern of a selected target behavior.

Preventing a slip or a lapse from becoming a full blown relapse is one of the main objectives of the relapse prevention programme. Relapse is viewed as not taking place as one event, like turning on a switch, but through a series of cognitive, behavioral and affective processes.

A model of relapse based on such a view has been formulated by Marlatt and Gordon (1985) in the next figure:

High–risk situation



The principles that apply to all patients who abuse substances, are:

1. Cognitive therapy is based on a unique cognitive conceptualization of each patient.
2. A strong therapeutic alliance with the active collaboration of patient and therapist is essential.
3. Cognitive therapy is goal oriented and problem focused.
4. The initial focus of therapy is on the present.
5. Cognitive therapy is time sensitive.
6. Therapy sessions are structured, with active participation by both therapist and patient.
7. Patients are taught to identify, evaluate, and respond to their dysfunctional thoughts and beliefs.
8. Cognitive therapy emphasizes psichoeducation and relapse prevention.

Conceptualization of the case includes an analysis of the current problematic situations of substance abusers and their associated thoughts and reactions (emotional, behavioral,and physiological). Therapists and pacients look for themes expressed in the patients automatic thoughts and the meaning of their thoughts to identify their most basic, dysfunctional beliefs about themselves, their worlds,and other people (e.g. "I am inadequate,worthless, weak", "The world is a hostile place","People will take advantage of me"). They also identify the consistent patterns of behavior that patients develop to cope with these negative ideas (e.g. taking drugs, distancing themselves from others).

At an initial session and periodically after that, therapists ask patients to set goals. They guide patients to specify objectives in specific behavioral terms by asking "How would you like to be different by the end of therapy and what would you like to be doing differently?" As they have unrealistic expectations ("being happy"), therapists would aid patients in identifying shorter–term goals, in behavioral terms, like getting a job he or she enjoys,entering into a satisfaying intimate relationship,getting along better with her family, and staying off drugs.

Therapists initially emphasize current problems and specific situations that are distressing to the patient. When the patient has a comorbid diagnosis, it is important to address problems related to both (how to learn coping strategies, how to decrease the anger by rehearsing a coping statement addressing her activated core belief, how to use anger management techniques such as controlled breathing and time out, and how to talk in a reasonable, effective manner, through role playing, how to respond to automatic thoughts).

The course of therapy for many patients with substance abuse varies dramatically, depending on the severity and course of the substance use. Weekly sessions are recommended until symptoms are significantly reduced and substance use has diminished or stopped. With effective treatment patients stabilise their moods, learn more tools, and gain confidence in their ability to use alternate coping strategies when in distress. At this point therapist and patient may experiment with spacing out therapy sessions. Typically they reduce the frequency of sessions from once a week to once every two weeks, then to once every 3 or 4 weeks, until termination, unless otherwise indicated. After termination, patients are advised to return to therapy when life stressors activate dysfunctional beliefs and they find they are tempted to resort to drug use again.

Typically, therapists try to adhere to a fairly fixed structure to function efficiently during the session. Usually therapists first check their patients mood (preferably eliciting a self–report as well as by using objective measures of depression, anxiety and hopelessness). Therapists also ask a standard question about the frequency and amount of substance use in the past week.

Next the therapist and patient collaboratively set an agenda and decide which problem to focus on in the session. Standard agenda items include the successes and difficulties the patient experienced during the past week in dealing with high–risk situations and cravings and upcoming situations that could lead to drug use or drop out.

Research into the relapse process has shown that the primary obstacle that a person encounters in the maintenance phase is exposure to a high–risk situation (HRS). A HRS can be defined as any situation or condition that poses a threat to the individual's sense of control (self–efficacy) and increases the risk of potential relapse. Research shows that HRS are associated with intra–personal

determinants such as negative and positive emotional states and inter–personal determinants that include the inter–personal conflict and the social pressure.

The negative emotional states (moods and feelings) such as anger, frustration, anxiety, sadness, depression and boredom are conditions placed within the individual, that were perhaps previously dealt with by indulging in the addictive behaviour. If this was the case, the individual would have poor coping responses to deal with this states.

The inter–personal determinants include conflicts with friends, marital partners, family members, co–workers and employers. Direct or indirect social pressure is another general situational category associated with high rates of relapse. An example of direct pressure would be a situation where an individual or group coerce or attempt to persuade an individual to indulge in the addictive behavior. A situation of indirect pressure would be one in which the individual perceived a pressure to conform, perhaps by lighting a cigarette at a party because everyone else was smoking.

Some of these situations may be avoidable but the majority may not be. Hence whether or not the person has the ability to cope with high–risk situations becomes a crucial factor in preventing relapse.

Coping is a key element in the relapse prevention model which has it's foundations in health psychology and behavioural medicine.

Together with increasing awareness and lifestyle change, identifying, learning and strenghtening coping responses forms the main goals of relapse prevention. They are dealt with as:

(1) ***Specific intervention strategies*** (e.g. skills training).

(2) ***Global intervention strategies*** (e.g. lifestyle change).

The specific intervention strategies include any intervention that is target towards a client's specific vulnerabilities or high–risk situations.These are interventions that are focused on immediate causes/events that point to relapse. For example, for a client with a drinking problem who has a tendency to relapse when under social pressure to drink, assertiveness skills training would be a specific intervention strategy. For a client who lights up a cigarette when feeling anxious or tense, teaching relaxation techniques would be a specific intervention strategy. The aim of specific intervention strategies is to teach the client the skills of anticipating and coping with high–risk situations.

The global self–control strategies are aimed at making general and global changes in the individual. The interventios included in this category range from interventions that are aimed at how a person approaches and solves problems to changing their whole lifestyle. Whereas "specific interventions"aim towards developing mechanistic type responses (how to cope with a given high–risk situation), "global interventions"aim at more general,deep–structured long–term change in the individual. The latter could include, for example, interventions to change attitude, lifestyle, diet, self–confidence and ways of interpreting situations.

From a therapist's point of view the category of global interventions can include the whole spectrum of psychological therapies depending on the client's needs. This could range from problem solving therapy to long– term dynamic psychotherapy.

In general, especially in short–term therapy, both specific and global interventions can be used concurrently in relapse prevention. Some strategies, such as assertiveness training can be both a specific and global intervention.The dichotomy is only made so that the therapist would be clear in his or her mind and could communicate clearly to the client the overall aim of each intervention.

The intervention strategies of the relapse prevention programme can be placed in the following broad categories:

– Assessment procedures.
– Insight/awareness increasing procedures.
– Skills training.
– Cognitive strategies.
– Lifestyle interventions.

The distinction between assessment and intervention is sometimes arbitrary. This is indeed the case in relapse prevention where many of the assessment procedures (e.g. self–monitoring) often prove to be very effective interventions.

Behavioural assessment is mainly aimed at quantifying the addictive behavior (the number of cigarettes, units of alcohol, consumed per day), identifying high–risk situations, coping skills and deficits. In general behavioral assessment is used at the beginning of a relapse prevention programme. On the other hand assessment techniques such as self–monitoring (the craving diary) can be used throughout a programme.

Assessment methods that can be used in a relapse prevention programme are listed below:

1. ***Direct observation.*** This could be carried out in natural situations (observing a problem drinker in a pub,a smoker at a party) or in analogue situations (role–play). In analogue situations, which afford the luxury of pre–planning and setting up, the use of video camera is an invaluable aid. This enables close analysis of bahavior that is not possible otherwise.

2. ***Self monitoring has the widest application in the relapse prevention.*** Getting a person to keep a detailed record of an activity is all that it entails. When this is suggested to clients it is often met with a response of bemusement or indignation. A common response from clients who are uncomfortable or resistant to the idea is "I can tell you now", followed by a description of their activities. Yet, once persuaded to do so, clients invariably return with very positive feedback with the exercise having considerable impact. With some clients the insight gained from this intervention alone has proved sufficient to change behaviour.

The objectives of self monitoring can be listed as follows:

– to get the client to conciously focus on the behaviour he or she whishes to change;
– to discover the behaviour or habit patterns (when, how and where);
– to identify possible triggers;
– to identify high–risk situations (low mood, conflict,social pressure,etc.);
– to identify the consequences of the behavior to the individual/people around them;
– to calculate the cost to the individual in physical, emotional and financial terms.

Self–monitoring can be used at any stage of the programme. In abstinence orientated programmes "craving diaries" are an example of self–monitoring that can be used throughout the programme.

Self–monitoring also helps the client to break down systems of denial and identify errors of thinking (cognitive distortions).

3. ***Interviews.*** These are standardised interviews designed to collect information for behavioural assessment.

4. ***Role–play aims to find out whether or not a client has specific skills*** (e.g. assertive skills) to cope with the high–risk situations (for example body posture when refusing drink).

5. ***Questionnaires.***

Insight / awareness increasing procedures.

We get the client to describe past relapses or possible future relapses in a form of a map .Clients are encouraged to identify possible future dangers (high risk situations) as destinations and to identify too, early warning signs that would indicate that they are heading towards their destination. The early warning signs are explored as decisional points where turning off to take an alternative route could be made. At each decisional point clients are advised to list the arguments against heading towards the destination. These techniques could also be used toward the end of the programme when a client can be asked to describe alternative routes in terms of skills, techniques and strategies to avoid these destinations that have been learnt in the relapse prevention programme.

Identifying and coping with high–risk situations were described as the main goals of relapse prevention. Getting clients to produce relapse fantasies is another useful technique to help achieve these goals.This tool offers information about the client's self image and the role of the addictive behavior in that image. As an intervention strategy it invariably produces increased awareness in the client about his or her vulnerabilities and high–risk situations.

Skills training and behavioural procedures.

Relaxation training

Anxiety often lies at the root of addictive behaviours and acts as a major factor in their maintenance. Many clients would not have learnt other coping responses or would have lost other coping skills, thus taking away the addictive behaviour would make them feel particular vulnerable when faced with anxiety. For a person without coping skills, everyday life stressors could become high–risk situations. Relaxation training is a tried and tested (Jacobson,1976) strategy for coping with anxiety. Relaxation training is recomended at the end of each session.

Assertiveness training

Social skills deficits are often found in individuals with addictive problems.

Assertion is the ability or insistence to stand up for one's own rights or opinions while not infringing on the rights of others. Assertive behavior is needed when there is some conflict of interests, for example creating time for oneself rather than looking after friends. The ability to be assertive is essential for balancing lifestyle.

An individual can respond to conflict situations in one of three ways. These are:

– to be passive, fearful and to flee.This may include avoidance behavior and refusing to recognise or deal with feelings;
– to be aggressive, to show anger and fight.This may include a personal attack, using retaliation, pulling rank or condescension and assuming superiority;
– to be assertive, self–confident and confront the situation directly.

Assertive behaviour conveys a sense of one's own self–assurance and respect for the other person. It is about stating one's position clearly and distinctly while the norms of personal space are observed and kept within an acceptable range. Being assertive can be divided into three broad areas:

• Speech
• Body language
• Thoughts/cognitive processes

A person appears more assertive when all the components are used together. The speech is divided into what is being said and how it is being said. What is being said would largely depend on the individual's interpretation of his or her rights. Statements should be clear and distinct. What is being said is important, but how it is said is vital.

Body language is comprised of a number of elements, including posture, distance, facial expression eye contact and gestures. Posture should be relaxed, upright, open and balanced. Being tense and erect will give the impression of being aggressive, while being slumped and closed in will give the impression of submission.

Expectations of being able to carry out a certain behaviour will affect whether that behaviour is carried out. Similarly, expectations of the consequences of the behaviour are likely to influence behaviour. Assertive behaviour is also closely tied to an individual's beliefs in his or her rights and other people's rights. Some of the basic rights include:

• Expressing oneself.
• Being treated with respect.
• Stating one's needs and priorities.
• Dealing with people without having to make them like or approve of you.

Research shows that people with addictive behaviours are particularly defficient in assertiveness skills.

Cue Exposure

The exposure to cues associated with the addictive behaviour give rise to urges and craving that leads to slips and relapses. For some, exposure to cues constitutes a major high risk. Cue exposure is a counter conditioning procedure that can be used to deal with conditioned craving. This involves exposing the individual to stimuli associated with the addictive behaviour under control conditions (such as in the presence of a therapist). The rationale behind this is that exposure to stimuli would result in adaptation / habituation. Riding out urges and cravings this way, not only diminish-

es the effectiveness of the stimuli to trigger a response, but also helps increase the clients' confidence (self–efficacy) of being able to resist the response.

Cognitive strategies

Relapse in addictive behaviours is often associated with errors in thinking and typical patterns of thinking such as rule violation effect and seemingly irrelevant decisions. Identifying and changing this patterns of thinking and thinking errors form a major part of relapse prevention interventions.

Some of these kinds of distortions or faulty beliefs that must be restructured by the cognitive therapy are:

- All or nothing thinking, black and white categories.
- Overgeneralisation: you view a negative event as a never–ending pattern of defeat.
- Mental filter: you dwell on the negatives and ignore the positives.
- Discounting the positive: you insist that your accomplishments or positive qualities and achievements don't count or anyone can do them.
- Jumping to conclusions.
- Magnification or minimisation.
- Emotional reasoning.
- "Should" statements.
- Labelling.
- Personalisation.

Lifestyle interventions

Marlatt and Gordon's (1985) model of relapse places unbalanced lifestyle as a fundamental factor in the relapse process. The underlying assumptions in the relapse prevention programme are that:

– stress of various kind makes relapse into addictive behaviour more likely;
– relapse may be prevented if either the sources of stress are reduced or one's capacity to cope with them is improved.

A balanced lifestyle implies a balance between the stress and the coping mechanisms.

Coping include anxiety management skills,social skills and self–monitoring of depressive thoughts.

The sources of stress are: major life events, daily hassles and imbalance between should and wants.

Substitute indulgences

A substitute indulgence could be any activity that could provide immediate gratification and act as a diversion from indulging in the addictive behavior. The therapist could work out with the client a list of activities that could be used when the client is experiencing a strong compulsion (urge, craving) to indulge in the negative addiction. If this activities can be built into the client's lifestyle it then becomes a global intervention. Having a deep bubbly bath when feeling an urge to drink instead of going to the pub can be taken as an example.

Relapse prevention is aimed at the maintenance phase of habit change.This phase is preceded by either an initial phase of treatment or a clear decision about change and goals.

For addictions such as drug and alcohol misuse, the premaintenence or initial phase of treatment may involve detoxification in an inpatient or community setting. In general the initial phase of treatment for addictions may include intensive psychological therapy or assessment (for example motivational interviewing). An intensive initial phase of treatment is particularly applicable when the treatment goal is abstinence. The initial treatment would focus on the immediate physiological and psychological consequences of withdrowal. This may involve chemical and psychological interventions to deal with physical disconfort and acute anxiety (withdrowal distress) associated with the cessation of the addictive behavior.

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LEGISLATIVE PROVISIONS REGARDING DRUG CONSUMPTION AND ADDICTION VERSUS SPECIALIZED MEDICAL CARE

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Motivation

More and more voices from the millieu authorized and qualified for the struggle against the illicit drug consumption and the care of addicts complain about the lack of some firm, explicit and complete normative acts.

Such attitudes are partly justified by the fact that the normative acts in action regarding this phenomenon were elaborated during a historical stage when in our country the consumption of substances and the presence of addicts were a sporadic, seldom, medically and socially irrelevant phenomenon.

Due to the perspectives – underlined by more and more specialists involved into the estimation of this phenomenon (police, medical bodies, mass media, justice etc.) of changing our country from one of transition for drugs into a country of drug consumption it appears necessary that the provisions of the normative acts should correspond to the new epidemiological situation of the consumption of substances.

In this respect, we remind that in the analysis of the stage of the health program no.10 regarding the surveillance of the health state in children and young people communities, the responsible factors from our national health system recognized that in June 1999, in an analysis carried out in the county of Bistrita Nasaud, 2% of the school people would take in drugs.

Extremely eloquent are in this respect the data offered by the ex–Centre of Intervention in Addiction within "Al. Obregia" Hospital for the period 1.07.1999–31.12.1999, according to which there were 125 addicts in 1996; 480 in 1997; 839 in 1998. It is also mentioned that out of five addicts only one is hospitalized. During the period mentioned here the number of addicts increased four times.

Premises of presentation

As to the above mentioned situation, difficulties in the struggle against drugs and addiction versus medical care appear due to a less efficient, absolutely incomplete characteristic of the main normative acts in this field faced to the social and economic and morbidity realities of the present–day Romanian society. It is to be added that the current legislation is less known in the public concerned with illicit drug consumption and addiction and possibly made use of without taking into

account the spirit and the essence of the special provisions in this respect. The body of professionals both in the field of the institutions authorized to maintain public order (police), activities in justice (lawyers, judges, prosecutors) and in the field of medical and sanitary care are not familiar with the special utilization and differentiated application of the present provisions to be found in the current normative acts. It is due to the fact that they did not manage to elaborate a common viewpoint as adequate as possible able to solve practically in the territory the problems raised by the present situation of the illicit drug consumption and addiction within their interdisciplinary scientific activities such as conferences, symposia etc. At the same time, for the present, there is not available to the factors of emergency actions any working instrument such as a directory, inventory, files of normative acts with comments able to solve the concrete situations.

Special legislative provisions

According to the provisions of the general legislation regarding the care delivery for the pacients and the prophilaxy of the diseases with social risk, the drug consumers and addicts have the same rights as any other pacient. In this respect the significant provisions of Romania's Constitution are the Decree no.246/1958 regarding the reglementation of medical care and medicines, the Law no.3/1078 regarding health assurance.

– Special provisions regarding the struggle against drug consumption and addiction comprising the following norms:

– Law no. 73/1969 regarding the regime of drugs and narcotics;

With this law, our country adhered to the international regulations regarding the legislation on narcotics – the Unique Convention of Narcotics adopted in 1961 by UNO. Out of this law the provisions of the art.10 is worth–keeping in mind. It says: all human and veterinary medical and sanitary personnel and any other person who – due to the specificity of their activity is supposed to handle narcotics and who has knowledge of cases of addiction are under the obligation to inform as soon as possible County Sanitary Departments or the Sanitary Department of the Bucharest which are authorized to take legal steps ".

– The instructions no.103/1970 of the Ministry of Health for the practice of the provisions of the Law no.93/1969 regarding the regime of drugs and narcotics. In the Chap. 8 of this Order it is especially and explicitly mentioned that the addicts should be taken care of in services of psychiatry. At the time, it is underlined the obligation of the medical services the addicts are admitted in –even those who are admitted according to their own will – to inform the criminal pursuit officials of the area the addict comes from. Such information is motivated by the necessity of pursuit and depiction of the drug sources.

– HCM (Decission of the Ministry Council) no.889/2.07.1970 for the settlement and sanctions of the infringements of the norms regarding the regime of drugs and narcotics. According to this normative act – see art.20 – when the sanitary departments are not informed by the sanitary personnel or by any other person who – due to the specificity of his/her work are supposed to handle drugs and narcotics and who have knowledge of such cases – it is subjected to administrative sanction. At the same time to the regime of administrative sanctions are subjected the persons who – see art.21 – do not inform the officials pursuing drug consumers and addicts and who previously confirmed such cases.

– Decission no.534/1.07.1999 regarding the set–up of the Interministry Committee for the struggle against drugs. This recent administrative act created the premise that by applying it the struggle against drugs and narcotics, the care for addicts would be considerably improved s compared with the situations provided by the former normative acts.

– At the same time, for the care of addicts under the form of obligatory subjection to out–hospital treatment there are provisions more or less declared as such:

– Decree no.313/1980 regarding dangerous psychic pacients. The provisions of this decree may be used especially in the case of the persons (addicts) who reject any recuperatory actions, have an attitude of denying the disease, do not want to subject themselves to desintoxication cure. The complex and complicated procedures, the implication of certain extra–medical factors in achieving this normative act, its lack of correspondence with the social, economic, juridic and administrative realities that appeared after 1989 determined that nowadays this decree should be practically non–functioning. In spite of the criticism that was brought in under various forms, the future provisions of "de lege ferenda" for the struggle against drugs should take into account the maintenance of the prophilactic spirit of this type of legislation. The non–medical, juridic and medical circles concerned with the struggle against drugs should form a group of pressure upon the decission factors in order to replace the Decree no.313/1980 with a legislative act able to create for sanitary networks possibilities to rapid action with a minimum of beaurocratic formalities in prophilactic aims without minimizing specialized hospitalizations for desintoxication cures and recuperatory treatment.

Everyday observations of psychiatric medical practice show that for addicts as well as for dangerous pshychic pacients physicians should have available a clear, explicit and efficient juridic instrument subjected to the juridic control. However, it must not be paralysed by juridic arguments supported by unsignificant facts regarding individual freedom and the rights of man. In this respect, abuse appears when the sanitary network is taken the right to approach addicts and not through their admission in specialized services against their own will. More than in other domains the physician – as mandatory for the sanogenesis of society should have the possibility to promptly intervene according to the exigences of his profession, giving him necessary liberties and responsabilities

– Art.112, l.b, 113,114 criminal code;

The provisions of the criminal code through the articles mentioned above may be used exclusively only in cases of the addicts who commited dangerous social actions. The out–hospital medical care of such pacients or under the form of provisional or definitive hospitalization is possible only after an Order of the Org. of Public Ministry (Court) or certain Judge decission. For the current practice the use of such provisions is relatively rare and are made exclusively based on special indications of judicial appointment, the sanitary network being obliged to strictly obey the provisions imposed in such circumstances.

Discussions. Conclusions

The provisions of the current normative act are recognized by most specialists in this field as regards drug consumption and the struggle against addiction as being out–dated as compared with the new social and economic realities, with the international legislation in practice in the economically advanced societies. At the same time, though our country adhered to the three conventions regarding the struggle against drug consumption and addiction it did not create the juridic and organizing instrument for its proper application. The alarming aspect of drug consumption and addiction makes it necessary to create an adequate legislative frame. In this respect we consider that in our present stage a public debate would be necessary both within specialized societies with an interdisciplinary component (Police, SRI, Court, Justice, Education, Health, Social provisions, protection and care etc.). As a consequence of such debates we think it would be necessary that interested groups of specialists, especially interdisciplinary teams should forward through Ministries of concern such as Ministry of Inner Affairs, Ministry of Health, Ministry of Justice, suggestions of "de lege ferenda" to the right legislative forums.

SEVERAL STATISTICAL ASPECTS OF DRUG ADDICTION IN A COUNTY PSYCHIATRIC HOSPITAL

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I. General data

1.0. Nowadays there is a consensus regarding the definition of substance addiction (including medical substances). It refers to the "repeated non–medical usage" (medically non–indicated), which produces psychological (and not only) alternations to the user, who feeds its "necessity" as an emergency that might be hardly or impossible to get rid of by one's own (1,2).

1.1. Therefore, the definition refers to a formerly optional and finally instinctive (biologically rooted) behavior, as well as to a toxic one, hinting at a pathological intoxication condition which generates the motivational subjugation and behavior disorder. The definition does not include the administrated dose, the intoxication duration, its rhythm or the other psychic and somatic symptoms produced. They are included in the description of the case evolution and they are considered evaluation criteria of toxicomania development and seriousness, as they offer more to intoxication.

1.2. From this point of view there is no difference between a drug which has become toxic and generated addiction, and any other substance. It is to be noticed that the administration duration is more important than the dose in the addiction development. Thus, "15 mg diazepam / day x 2 years produced a stronger addiction than 50 mg / day x 6 weeks"! (1).

1.3. As far as danger is concerned, two agents are included: the drug potential and the future addict's psychic and neurosomatic structural features. The term of drug addiction generating potential is suggestive, but also ambiguous and abusively defined. This virtual potential depends on the increased rigidity and stability of the link between the substance and some neuroreceivers, modifying the respective ionobiochemical structures by changing some connections between the ionobiochemical systems. The person's neurosomatic structural feature is likely to refer to similar aspects. However, the two "potentialities" are consensuous and valential, because no matter which are might miss, the result (addiction) will miss, too. They make a stable link, like two chemical elements are valentially connected making up a new compound (H_2O).

1.4. It is still not clear whether the psychic (predisposed) potential acts like a premise or a more important agent in causing addiction. Some already checked arguments like "the former alcoholics or members of families with alcoholics or hypnoanxiolitic addicts have a greater predisposition to a benzodiazepine addicted or abusive consumption behavior "(1) do not say more than that because it is about both a genetic kindred inheritance and an ontogenetic imitation of some common behavioral patterns and personological profiles.

1.5. There is some other empirical evidence. Thus, alcoholism and hypnoanxiolitic addiction may cause or be the result of depression. In abstinence, after the rise of the toxic curtain about 10%

(1) "proves to be major depressions". This comorbidity raises the problem of an innate non–specific vulnerability potential, the above mentioned predisposing vulnerability.

1.6. However the fact that after 4–6 years "84% of the patients treated for hypnoanxiolitic addiction relapse, 52% resume taking too much drug, 42% are put into hospital again, out of which with scofage convulsions" (Algulander, Borg and Vikander 1984, quoted by 1) suggests that such a stability of the behavior pathologizing is more than psychological. It has an organic basis. We do not know if it is the mere expression of vulnerability, or if the meeting between the neurosomatic substratum and he drug has produced another quasiconclusive and annoyingly stable formula of the relationship between the biochemical complex systems. Statistics state that 58% of those who used hypnoanxiolitic substances more than they were prescribed have problems when they want to give up on them.

1.7. However, relapsing defines addiction. We still do not have any criterion of estimating abstinence duration according to which relapsing should be considered an argument in defining addiction. Some authors speak of 10 days, others of 30, while others refer to 90 days. It seems that however, there is a non–arbitrary period which can be used as such a criterion. More authors speak of a six month cycle (or multiples of 6 months) which might characterized the change of relationships between the ionobiochemical complexes. However, it has been clinically observed that the patient groups hospitalized for more than 6 months had a significantly lower relapse percentage than those put into hospital for less than 6 months.

1.8. Mellinger (quoted by 1) says in 1984 that "1.6% of the Americans" (using a group of 3000 people) "are long–term benzodiasepan consumers". Thus percentage referred mainly to older women, having more psychopathological symptoms and health problems. The DSM – III – R (p. 202) states that in 1981 1.1% of the adult American population had symptoms of sedative hypnotic or anxiolitic overuse or addiction*.

1.9. The drug addiction incidence and prevalence leaves much to be desired. That is why we intended to see which were the statistical aspects on a given groups in our hospital.

II. Material and method

2.0. We had access to the charts of the hospitalizations into a county psychiatric hospital (which has been a university clinic for two years), between 01.01.1990 – 31.06.1999 (nine years and a half). The group includes 42.932 hospitalizations cases (acute or psychiatric emergencies). The hospital has a 7 bedded ward for chronic patients who have been steadily hospitalized (for social reasons or as an aid in the household) for more than these nine years. The hospital secures about 95% of the hospitalizations of acute cases or psychiatric emergencies in a county (Bihor) with a population of about 600.000 inhabitants.

2.1. The data in the following charts were collected from the clinical tables as they were filled in at that time.

Table 1

Year	Total number of hospitalized patients	Number of drug addiction cases
10 years	1 case/ 7155 hospitalizations	$1.1\ ^{00}/_{000}$

See Table 2

* Câmpulung Moldovenesc, October, 6th-9th 1999, The First National Conference on Drug Addictions

III. Results analysis

3.0. The member of the analysed hospitalizations is big enough (42.932) so that the collected data should be significant at least the practical use of drug addiction diagnosis, if not its frequency.

3.1. Thus, from almost 43.000 cases, just one has polytoxicomania (also including drug addition) as a prime diagnosis and only 6 cases have this diagnosis label. That means 1 case for each 7,155 hospitalizations or about 1 case per 1.5 years. That also means about 1.1‰ cases in ten years. If we relate this figure to the Chart 2

Table.2

Case No.	Sex	Job	The first psychiatric addiction hospitalization age	The first drug addiction hospitalization age	Total no. of psychiatric hospitalizations/ year no.	Prime diagnosis	Associated diagnosis (comorbidity)	Drug addicted
1.	F	Pharmacist	48	50	7 in 4 years	1st type bipolar emotional disorders	Tiro-ovarian insufficiency drug addiction	Cyclobarbital
2.	F	Physician	51	51	3 in 3 years	Polytoxico-mania	Toxiethanolic addiction	Diazepam Meprobamat Pfenobarbital
3.	F	Physician	32	35	32 in 19 years	Emotional disorders – major relapsing depression	Drug addiction ethanolic toxicophilia	Sodium Amital Meprobamat
4.	F	Lawyer (physician husband)	51	51	1 in 3 years	Anxious – depressive disorders	Drug addiction	Levomepro-mazin Diazepam
5.	M	Jobless (unskilled worker)	19	24	23 in 9 years	Personality disorders	Glue addiction Polytoxico-addiction	Diazepam Meprobanat Phenobarbital
6.	M	Jobless (unskilled worker)	33	35	10 in 8 years 76 / 46 1.8 times / year	Personality disorders	Polytoxico-mania (Alcohol + Drugs)	Levomepro-mazin Meprobamat Tranxene

prevalence stated by the American literature (1.1% and 1.6%), there is a difference more than 1,000 times smaller, which requires some remarks.

3.2. Of course, there is a great cultural difference between our people's behaviour and the Americans'. Besides, the drugs having a toxic addiction developing potential seem to be more contiously prescribed. Moreover, in spite of the difference between poverty and richness, it seems that in Romania the average level of health education is higher and wider spread (one of the few benefits of standardization). But, certainly, such a prevalence difference is not possible, as addiction has two non–psychological premises (chemical and neurobiological) and only one which is pure psychological. Then the explanation left is less pleasant one. Pathology is lender diagnosed. Our colleagues do not watch this psychopathological side systemically and they acknowledge only the strikingly obvious cases. Another remark is that the used chart does not contain a special column whose filling require the searching for this usually disguised and not always perceived pathology.

3.3. The second chart contains a surprising element / the vulnerability degree of the cases> women of a life countdown age with emotional disorders as a prime diagnosis and two "unskilled" men with personality disorders.

3.4. Besides, the women are pharmacists, physician and physician wife, thus having an unlimited access to drugs. Four out of the six cases had drug addiction symptoms only after they had been given psychiatric treatment in hospital, so they became addicted as a result of a prescription. Can we speak of iatrogenization here?

3.5. There is no case hospitalized for an emergency pathology produced by drug addict consumption. Only the patient has polytoxicomania (and alcohol) as a prime diagnosis, drug addiction is recorded only as comorbidity in the rest of the cases. That means prevalence is indeed very low among the population, even if not at the discovered level.

3.6. The incriminated drugs are hypnotic and anxiolitic (Levomepromazin was prescribed as an anxiolitic) and there was not any pure drug addiction, which emphasizes the people's lack of habit of spontaneous and face will appealing to drugs and barbiturates before getting to addiction.

3.7. The high frequency of relapsing is to be signalled: 6 cases with 76 hospitalizations, 1/1.8 years, which means 2 hospitalizations per year. This means a high social cost.

IV. Conclusions

1. Drug addiction is underdiagnosed in Romania. A special chart column would compel to pathology searching.

2. The existence of a vulnerability pattern and the iatrogenic medical contribution in causing this pathology are obvious. Thus, any prescription of hypnoanxiolitic drugs compel us to warning against the risk of drug addiction and to a severe control to limitate their long–time consumption.

3. The age of the descriptive psychiatry – in the way of organizing information – seems to have gone. The informationally modular psychiatry – as strictly organized information sets which can be processed on computer, implies another type of chart containing special columns for these sets; their filling in would not allow any piece of information to be forgotten or omitted. Our charts contain a lot of columns dedicated to some almost useless details, but they do not have any column regarding drug addiction, the therapeutic compliance, the last year's stress, the potential stress which caused the relapse etc. That is why the drawing up of a complete standardized chart is absolutely necessary. It is the duty of R.P.A. to do it in a very short time, as part of the reform process in psychiatry, which cannot begin but with the reform in thinking. The drawing up and printing of the first instalment of this standardized chart for the whole country can and must be financed by a health programme.

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ADDICTION AND THE PROBLEMS OF THE CARE UNDER OUT–HOSPITAL CONDITIONS

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Documentation

The problems of the care delivery to addicts are at present under the conditions of our country at its very beginning. According to the provisions of the Law no.100/May 5,1998 regarding care of public health Annex no.8, Ministry of Health is authorized to organize an finance the National Program of prevention and control of addicts and induced pathology as well as no.13 – the National Program of mental health and prophilaxy in psychiatric and psycho–social pathology. So far, related to the prevention and the control of addiction and induced pathology neither did this program become official nor was it put into current medical practice.

The number of drug consumers alarmingly increased lately, the anti–drug struggle has not got a well structured material strategy, there is no legislation brought to the day irrespective that Romania adhered to the three international conventions on drugs.

Starting on July, 1996, the Ministry of Health proceeded to take some initial steps in order to create an institutional frame of struggle against drug consumption and the care for addicts.

Thus, at "Al. OBREGIA" Hospital, a Centre for Intervention in Addicts was founded and done away with later on. A form of care delivery with a similar profile began to be organized in some other areas of our country, "Socola" Hospital included, "where there still was functioning a desintoxication centre with 30 beds". In instances of acute intoxications the addicts enjoy at present the specialized care proper to their morbidity at "Floreasca" Emergency Hospital, Bucharest. It is already known "best of the cases – out of 5 drug consumers only one comes to the hospital." According to this estimation, there ought to be at least 4–5 thousand addicts who would be in need of specialized care.

At present the care for drug consumers and addicts does not achieve a real therapeutic chain, it is not based on an informational and education system well organized, it lacks, at national level, a sanitary personnel specialized in treating acute and chronic intoxications and the steps of prophilaxy and recuperation. In fact, in Romania for the out–pacient care of addicts there is only one Day–centre for the treatment of the addicts coming from the Mental Health Laboratory in Berceni (Dr. Cristian Bengescu).

The situation of out–hospital care in our country for drug consumption and the treatment of addicts is in an obvious contrast with the one in the geographical neighbouring. We only remind that in the Republic of Moldova there is an autonomous network of narcological care with specially nominated narcologist psychiatrists, nurses, clinics, specialized offices. Even if we admit that the situation of drug consumption and the morbidity due to addiction in our country is very much dif-

ferent from the on in the Republic of Moldova, we cannot ignore some organizing achievements in this field, including the existence of an institution with a methodological profile and the quality of a service of reference such as Dispensarul Republican of Narcology in Kishinew.

Premises for research

The observations carried out by us in the Mental Health Labortory of Iasi, during the last 5 years show the fact that the problem of drug consumption and the care for addicts within the current network of out–pacient care is practically impossible to achieve due to numerous factors. Among them we mention the most significant:

1. lack of a institutionalized legal frame for the sanitary network for starting the struggle against drug consumption and the care for addicts under out–hospital conditions
2. lack of legislative provisions and normative acts regarding the perspective of an adequate intervention in the problem of addiction and the struggle against drug consumption especially under out–hospital conditions.
3. lack of a medical and sanitary personnel specialized and familiat with the specificity of the activity regarding the struggle against drugs and the care for addicts.
4. the daily realities of the psychiatric out–pacient care suggests that the general psychiatrist is exceeded by the numerous problems he is confronted with as well as a work in excess.
5. the decission makers in the field of organization of sanitary services ignore the specific characteristic of the medical care in drug consumption and addiction. In this area a special logistics, the confidentiality of medical services, the security of medical secret are needed under the conditions in which the current and the future legislation would impose not only statistic reports but also *ad personam* reports for those who require such services.
6. lack of instructions, technical norms regarding the relations with the officialdom involved in the struggle against drug consumption and addiction (Polica, SRI,Court, Justice etc.) as well as the special protection of the drug consumers and addicts.
7. lack of a normative frame for the protection of the personnel engaged in activities of the struggle against drug consumption, prevention and the out–pacient therapy of addicts. Everyone and especially the decission makers should know such pacients since they show a behavioural complex extremely extended, from frank and declared anti–social expressions up to a total subjection.
8. lack of any material and financial means for activities of prophilactic and therapeutic struggle against drug consumption and addiction.

Critical discussions

Out of the data presented and the confrontations of opinions between specialists it results that the out–pacient care of addicts should be provided by forms of specially nominated care. Such forms might function at the beginning within the mental health laboratory as Day–centres. It is necessary that they shoud be taken as such in the National Program of prevention and control of addiction and induced pathology. Under the conditions in our country, such forms should be organized only within public sanitary departments. A problem we consider to be of a great importance is the one regarding the financial regime of the services imposed by the care of this category of pacients. It is a notorious fact that addicts are in most cases persons without social and professional insertion and implicitly without the rights provided by the Law of social protection from 10 July, 1997 with its further modifications. Therefore we suggest that they should enjoy free services provided through integral financing from the state budget and, according to the specific instance from the special fund afforded to public health. In this respect we mention that the Decission of Romania's Government no.443/August, 1998 provides in Annexes no.1: psychiatric and logopedic laboratories and centres

are integrally financed from the state budget and according to the case from the special fund of health. The same situation is for the desintoxication centres, cure and post–cure for the treatment of addicts, institutions that so far are not enlisted in the organizing nomenclature of public sanitary institutions.

Another aspect of stringent necessity is that regarding the preparing of a number of specialized personnel – physicians, nurses, social workers, psychotherapists, sociologists, psychologists and elementary sanitary personnel in the field of the care of addicts.

Conclusions

Out of the five years of experience in the field of the care of cases of psychic diseases of narcological significance it is necessary the impose the conclusion of foundation and organization of forms for the struggle against drug consumption and the care of addicts. We suggest that such forms should be organized within the mental health laboratories due to the present conditions of sanitary and medical care during the period of transition. Further on we consider that such forms should be integrated in the structure of the desintoxication, cure and post–cure centres that are already considered in the normative acts for the reorganization and functioning of sanitary services.

CULTURAL CHANGES AND THE CHANGING FACE OF YOUTH SUBCULTURE AND DRUG USE. SOME COMPARISONS BETWEEN WESTERN AND EASTERN EUROPE

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Introduction

Drug use is not an isolated phenomena. Beside the genetical, sociological and psychological causes of the addictions there is a strong cultural factor effecting the quality and quantity of drug use in a given society. Cultural, subcultural changes always effect the ways drug is used by youth. In the following I will examine the change in drug using trends in Europe in the context of youth subculture. I would like to show what kind of relationship can be observed between the two and I will give an example through the presentation a survey measuring drug use in discos.

Historical background in Eastern Europe

Before the political changes in 1989 illegal drug use was quite rare in Eastern Europe. In Hungary, however drug use existed already before the first world war[1], the authorities date the beginning of the problem from the end of the 60s. That was the time when first time drug users were arrested in Budapest. All of them used Parkan, an antiparkinsonic medicine with hallucinogenic effects. The drug use of the 70s and 80s is characterized by the abuse of medicines and the use of poppy on different ways. Beside this two, inhalant use was also observed, mainly in the more power, urban areas. Cannabis use was rare an connected to intellectual circles.

The changes came at the end of the 80s, beginning of 90s. Since the turn of the decade the media has been increasingly giving weight to the context of drug use. One reason for this trend is that in 1985, in response to an MSzMP[2] Central Commission decision, the drug problem lost its taboo quality, and could be uncovered in the news. This dispersal of taboo was also signified by the fact that in 1987 the government health organizations allowed the first drug out–patient centers and addictological hospital departments to be opened, and the Interministerial Drug Commission was set up (Gerevich & Bácskai, 1996).

At the same time drug use started to increase and we could witness also important qualitative changes. The opening of the borders allowed much easier access to illegal drugs. The earlier use

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of poppy tea, poppy cuttings and codeine derivatives was now replaced by heroin, often administered intravenously. The use of cannabis which was earlier characteristic primarily in intellectual circles, started spreading; hashish and marijuana became widely available, especially to young people. Cocaine also appeared on the market, albeit in smaller quantities than the formerly mentioned drugs (Bácskai & Gerevich, 1994).

In Hungary almost all of the indirect indicators signal a rise in drug use (Paksi and Demetrovics, 1999). The number of drug–related crimes and court cases tripled in 1992 compared with the previous year (Fridli, Pelle & Rácz, 1994). The amount of illegal substances seized by the authorities is constantly growing (Katona & Talabér, no year), and the number of drug users seeking help at treatment centers is also rising. For example, in 1996, 33% more people registered for medical treatment because of drug use than in the preceding year (OPNI, 1997)[3]. Gerevich and Bácskai (1995) – in a survey carried out among house doctors – also found a rise in the number of drug users between 1990 and 1992. The results show that both the number of illegal drug users and of psychoactive medicine users are increasing, and in the latter group this growth is more significant. (It is possible however that these surprising results are the consequence of that it is rather the psychoactive medicine abusers who seek help from house doctors, than illegal drug users.)[4]

According to the results of the 1995 ESPAD survey, 10% of 16 year old high school students have already tried some sort of illegal substance during their lives. However, this value did not show a significant increase between 1992/93 and 1995 (Elekes & Paksi, 1996; Paksi, 1997), the recently carried out follow–up of the ESPAD survey seems to show a sharp increase in this regard (Paksi, 1999, personal communication).

Westernalization versus Eastern patterns

Gerevich (1994) suggests that the drug–use map of Hungary has a double character. On the one hand, there exists the 'poverty drug use' (see Bácskai & Gerevich, 1994) and this is primarily characterized by benzodiazepin–, barbiturate– and inhalant use among those living in low infrastructure rural areas. On the other hand, there is an observable process of westernalization that brings on the appearance of a western type drug use tendency in Hungary some years later than in Western–Europe and North–America. It seems in the case of the latter form, the picture is more shadowed.

The growing use of substances containing opiates, especially heroin in Hungary, shows the opposite tendency as in North–America or Western Europe, where epidemiological studies reported on an increase in use about 20 years ago, and it now seems to be stabilizing or even falling, with the users' average age growing (Kozel & Adams, 1986; Peveler, Green & Mandelbrote, 1988; Sandwijk, Cohen & Musterd, 1991; Gfroerer & Brodsky, 1992)[5]. Hartnoll, in his summary study (Hartnoll, 1994), however, draws attention to the significance of the heroin problem, and does not exclude the possibility of a new wave of use.

It appears, however, that while in the case of the opiates, in Hungary the western patterns of drug use from the past 2 or 3 decades can be observed, in regard to the psychostimulants, generally parallel patterns can be drawn with the Western European situation, with only a couple years of lag in Hungary.

Drugs and Culture: some connections

Examining drug use in the East and West, we can never forget to observe other cultural patterns also. In West Europe and North America the most characteristic phenomena since the end of 80s is the decrease in opiate use which goes parallely with an increase in psychostimulant use. At the same time we can witness changes in youth subculture in global also. Musical trends change interestingly. Traditional disco music seems to be replaced by techno, acid and rave. This music is much

faster, having a rhythm of 120-140 beat per minute or more. Gabberhouse for example has a rate of 200 beats per minute (Koster, 1992). In a disco this music continues on all night long without any rest. This kind of speeding up is not only characteristic for the musical world of the 90s; we can witness the same pattern in other cultural phenomena's also, we can even say that this speeding up is a general characteristic of the global trends of the last decade. The same pattern can be seen in the movies where short cuttings become popular, long conversations disappear. It becomes more and more difficult to attract the attention of young people. Again, watching advertisements, we see the same phenomena. The examples could be continue on; all of them represents a kind of speeding up, where the continuous stimulus is important, for the aim of never loosing the attention of the watcher of listener. This phenomena works of course as a circulus vitiosus, which means that in turn, those who grow up in the times of this "speeding up" will also have a need for it. In the light of this approach it is not surprising if we witness that these changes go parallely with an increase in the use of psychostimulants. In Western Europe Ecstasy became the second most popular drug after marijuana (Korf et al 1993, 1995, 1997) and ecstasy use seems to be connected very strong to outgoing to dance parties (see Korf et al, 1991; Solowij et al 1992; Adelaar, 1996; Cohen, 1998). It seems - not surprisingly - that psychostimulants are those drugs which can satisfy on the most perfect way the stimulus hunger of the youth of the 90s.

Changes in Communication between East and West

Examining drug use trends we cannot forget that not only trade but also communication became much easier between East and West. The first means also that drugs, which are available in the western world became available in the former communist countries also. However, this alone does not necessarily mean that the drugs become used also. Nevertheless, in Eastern Europe they did. In the background of these changes, at least partly, we can assume the more effective communication between the eastern end western part of Europe. However, earlier the iron curtain meant also a communicational wall between East and West, now almost the same cultural effects can be observed all over the world. The same movies can be seen, the same advertisements are popular, exhibitions move from one town to the other, the top ten lists of LPs are almost the same everywhere. The world wide web make the same information available for everyone in the world and direct communication is also possible without borders. All these things make possible the so called globalization of (youth) cultural processes, and we can say these processes create some kind of background for drug use also, which then will be similar all over the world. One of the fields can be observed is the relationship of drug use and the dancing subculture, which relationship, according to western studies, seems to be strong (Solowij, 1992; Adelaar, 1998). In the following I present a study carried out in Budapest, examining the drug use of young people visiting clubs and discos with dancing possibilities. As we will see the situation is quite the same in Budapest as in other Western European countries.

Drugs and Disco in Budapest

Surveying the dance parties in Budapest (Demetrovics, 1998a & 1998b), we were able to discern four types. (1) The first category is comprised of the traditional '*discos*,' which can be found mostly separate from the city center, yet are easily accessible. In general they simultaneously offer two types of music in different rooms, pop music in one and techno, house, acid, rave, etc. in the other. (2) The second category contains what we call '*parties*', which are tied more to the promoters than the clubs where they take place. Parties usually happen in the city center, and only play so–called party music (house, acid, rave, etc.) provided by DJ's. (3) We put smaller *'clubs'* in the third category, which go on throughout the week, alongside other recreational opportunities (i.e. billiards, etc.), and also

offer dancing space. (4) The last category comprises the exclusively house or acid music events that take place away from the city center, usually in suburbs of Budapest, in warehouse type spaces where the capacity is in the thousands. None of the promoters who organized events in the fourth category were willing to let us distribute the questionnaires.

In the study we examined drug use at 7 places (2 discos, 2 parties and 3 clubs) in total at 17 different occasions.

			On which day the data collection took place			
			Friday	Saturday	weekdays	Total
Where the data collection took place	disco		86	68		154
		%	23.1%	18.2%		41.3%
	party		55	49		104
		%	14.7%	13.1%		27.9%
	club		43	29	43	115
		%	11.5%	7.8%	11.5%	30.8%
Total			184	146	43	373
		%	49.3%	39.1%	11.6%	100.0%

Table 1. Distribution of questionnaires in the analysis according to place and day

In our study we utilized the alloys of methodological opportunities. Thus however we met the target population in its natural setting, the discos, nevertheless chose the questionnaire method as opposed to the more qualitative method of participant observation. A total of 422 questionnaires were filled out, 49 of which (11.6%) due to inconsistencies or large gaps could not be used in the analysis.

Results

Two–thirds of the subjects were male and the sex distribution according to place did not show significant differences.

			sex of subject		
			male	female	Total
Where the data collection took place	disco		87	67	154
		% / sex	56.5%	43.5%	100.0%
	party		69	35	104
		% / sex	66.3%	33.7%	100.0%
	club		71	44	115
		% / sex	61.7%	38.3%	100.0%
Total			227	146	373
		% / sex	60.9%	39.1%	100.0%

Table 2. Sex distribution according to place

The average age of subjects was 20.62 years (sd=3.31), with no difference by sex. Over two–thirds of the subjects were between the ages of 17 and 22, and a total of 10.7% were younger than 16 or older than 27.

83% of respondents live in Budapest. The majority – 51% – live with their parents, while 16% live with one parent in a shared household. 10% live alone and another 10% live with a partner.

The majority of parents, 47% of fathers and 39% of mothers, have intellectual careers. A further 26% of mothers work in an office or do light physical work, while 16% of fathers are blue collar workers. The subjects were primarily students, that is the ratio of students to workers is 2 to 1, and a total of 5% do neither.

Recreational occupations

About one third of the subjects spends at least 5 nights per week at home, and a total of 20 individuals (5.4%) said they go out every night if possible. Though the men go out more often, the difference between sexes were not significant.

Smoking and Alcohol

A total of 34 people (9.1%) reported that they'd never smoked, while 57.4% smoke daily. A total of four people claimed they have never had a drink, and a further 16.6% hadn't drank in the past month. The rate of daily drinkers is 2.1% and for those who drink regularly during the week it's 18.2%.

Marijuana / hashish

Almost two third of the subjects (64.9%) had tried marijuana or hashish at some point. The majority of those who have tried them were found at the *parties* and *clubs*, where almost everyone had smoked marijuana (93.3% at *parties*, 81.7% at *clubs*), while at *disco's* this was true of 'only' one out of every three individuals.

		Where the data collection took place			Total
		disco	party	club	
Hashish/ Marijuana	never	103	7	21	131
	% / place	66.9%	6.7%	18.3%	35.1%
	not in past year	15	4	8	27
	% / place	9.7%	3.8%	7.0%	7.2%
	not in past month	6	8	12	26
	% / place	3.9%	7.7%	10.4%	7.0%
	occasionally	25	40	30	95
	% / place	16.2%	38.5%	26.1%	25.5%
	several times a week	2	29	27	58
	% / place	1.3%	27.9%	23.5%	15.5%
	daily	3	16	17	36
	% / place	1.9%	15.4%	14.8%	9.7%
Total		154	104	115	373
	% / place	100.0%	100.0%	100.0%	100.0%

Table 3. Use of hashish/marijuana according to certain places

Other drugs

50.9% of the subjects had tried one or more illegal drugs besides marijuana. If we also take marijuana into account the number of those who have never tried any illegal substance drops to 117 people (31.4%). The age of subjects, monthly income, urban or suburban home and level of school-

ing had no connection to trying illegal drugs; however, those who had no occupation were more likely to have tried illegal drugs than those who study or work, and similarly men were more likely than women to try illegal drugs. It is significantly more likely that people who went to some kind of dance party 6 or more times in the past four weeks had tried illegal drugs than those went there more rare.

The total number of those who ever tried an illegal drug is 256 individuals (68.6%), and of these every fourth had only tried marijuana. As it is clear from the Table below, the most popular of the other drugs is *amphetamines* (excluding ecstasy), over 40% of respondents had tried it. The rate for LSD is almost the same, while for ecstasy and cocaine it is somewhat lower. The rate for ever having tried some kind of opiates is 18.2%, while 22 individuals had tried inhalants. With respect to drug use in the past month, this order does not change, though the proportion of actual users varies in the view of those who ever used the given drug.

	never used	**ever** used **intravenously**	**ever** used total	**experimenter** triedat some point, but not in the past 3 months	**regular** in the past 3 months, but not in the past 30 days	**actual** past 30 days
amphetamines	222	24	151	39	15	97
%	*59.5*	*6.4*	*40.5*	*10.5*	*4.0*	*26.0*
cocaine	296	12	77	36	9	32
%	*79.4*	*3.2*	*20.6*	*9.7*	*2.4*	*8.6*
ecstasy	269	6	104	41	13	50
%	*72.1*	*1.6*	*27.9*	*11.0*	*3.5*	*13.4*
LSD	232	12	141	64	18	59
%	*62.2*	*3.2*	*37.8*	*17.2*	*4.8*	*15.8*
opiate total	305	11	68	35	11	22
%	*81.8*	*2.9*	*18.2*	*9.4*	*2.9*	*5.9*
heroin	328	11	45	22	8	15
%	*87.9*	*2.9*	*12.1*	*5.9*	*2.1*	*4.0*
poppy	335	5	38	24	4	10
%	*89.8*	*1.3*	*10.2*	*6.4*	*1.1*	*2.7*
codeine	352	2	21	10	6	5
%	*94.4*	*0.5*	*5.6*	*2.7*	*1.6*	*1.3*
glue, inhalants	351	0	22	22	0	0
%	*94.1*	*0.0*	*5.9*	*5.9*	*0.0*	*0.0*

Table 4. The use of other drugs (n=373)

Summary

As we have seen, as regards the use of illegal drugs, marijuana and hashish were the most popular, just as in other parts of the world (Adams et al., 1989; Irgens–Jensen, 1991; Korf & Steenhoven, 1993; Korf, Nabben & Schreuders, 1995) followed by the use of *psychostimulants*. These drugs seems to have a recreational character (Peroutka, 1987; Solowij et. al., 1992), and in the present study we found also that the use of amphetamines is strongly connected to going out, and at the same time rare at other occasions. It is indisputable, that the *primary location* of the use of this kind of drugs is the disco.

			sex of subject		
			male	female	Total
Relationship between XTC use and disco's	I only use XTC at such places		33	17	50
		% / sex	47.8%	63.0%	52.1%
	I mostly use XTC at disco's, otherwise not so much		16	2	18
		% / sex	23.2%	7.4%	18.8%
	I use XTC the same everywhere		8	3	11
		% / sex	11.6%	11.1%	11.5%
	I never use XTC at disco's		3	2	5
		% / sex	4.3%	7.4%	5.2%
	other		9	3	12
		% / sex	13.0%	11.1%	12.5%
Total			69	27	96
		% / sex	100.0%	100.0%	100.0%

Table 5. Relationship between ecstasy use and discos

While one third of those having smoked in the past month, and one half of those having drunk alcohol, indicated discos as primal or exclusive places of their cigarette or alcohol use, almost 75% of those who use ecstasy or amphetamines reported so. In the case of the latter substances, only every 6–9th person reported their use to be independent of discos.

More than half of those who had ever tried ecstasy has do so at some dance party, and a further 18.8% is more likely to do the drug at such places than elsewhere. Only a total of 5 individuals noted that they never use ecstasy at discos. As a contrast it is worth mentioning that almost half of those who have smoked marijuana in the past 30 days said this was independent of the disco, and that they smoke just as much everywhere else. It seems, therefore, that the term 'disco drugs' for amphetamine derivatives is reality based.

Conclusions

These results by all means support our hypothesis of the introduction, that although the increasing opiate usage runs counter to western trends in Hungary, we can also witness the parallel emergence of a tendency towards psychostimulants (Demetrovics, 1998b). In the background of the latter trend we can observe a global tendency in youth subculture which leads toward a "faster world" characterized by the hunger for stimulus. The results of the above study present this connection through underlining the relationship between the discos, with a much faster music than just couple years earlier, and the growing use of psychostimulants. Nothing shows better the strongness of this connection than the fact that in our sample amphetamine use 40.5 times higher than among the 16 year old high school student population of Elekes and Paksi (1996).

Nevertheless, I have to emphasize that however drug use and going out to disco's are strongly connected, we cannot conclude that disco's are responsible for the growing use of illegal substances. It is more likely that the growing popularity of dance parties and use psychostimulants both has the roots in the rapidly changing, speeded up culture of our times. This means also that interventions, like closing disco's or party locations would by no means result in a decrease in the use of illegal substances. These drugs are present and the world of disco–culture is an appropriate place for drug use where loud, speedy music is played. In my opinion this connection is a 'natural' one and we thus conclude that our task is rather the prevention and modification of drug using behavior toward less dangerous ways by distribution of information and peer–counseling.

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[1] This time drug users were mainly physicans, who abused morhine.

[2] the former Hungarian Kommunist Party

[3] Nevertheless, we have to emphasize that man can find significant inconzistencies in the data published by different institutes or sometimes even in the data provided by the same organization.

[4] I have to emphasize that all these studies do not only bring the problem of accidental and accidentally inexact data collection to the surface, but the degree to what we extrapolate from these to estimate the incidence of drug use is also a problem (Paksi, 1997; Paksi & Demetrovics, 1999). At the moment, problems in gathering data make it difficult to answer the question of whether the drug problem really is growing, or the activities of the police and border control are increasing (see records of drug seizures or court cases), or the use of more dangerous substances are rising (see drug-related deaths), or greater capacities of hospitals and treatment centers and the more tolerant drug policy (?) allows more options for entering treatment and the number of possible distorting factors could continue.

[5] Epidemiologic increase in heroin use occured between 1971 and 1977 in the United States. Smaller, probably rather local than national growth took place also in the early 90's (Kozel & Adams).

DEONTOLOGICAL IMPLICATIONS AND MEDICAL RESPONSABILITIES IN THE CARE OF DRUG CONSUMERS AND ADDICTS

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The drug consumers and addicts represent a section of the general population being in an obvious tendency of growth. Their contact and interrelations with medical professionals and the institutions of medical care delivery are subjected to complex, dilematic and sometimes contradictory aspects. The recognition and/or the statute of a pacient for a drug consumer or addict implies to label with consequences that under certain circumstances and professional interrelations can be beneficial for the patient. The relationship physician + drug consumer/addict is subjected to particular regulations outside raditional medical practices. We cannot ignore the fact that the drug consumers and addicts only rarely go to check up with a physician out of his/her own will, conscious of the risk drug abuse jeopardizes one's health. Even in this situation, in the regular medical practice there appears a certain distinction between the medical activities carried out as a private practice and as a practice within public institutions. While in the former offices it is supposed that the subjects always come willingly in the former ones the patients are usually brought in by authorities.

Aspects regarding the deontology of the care delivery for the above–mentioned patients are dealt with in the specialized publications, handbooks from a general viewpoint at the level of declarations of principles. These aspects neglect the historical, social and cultural, organizing, financial and legislative peculiarities at a given time. It is not rare the situation when the specialized publications regarding drug consumption and the presence of addiction presented standpoints with a more or less dissimulated political underlayer – a fact that complicates the deontological problems.

The present situation in our country with its characteristic of a transition society subjected to a process of reforms in most fields of life adds to this problem vatrious aspects both in the sphere of theoretical approach and practical activity.

Deontological premises and premises of normative acts

According to the Deontological Code of the Romanian Medical College (RMC) the physician "should permanently take into account that there is no medical practice without trust and it is based on professional secret as absolute as possible" (art.4) and that "the medical secret is obligatory"(art.13), being "disciplinary responsible in case of disclosing professional secrets." (art.16). The same Code provides that the interest of the society (prevention and struggle against epidemics of venereal diseases, of the diseases prone to spread into the population) is predominant against personal interest"(art.113). A legitimate question raised for every physician and all in similar situations of medical care for drug consumers and addicts is whether in our country the ilicit drug consumption and addiction are officially considered to be diseases able to spread into masses. Out of the nor-

mative acts that we reviewed there is not a positive answe to that question. According to our opinion such an answer should be given by the Interministry Committee for the struggle against drugs through which the HGR (the decission of Romania's government) no.534/7 VI 1999 performs its activity by services such as: General Department of Medical Care wihin The Ministry of Health, The Department for Health Promotion and communitary health within the Ministry of Health, the National Coordinator of the PHARE Program for the Struggle against drugs within the Brigade of the Struggle Against the Organized Crime and Coruption. We consider that the technical aspects in relation with the care for drug consumers and addicts should be explained by Instructions elaborated by Specialized Interministry Councils and especially by the Commission for Prevention of Illicit Drug Consumption, Medical Treatment and Social Reintegration of Addicts.

The viewpoint expressed by the Deontological Code of the RMC is in fact a desire especially in the case of the inter–relations physician–consumer/addict. In reality, the provisions to be found in the current normative acts in our country, i.e. the Law no. 73/1970, Instructions of MH no. 103/1970, HCM (decission of the ministries council) no. 899/1970 that regulate the struggle against drug smuggling and the care for addicts clearly oblige the medical and sanitary personnel under the danger of administrative sanctions to inform the sanitary authorities and Police the names of the drug consumers and addicts. For some people such an obligation might be labelled deontologically as an infringement of medical secret and for the physician–pacient relationship as a delation.. Such an instance might generate a counter–productive transfer along the process of the care for drug consumers and addicts sometimes with unpredictable implications for the reputation and the exercise of medical profession. If in the medical and psychiatrical millieu the drug consumer and addict are percieved as persons with a physical, psychical, social and communication suffering, for the current opinion and mentality especially those entertained by mass media the dissocial and anti–social connotations are amplified, sometimes hyperbolised, the penal aspects prevailing against the medical and recuperatory aspects. The physician is always placed in the situation to see in the same person both a drug smuggler, therefore a subject with criminal implications obvious and clearly expressed by our current laws and, at the same time, a real pacient to whom he should give a special attention and professional care. In this circumstance of a real connection between criminal and medical aspects, within the antagonistic inter–relations for an efficient medical care, the physician is obliged make a difference between his own system of moral and professional values. Such circumsatances have no correspondence in the medical practice of forensic psychiatry where the statute of an expert or practitioner is clearly defined in both penal and civil legislation. In fact, irrespective the risk to be sanctioned most physicians – out of mere ignorance or dominated by the traditional medical humanitarism give the addicts a similar status with general pacients. Such a practice is explained by the fact that, within the sanitary system in our country, the addiction has been non–significant as an epidemic and the normative acts elaborated in the conditions of a totalitarian system do not find a *de facto* applicability under the social, economic, political and ideological conditions after 1989.

Discussions

The deontological problem of the care for the drug consumers and addicts raises – for the present and for the entire medical staff – many question marks and offer new perspectives for differentiated answers according to certain concrete situations. Each medical approach of such pacients must consider should consider:

– the interrelations with the subject who willingly requires medical care;
– at family's request and (or relatives for under aged, persons without discernment)
– at the request of authorities (police, military staffs); education bodies;
– the juridic and institutional frame of medical practice;
– within the system of private medical practice irrespective the request;

– within the system of public care under medical current requests from authorities in circumstances with criminal perspectives or current regime;
– at the request of the Public Ministry or justice. Within the security measures with a medical; characteristic in a regime of temporary medical admission, long term medical admission, ambulatory obligatory treatment.

For the present, when in our country there is no official recognition the speciality and super–speciality, competence in narcology, the instances refering to drug consumption and addiction and their care fall into the province of psychiatry. The current medical practice shows that such subjects reach the psychiatrist in the forms structured by somatic and psychic complaints. The early forms justified by efficient recuperatory interventions are refered in fact to family GPs, general medicine, school doctors, physicians of various specialities (surgery, dermatology, ginecology, etc.) The cases of emergency belong to the speciality of ATI.If the psychiatrists are more sensible and familiar with the problems of human rights, persons' dignity with or without mental disorders, the therapeutic procedures according to the unanimously accepted standards not the same thing can one say for other categories of physicians who are more sensitive to mixture with the limitation of professional independence. The more and more frequent presence of drug consumer and addicts in the routine medical services raises deontological problems unknown so far in medical institutions and the physician–pacient interrelations before 1989. The message of this communication to the medical scientific community as well as to the factors concerned with the struggle against drug consumption and addiction is to subject to discussion a problem which the traditional medical deontology finds more and more difficultly an answer for. It is a situation of a deontological step where sometimes the freedom of the mentally disturbed persons, the consent for specialized treatment, are excessively valued etc. under the conditions of a real legislative gap.

Conclusions

Medical psychiatric care of drug consumers and addicts occurs at present in our country in the conditions of an oscillant, fluctuant, imperfect general legislation influenced by the transition to an ample reform of sanitary system. As to these pacients, the medical professional are requested – according to the deontological standpoint in the Code of RMC – to fulfil certain desires such as the professional independence of the physician, inviolability of medical secret, freedom of medical intervention with no administrative or other form of compulsion. Clinical and social reakities as well as the need to preserve the health of the society and the achievement of prophilactic steps impose the necessity that the drug consumers and addicts should enjoy a well–defined set of rights and obligations. The traditional deontological requirements of medical care delivery as well as the physical and professional moral safety of the sanitary and medical personnel cannot be achieved but in a realistic normative, pragmatic, complex, interdisciplinary frame establishing new, clear tasks for the institutions of public health and communitary factors.

FAMILY ROOTS OF CHEMICAL DEPENDENCY

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Overview of some approaches to drug use

There are numerous theories to explain opiate addiction.

The biological approach operates primarily on the notions of positive and negative reinforcers, and along these lines they emphasize the strengthening role of the mesocortico–limbic dopamine system (Koob, 1992). In the incentive–sensitization theory the secondary incentives receive growing emphasis, thereby offering the possibility of returning to the social aspects.

The sociological perspective views drug use as a deviance, placing it in the realm of deviant behavior. In accordance, the theory of anomie sees deviant behavior, and therefore the development of drug use, as the discrepancy between conventional internalized goals and the opportunities of one's social class (Merton, 1968). The micro–sociological, social psychological and social anthropological perspectives look at the more immediate social sphere, with the primary focus on drug–using subcultures, relationships with non drug–using peers and the family (Rácz, 1992 and 1995; Demetrovics, 1996). These theoretical views see the development of drug–using behavior connected to the socializing influence of the social environment (social learning theory), its insufficient or not properly internalized social controls (social control theory), or the presence or absence of protective and risk factors therein (Gerevich & Bácskai, 1996a and 1996b; Hawkins et al., 1992). The advantage of these theories lies in that they can deal – at least in a limited way – with the structural and relational characteristics of the family, as factors conducive to or protecting from drug use (Hoffman, 1995; Marcos and Bahr, 1995).

Further areas of research examine the personality viewpoint and psychodynamic perspectives. Until now, the search for personality dimensions, which are in the background of drug use, has not been successful, and it is possible that such exclusive, valid factors do not exist. Therefore competent research approach points to drug preference studies (see Kern et al., 1986).

Psychoanalytic and psychodynamic theories consider addiction as a secondary symptom of a primer illness or problem. The majority of the early analytical approaches, based on Freud, stress the role in drug use of regressive wish–fulfillment, orality, masturbation, self–destructive tendencies. Another early analytical viewpoint maintains that the impossibility of confronting, overcoming or escaping unbearable circumstances brings about drug use (Wurmser, 1989). In a modern perspective, but one still based on traditional analysis, Hopper (1995) sees latent homosexual fantasies as playing a significant role in the background of drug use. These theories already imply the thesis, which

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became explicit after the second World War, namely that drug use in every case is secondary and covers some other personality disorder.

Khantzian (1985) asserts that the use of a given drug is never an accidental choice, but rather the individual chooses the drug whose psychopharmaceutical properties interact to alleviate the specific dominant pain that the person is mainly experiencing. In this context drug use is a *form of coping, however maladaptive it may be.* Drug use therefore can be seen as the individual's own attempt at self–medication. The goal of the opiate user is the treatment of painful affective states, the handling of stress and dysphoria, the braking of unconscious aggressive impulses and making outside aggression bearable. Clinical data show that the above–mentioned withdrawal syndrome already exists before opiate usage, and that the opiate usage helps to alleviate these symptoms.

All these theories imply the role of family in some way considering the development of drug use but the interpersonal viewpoint becomes more clear in the object–relations theory.

Addiction and object–relations theory

The field of object–relations theory, which has emerged in the last half of this century, though it does not specifically deal with the problematics of addiction, nevertheless has been of considerable help towards an understanding of the problematics of drug use. One of the most important roles of this approach, in view of our subject, is that it makes possible the placement of what was until now in the intrapsychic context into the interpersonal sphere.

Clinical case studies highlight early mother–child relationship disturbances and the lack of primary maternal preoccupation (Cserne, 1992). On the basis of therapeutic work with the parents of drug users, Kati Varga (1993) sees the mother's narcissistic personality development and the fact that separation–individuation trauma has not been worked through by her in her own development. In this way, even when the mother is quite capable of functioning in other areas her mothering is inadequate during the phase of separation–individuation (Mahler, 1963). The borderline and narcissistic features observed in opiate users, as well as they preferred mechanisms of splitting and projection highlights the importance of the separation–individuation phase of development in the etiology of drug use. This assertion corroborated by clinical observations of drug users' mothers (Varga, 1993).

On this point it is worth leaving the psychodynamic approach, and studying the above through a broader family dynamic.

Characteristics of the drug user's family

Research identifies three characteristics of the families of drug users (Clerici et al., 1988). The first is the broken home, in which mostly the absent father is defined in the literature (Stanton, 1979; Bekir et al., 1993). The second characteristic is the presence of an over–protective mother, which often coexists with a neglectful father (Textor, 1987), who reinforces the overprotectiveness of the mother. This latter situation means the father's emotional or symbolic absence. The third characteristic is that certain family changes resulted by substance abuse, reinforce and perpetuate the drug habit. As Stanton et al. (1978) maintained, the family structure is capable to reinforce the individual's drug use.

Stanton (1979) writes about the heroin addict's father as a mainly rough and inconsistent discipliner, full of negative emotions. He also notes that many studies show the opposite, that the father plays a secondary, submissive role next to the mother. Schwartzman (1975) calls the former aggressive, autocratic father, who is nevertheless easily controlled by the mother, the

'strawman–type,' while the latter, who fills an openly secondary role he calls the 'distant' type. Studies show that drug user's mothers have significantly higher symbiotic needs than the mothers of schizophrenics or normal individuals (Stanton, 1979). Accordingly, the child who later uses drugs often becomes the favorite child (Stanton et al., 1978) and is treated as the weaker, helpless one. And so the atmosphere is characterized by lenience, even encouragement that the child should chose to escape from, rather than overcome, frustrating situations (Stanton, 1979).

Along with the above, many studies call attention to the strength of family ties, primarily in the mother and child's relationship of drug using youths (Stanton, 1978; Textor, 1987; Vukov & Eljdupovic, 1991). According to the results of Cervantes et al. (1988), 58% of sponsors of heroin users in methadone programs tends to be a family member, and in the majority, 23%, one of the parents. 26% of drug users live with one or both parents. 76% of young people acknowledged a tight relationship with the mother, while according to the data closeness with the father is lower. Often, even if the drug user moves from home he or she remains in the neighborhood, and even in the case of street drug use this close relationship is not readily given up (Stanton, 1978).

In summary, the most common picture that emerges is an aggressive, autocratic, hostile father, and rarely a submissive father, and an overprotective mother who has a symbiotic relationship with her child.

Interpersonal directions in the opiate user's family

In Schaefer's model (1959), who described parental behavior as two–dimensional, love–hate and lenient–controlling, we can place drug users' parents in the upper two quarters. While the fathers are dominated by negative emotions, the mothers are characterized by an overprotective, warmly controlling attitude (fig. 1).

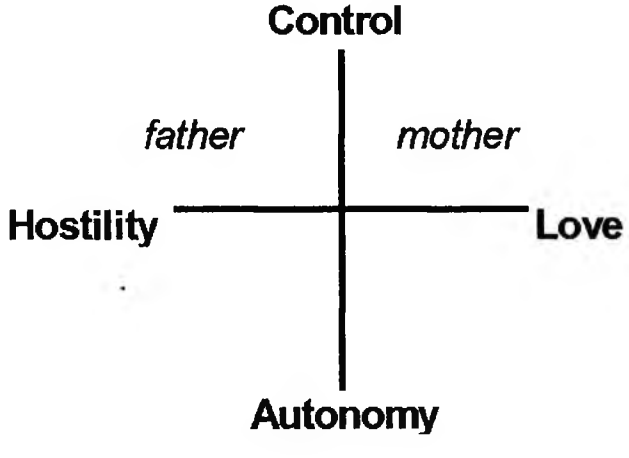

Fig. 1. Parents of drug users in Schaefer's model (1959)

I examined this supposition using the Hungarian language version of Leary's Interpersonal Check List (Leary, 1957; Kulcsár, 1973 and 1981).

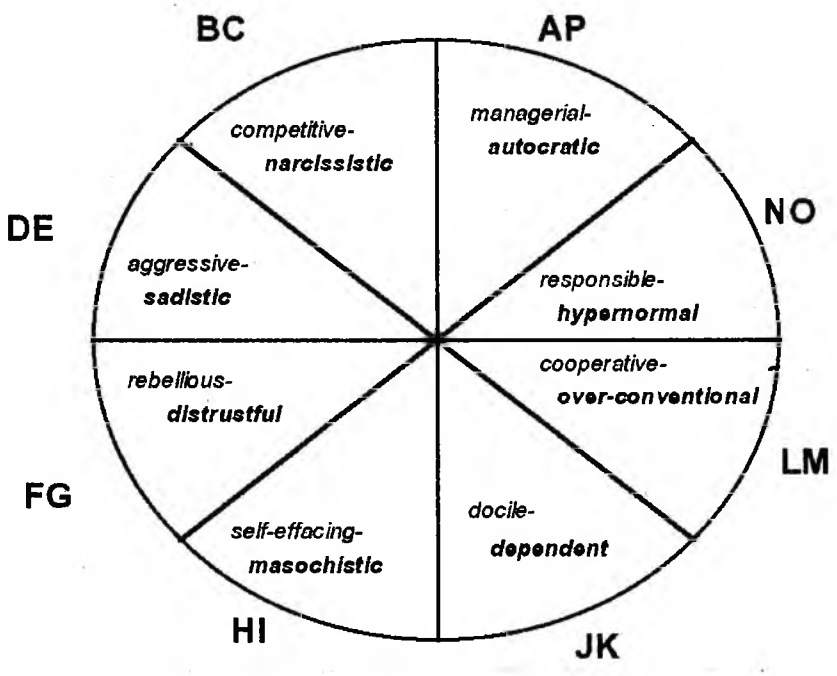

Fig. 2. Leary's Interpersonal Circle

On most points the acquired data supported the hypothesized interpersonal directions. Thus opiate users showed a significantly higher value in the JK (docile–dependent) dimension, and a significantly lower value for the dominance axis, than the control individuals. The opiate users showed especially high maladaptive values primarily in the LM, NO and FG dimension, as well as the lowered values for AP (autocratic) and BC (competitive) dimensions.

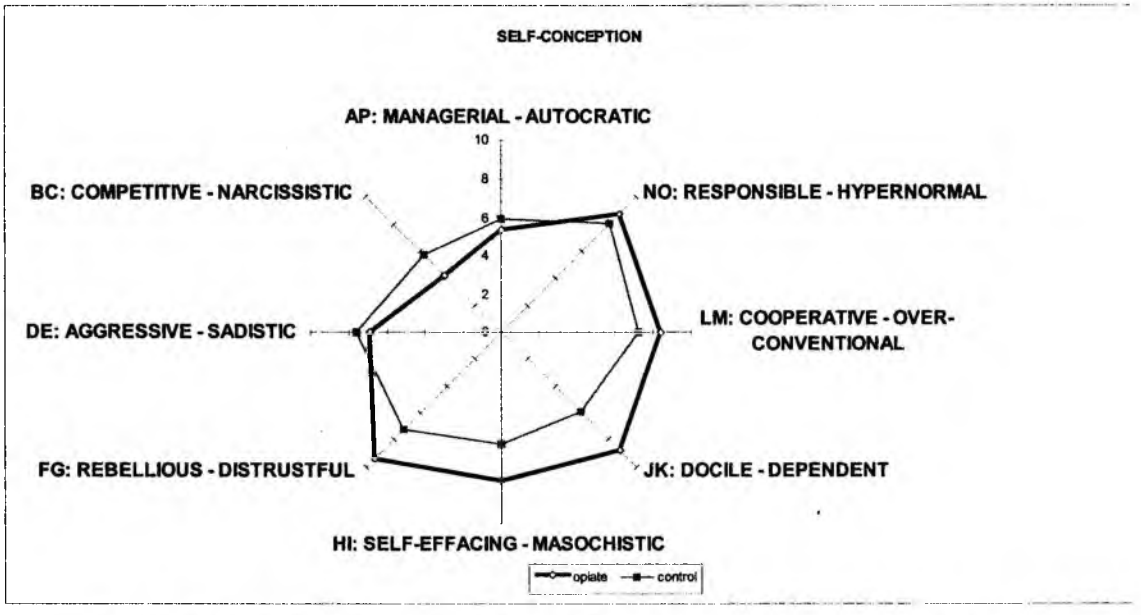

Figure 3 The self–conception of opiate addicts (n=13) and controls (n=19)

In terms of the mothers, though no significant differences were found, the opiate users tended to see their mothers as more responsible, dependent and narcissistic than those in the control group. As far as the picture held of the fathers, the opiate users saw them as significantly more autocratic (AP), competitive (BC) and aggressive–sadistic (DE) than the control individuals. A difference also arose on the lovingness dimension, where the opiate users felt more negative emotions from their fathers than the members of the control group (for detailed report and discussion of the results see Demetrovics, 1995).

Dynamics of the drug user's family

These results significantly coincide with the above clinical observations, and in terms of the dynamics of the phenomena an obvious picture opens up in front us. The tight mother–child relationship, the infantile symbiosis in adolescence, in the period of the "second separation–individuation phase" becomes a burden for the family. The adaptive nature of the child's drug use becomes clear in light of the whole family system. While the teenager's opiate use is a symbol of the separation, in reality it assures the maintenance and strengthening of the symbiosis. The drug use symbolizes a breaking away from the family, rebellion and independence, and yet it simultaneously represents in reality the festering of symbiosis. The endeavors emerge as merely pseudo–endeavors. While the teenager who enters the drug scene upholds the illusion of 'financial independence', after the onset of addiction, he or she relies even more on his or her mother for money, to help him or her through periods of withdrawal. The mother apparently does everything possible to save her child from the drug use and achieve abstinence; yet the desire to maintain dependence is always discernible in the background. The father's aggression can also gain a freer rein, since the child does not work, does drugs, renounces a conventional lifestyle. In the course of the problem the mother and father find each other again, and their relationship, which had often been crumbling, has new meaning in the face of this challenge. It is no accident that the greatest obstacle in the achievement of abstinence is the constellation of family relations.

In contrast to the linear approaches, Stanton sees the feedback mechanism's complex system significant in the perpetuation of the family interactional pattern. In his opinion, the drug user's symptomatic behavior becomes necessary when the parent's relationship is threatened by separation and in this way the family structure's balance seems to be in danger. The youth then becomes active and makes possible that the parents' attention is turned from the quality of the marriage to the responsibilities of parenthood. The effect is: "movement from an the unstable dyadic interaction (e.g. parents alone) to a more stable triadic interaction (parents and addict)" (Stanton et al., 1978, 138.). As soon as the balance returns, the youth begins to act less provocatively and leads a more competent life. Once the drug user begins to show truly competent adjustments, he or she begins to use less drugs, gets a job, and in this way pronounces his or her independence, the tensions in the marriage reassert themselves. And then the youth again responds circulus vitiosus–like by drawing attention to the drug habit and acting out self–destructively. The cycle may vary in intensity, dictated by the level of tension in the marriage. In this connection, therefore, the young drug user acts as an important protective factor, helping to uphold the sensitive family balance.

Historical perspective of the dynamics

The question remains where can we find the starting point of the above system. I studied this question through in–depth interviews of family history with ten mothers of opiate users. The interviews covered the entire family history from the mother's birth through to the child's addiction to opiates. Specific emphasis was placed in the interviews on mate selection, pregnancy, delivery procedure and the time of early mother–child relationship. In the following I will summarize the com-

mon characteristics found (see detailed results Demetrovics, in press) in order to present a unified picture of the *historical conceptualization of the development of drug using behavior.*

Most of the interviewed mothers had to take on a parental role in their early childhood, or at least were the objects of strict expectations and had to take on extensive responsibilities. At the same not one of the mothers had a close emotional relationship with her own mother, and the fathers were neither very present in the family's emotional life. In the dichotomy of the insufficient emotional care and strict expectancies the mothers were characterized by the ambivalence of simultaneously wanting to fulfill the responsibilities expected of them and of wanting to escape from the family. Despite the unfavorable constellation, most of the mothers managed to get through their situation seemingly adequately, without any serious pathology, and as a solution to the ambivalence, they chose an earlier independence for themselves. In the emergence of this solution, and the avoidance of pathological disturbances, two factors can be found to be of importance. First of all, oftentimes a grandparent or other relative or in some instances a neighbor family, afforded the possibility to experience a more ideal emotional environment. Second, it is observable in several of the mothers that in their choice of partner, whether dependent and passive or irritable and aggressive, but always constantly in need of care and attention, thus they were assured that in their adult life they would avoid weakness and pathological escape. In most instances the mother's career choice also reflects these tendencies[1].

In their choice of partner, the mothers tended to reconstruct their original family structure, and in part they took on the family's instrumental leadership, as well as all of the tasks of emotional leadership. Simultaneously, almost all of them lacked an emotionally supportive motherly example, and most explicitly stressed during the interview their feelings of incompetence as mothers. In spite of this, building upon earlier coping experiences, they assured bearing and rearing children as well as they managed their own lives adequately.

This is mainly the time when it became clear that the husband would not be a part in helping to 'solve' her childhood conflicts. This point, where for the mother the child becomes the last possibility to correct the unsolved dependence–separation or separation–individuation conflict through attempted correctional repetition. The mother, who until now performed perfectly in the 'masculine' role, cannot solve the emotional conflicts of her own childhood. She needed to escape from her family of origin, however, her dependent, at times aggressive and irritable husband maintains a child's role, thus forcing his wife into a parental role. For the woman, even–though this relationship has rewarding aspects by assuring the feeling of control, competence and adulthood experience, it nevertheless is lacking on two points. On the one hand, the husband distances himself in the everyday life, is always working, is not present, and in this way he constantly threatens his wife with separation, and with breaking the dependent, symbiotic relationship. On the other hand, he is not a partner in exchanging the parent–child roles, which would be especially important during expectancy when the mother would need help in fulfilling her regressive needs. In my view these are two experiences when the mother realizes that in terms of the husband the relationship merely abets a neurotic repetition, and in this way the marriage is leading to a divorce, either emotionally or in reality.

The rejective attitude of the husband brings back memories old patterns for the mother, and again she feels that she has only herself to count on, and that the child can give her the opportunity to emotional correction, hoping that this relationship will be easily kept under control. The goal becomes clear: she cannot let the child go.

The mothers experience pregnancy in a 'happy regression', perhaps at the first time in their lives, when they feel total symbiosis, and in this merging which is a new feeling for them, the other partner of the relationship, in this case the child, is also happy and satisfied, and they want to maintain this for as long as possible[2].

The postnatal period is happy for the mothers, the most typical feelings being pride, possessiveness (!), and sometimes disappointment. The mother's behavior has two aspects. The first is the managerial or instrumental role, in which through the repetition mechanism her own mother's

model is repeated. The other aspect is activated by the mother's own child ego state. The overprotective and dependent direction, which these mothers show towards their children, helps them to experience the loving mother–daughter relationship they missed as children. In the course of the interview these two conflicting attitudes became manifest and the ensuing ambivalence makes it impossible both for the mother and the child to take on an adult role. The mother would have to give up symbiosis, in the interest of achieving adult attitude, which would cut her off from the experience of the unlived emotional relationships in her own childhood through identification. On the other hand, the parental role she learned from her own mother would need to be changed into an adult position, for which she has no role model. In this conflict it is the latter, the one that upholds the symbiotic relationship, which becomes dominant.[3]

The crisis, as we saw also in Stanton's theory, arrives in adolescence, when the mother's conflicting attitudes towards her child become manifest. While on the one side she desires her child's growing up and independence, which is supported also by social expectations, she still cannot let go of the symbiotic attachment which caused her so much happiness. The maintenance of the symbiotic attachment is strengthened by the father's aggression, since the mother's balancing, protective role must be filled in the interests of keeping the family homeostasis. The child's drug using appears at the point when the balance cannot be upheld in any other way. Although the drug use appears to be a symbol of breaking away and independence, it nevertheless serves to maintain and even strengthen the reciprocal dependence with the mother. The drug user's mother is the person he or she turns to in times of sickness, withdrawal and attempts to quit. The mother does help in every instance, since the drug use simultaneously represents the inability of the child to break away, separate and acquire independence. In those families where the father is present, the balancing role that the drug use plays is understandable from his perspective as well, since it gives justification to the father's aggression towards the ne'er–do–well child. The father's role is emphasized on one other point. In these families, though the father works and takes on serious outside responsibilities, he does not take part, or only partially takes part, in the responsibilities within the family. He still plays a pseudo–individual role, and in reality he is completely dependent on the mother's caregiving. This is a significant example for the child, who takes from this the message that 'if I act as if I'm independent, then I will be taken care of and everyone will be satisfied.'

Conclusion

As we saw in the earlier detailed research, the study of the development of drug use in the family context gave us much more complex theoretical possibilities than the isolated study of some characteristics of the family.

In summary of the results of the above studies, we can claim that the mother's unresolved separation–individuation conflict combined with a very strong need for independence and control and struggle towards correction, *leads to pathology in the second generation*, namely the appearance of drug use. The mother can overcome her own crisis in a more or less adequate way, but one of her children becomes the victim of this coping process. The unusually strong symbiotic relationship helps the mother – through regressive and identification mechanisms – to experience the dependence she missed in her own childhood, but there is no model of how to resolve dependence and achieve separation. On the other hand, the pattern is obviously not one–sided. The child's qualities and temperament, as well as the mother's actual needs and later environmental conditions naturally all interact. Although the mother's need for dependence is definitely a starting point for the child's later drug use, it can not in itself explain the phenomenon; the reciprocal effects of countless factors is what ultimately leads to drug use. This also explains that while in the same family one child will become a drug user, the other will not.

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[1] With three exceptions the mothers had completed higher education, four of them work in the business sector, three as teachers, and one of each is a pediatrician, child care officer, as well as designer. Five work or have worked in executive jobs.

[2] In this connection it is not surprising that four of the mothers carried their child 1 to 3 weeks longer, and there was only one premature birth (an unknown indication induced labor!). In four cases occurred oxytoncinal induced labor, in several cases labor stopped once they reached the hospital.

[3] The symbiotic attachment is therefore present throughout childhood, though the child is traumatized in several ways by the mother. The mother nevertheless often prefers her responsibilities, work and the desire for competence, and the child then takes second place. And so the child learns quickly that if he or she reacts 'appropriately' to the mother's indications of separation, awakening in the mother her own childhood feelings of abandonment and emotional neglect, she will attempt to strengthen the symbiosis once again. The basic difference between the mother's and the child's development is that while the former had no other choice than to become independent and grow up quickly, her child, by pressing the right buttons, can 'demand' care and attention.

INTERDEPENDENCE BETWEEN THE SOCIAL & ECONOMIC STANDARD AND CHRONIC AND ACUTE ETYLISM

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Alcoholism represents one of the contemporary health problems; alcohol is much more dangerous than other illicitly obtained substances as it is part of the social activities, economic life and religious practice in many cultures.

According to OMS, chronic alcoholism is the fourth public health problem coming after cardiovascular mental and oncologic diseases.

The effects of alcohol on the population's state of health include acute and chronic diseases with progressive deterioration of the psychic and physical state of the individual, of social and family life.

The **purpose** of this paper is to evidence (on the basis of cases of patients of the Medical Clinic of the Emergency Hospital in Iasi) the effects of alcohol on the individual's state of health; so, the need for setting and development of specialized medical assistance for the treatment of alcohol–addicted patients as well as creating educational programs which would help change the social attitude toward heavy consumers of alcohol becomes obvious; persons in this category should be considered addicted patients as alcoholism is the most spread toxic disease.

Material and Method

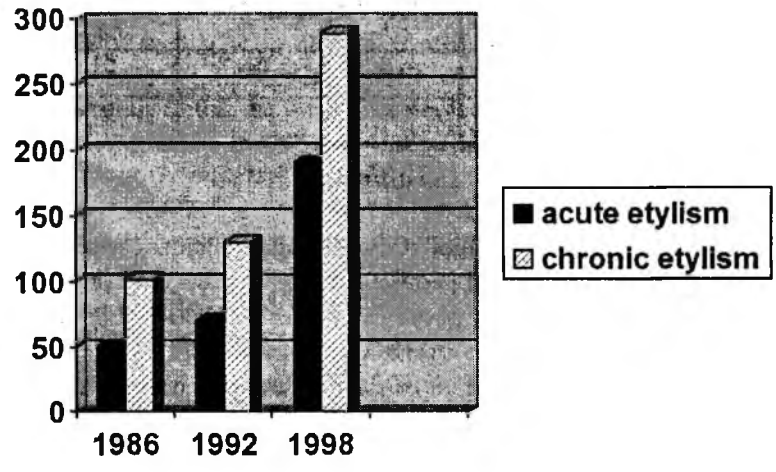
Our investigation includes a comparative statistic study of cases recorded over a longer period of time in which distinct social and economic structures are traced; the impact of these structures on the population can be interpreted by the frequency of the etylic behavior. We have taken as distinct periods the following: 1985–1989, 1989–1994, 1994–1999. The years 1986, 1992, and 1998 were also considered in a random way.

The data were taken from the observation files of patients questioned in the clinic in the period indicated; re–hospitalization of the same patients within the same year was not considered. Chronic etylism could not be defined by dependence on the daily consumption of alcohol and only on the basis of clinical symptoms, laboratory data and the patient's statements.

Results

The analysis of cases revealed the following:

– There is an increase in the number of cases of acute and chronic etylism – from 50 cases of acute etylism in 1986 to 191 cases of etylism in 1998. Cases of chronic etylism have become more frequent in 1998 (289 cases) as compared to 1986 (101 cases). This growth is shown in the following graph:



Graph. 1. The increase of number of cases of etylism

– There is a higher frequency of cases of acute etylism for age 21–30 and for chronic etylism between 41–70. Comparative figures are synthesized in Table 1.

Year	Etylism	15-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
1986	Acute	7	16	10	10	7	-	-	-
	Chronic	-	3	22	23	30	13	9	1
1992	Acute	1	25	20	12	8	4	-	-
	Chronic	2	12	23	16	31	31	10	5
1998	Acute	21	77	44	26	16	5	2	-
	Chronic	-	27	29	54	74	62	39	4

Table 1

– Distribution of disease on **sexes** shows a roughly equal number of cases for both sexes with acute etylism (22 cases females and 28 males in 1986) and an overwhelming number of male cases with chronic etylism (55 females and 234 males in 1998).

Etylism acute						Etylism chronic					
1986		1992		1998		1986		1992		1998	
F	M	F	M	F	M	F	M	F	M	F	M
22	28	32	38	70	121	18	83	23	107	55	234

Table 2

From the point of view of the **background,** acute etylism is predominantly spread in the urban area (120 cases in Iasi as compared to 52 cases in the rural area in 1998), whereas chronic etylism is predominant in the rural background (176 of cases in rural area and 83 cases in Iasi in 1998).

Place	1986		1992		1998	
	Etylism acute	Etylism chronic	Etylism acute	Etylism chronic	Etylism acute	Etylism chronic
Iaşi	37	43	54	40	120	83
villages	10	55	16	86	52	176
Other towns	3	3	-	4	17	30

Table 3

– A classification according to **social status/position** evidences an increase in the number of cases of acute etylism with unemployed people in 1998 (72 cases) as compared to 1986 and 1992 when most cases were regularly employed people (32 cases in 1986 and 40 in 1992). There was an increase in the number of cases of chronic etylism in 1992 and 1998 with retired people (49 and 141 cases, respectively) as compared to 1986 when chronic etylism was more frequent with working people (54 cases).

Profession	1986		1992		1998	
	Etylism acute	Etylism chronic	Etylism acute	Etylism chronic	Etylism acute	Etylism chronic
Unemployed	11	3	13	9	72	34
Agricultural workers	2	17	5	32	23	35
Regulary employed	32	54	40	39	56	68
Students	5	-	6	-	19	1
Retired	-	26	5	49	21	141

Table 4

Data processing evidenced differences between **reasons** for hospitalization of patients. So, the predominant reason in cases of acute etylism is the autolytic reason, alcohol associated with other toxic elements (drugs, organic phosphoric and organic chlorate insecticides, etc.), in 89 percent of the cases; only 12.3 percent of the cases of chronic etylism are caused by accidental ingestion of toxic substances on etylic background. The remaining cases are hospitalized for heart symptomatology (16.9 percent for arterial hyper–tension, 7.9 percent for acute fibrillation, 10.19 percent for heart ischaemia); lungs (11.15 percent for chronic obstructive bronchopneumonia, 5.3 percent for pneumonia), digestive (9.73 percent for duodenal ulcer, 6.1 for liver cirosis, 9,42 percent for colecistopathy, 10.76 for chronic hepatitis, 7.69 gastritis); the symptomatology is often very intricate.

Alcohol consumption is associated with **smoking**. So, from the total number of 520, in 168 cases the number of cigarettes smoked per day did not exceed one package and in 97 it exceed one package per day.

The **treatment** applied was that for acute intoxication in the cases of acute etylism and that corresponding to the symptoms of the disease in chronic etylism. Unfortunately, no treatment was used for the disease that caused the hospitalization – alcoholism.

Conclusions

1. The increase in the number of cases of etylism in time accounts for the idea of the social–economic impact of these times of change on the individual.
2. The strategies to be implemented in order to reduce the dangerous effects of etylism could be synthesized as follows:

Communitary programs focused on:

– regulation of prices and offer and increase of taxes on alcoholic drinks,

– regulation of the minimal age for buying alcoholic drinks.

- legislative measures with a view to fight alcohol consumption by drivers;
- stimulation of general awareness, education, and information programs by co–operation of sanitary units, schools, intervention teams; supplying the necessary written material for sanitary education;
- intervention on community level, health care – the family doctor's role in detecting, supervision, and treatment of the heavy drinkers;
- creating medical teams specialized in etylism in all hospitals;
- development of ambulatory structures specialized in etylism counseling;
- organization of network specialized in care of etylism patients as mini–hospitals with role in treatment and re–adaptation in post–treatment period;
- supporting non–government associations such as Alcoholic Anonymous, National Alcoholism Prevention Agency .

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PHARMACODEPENDENCE AT PHENCYCLIDINE

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Pharmacodependence at hallucinogenes is increasing both in person numbers using these substances and in chemical structures of used substances.

Hallucinogenes (named also psychodisleptics or psychotomimetics) determine a very intense pharmacodependence,and are the only substance which produce appearance of some anormal psychical state (hallucinations) very similar with some met in schizophrenia. Usually, psychotomimetics may be classified in 2 groups (Rang and Dale, 1987).:

A. Substances which have some resemblance with neurotransmitters from some biological active groups:
   a) LSD, psylocibine, bufotenina, DMA (related to serotonin)
   b) mescalina (related to amphetamine)

B. Drug unrelated to monoamine neurotransmitters: as tetrahydrocannabinoids, phencyclidine

Phencyclidine is a synthetic substance, designed initially as general intravenous anesthetic for dissociate anesthesia. It is not longer used in medical practice but its illicit use increased in USA and other countries . It has some structural resemblance with ketamine, a general anesthesic used in clinical practice. As chemical structure it belongs to arylcyclo–hexylamines. Phencyclidine (also known as "angel dust") may be administrated on different routes. Some dependent persons smoked it, some injected intravenously or swallow it.

Mechanism of action

All substances that produce pharmacodependences act on brain reward systems. According with Wise, 1982 Van Ree 1987, there are 2 rewarding systems in the human brain (and also in superior animals) .

a) Dopamine dependant reward circuits (located specially in mesolimbic) –for morphine, cocaine,etc
b) Dopamine independent reward circuits–e.g. rewarding properties of food are not strongly dependent on DA release in the nucleus accumbens

In reward systems are also involved: vasopresine, endogenous opiates, cathecolamines (other than DA), excitatory neuroaminoacid system, prostaglandins (Nechifor et al., 1989, 1992).

The details for mechanism of action involved in pharmacodependence at phencyclidine remain to be clarified. However, it is clear that phencyclidine stimulates these reward systems.

There are 2 characteristics for the phencyclidine mechanism of action:

a) Special receptors, identified in the brain (Kosten and Hollister 1999)
b) Multiple interactions with an important number of cerebral neuromediators

c) There are not known many things about phencyclidine receptors but it is positive that they are closely to opiate receptors but not similar with these.

Phencyclidine action is characterized by interaction with a great number of CNS mediators. This interactions is related to prejonctional release of neuromediator or its postsynaptic actions. Among these neuromediators we mention:

– dopamine and other cathecholamines
– endogenous opiates (Hiramatsu et al., 1986)
– acethyl–choline
– glutamate system and other excitatory amino acids (Kulkarami and Verma, 1991)

Hiramatsu et al 1989 conferred an important role to phencyclidine action as noncompetitive antagonist for NMDA receptors. Kulkarami and Verma, 1991, consider that phencyclidine effect is based on affecting normal balance between glutamatergic and dopaminergic systems in the brain.

Nitric oxide proved to be a intracellular second messenger and a modulator for releasing presynaptic neuromediators . NO synthesis is stimulated by NMDA receptor agonists (Garthwhite et al., 1988) and decreasing activation of this receptors by phencyclidine might decrease NO formation into the neurons. NMDA receptor antagonists, like nitric oxide synthetase inhibitors are substances that decrease NO level into the brain. Noda et al., 1995, have shown that NMDA agonists and inhibitors of nitric oxide synthesis protect toward neurotoxicity of NMDA receptor agonist (including seizures onset). On the other hand, phencyclidine (3mg/kg,administrated experimentally) induced hyperlocomotion and ataxia which are not modified by L–NAME (50 mg/kg) (systemic inhibitor of NO synthetase) (Noda 1998). It seems that symptoms that appear at phencyclidine administration doesn't depend on systemic level of nitric oxide.

7–nitro imidazole (selective inhibitor of neuronal NO synthetase) (without affecting NO synthesis from vascular endothelium) strengthen phencyclidine effects and specially increases hyperlocomotion. We consider that this plead strongly that noncompetitive antagonist effect of phencyclidine on NMDA receptors followed by a reduction in neuronal synthesis of NO play an important role in phencyclidine actions in CNS . This would be in accordance with Itzhak data (1994) that in symptoms given by cocaine (e.g hyperlocomotion) it is involved also nitric oxide. There are data that phencyclidine would block dopamine synaptic re–uptake and would raise synaptic levels of this neuromediator.

Phencyclidine blocks also serotonine and noradrenaline re–uptake in central synapses. There is a some agonist effect on sigma receptors (Crabtree and Richardson, 1996). The intake of phencyclidine produces a paranoid psychosis but it is not possible to predict neither which from the symptoms will predominate to a consumer or another or whom will be violent.

Regarding therapy about cessation and to prevent relapse, it was recommended dopamine receptor antagonists, benzodiazepines but with poor results.

The most important symptoms induced by phencyclidine are:

–hyperreactivity
–stereotype movements
–decrease of motor coordination
–ataxia
–hallucinations; confusional states
–nistagmus
–catatonic rigidity
–slurred speech
–amnesia

It increases arterial pressure (maybe by central mechanism). Phencyclidine significantly increases the violent behavior of consumers. It has the reputation to induce a stronger dependence than other substances and also to induce severe aggressions toward other persons.

In the case of higher doses it may produces seizures, coma and death (Aniline and Pitts, 1982). It was considered (due to specific effects) that phencyclidine administration in animal might

produce a close experimental model of schizophrenia (a human psychotic disease by excellence and practically impossible to be completely reproduced in animal). Noda et al. 1995 consider on the first line of mechanisms involved in schizophrenia symptoms to be a decrease in transmission on NMDA receptors. There are some variations (according to dose) of symptoms induced by phencyclidine administration. So, in experimental administration of phencyclidine in rat or mouse (3mg/kg), in the first line appear hyper locomotion and at higher doses (10 mg/kg0 more obvious is ataxia. The explanation of these changes is not clear.

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SUMMARY