UNIVERSITY OF MEDICINE AND PHARMACY
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DOCTORAL THESIS
SUMMARY

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CLINICAL AND ETIOLOGY ASPECTS IN THE RESISTANT AND
REFRACTORY SCHIZOPHRENIA

THERAPY WITH ATYPICAL ANTIPSYCHOTIC
AGENTS IN SCHIZOPHRENIC
PATIENT CARE

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SCHIZOPHRENIA = mental disorder characterized by fundamental and characteristic distortions of thinking and perception, and the affects that are inappropriate and used. Clear consciousness field and intellectual capacity are usually maintained although certain cognitive deficits can be installed during time. The disorder involves basis functions, giving a person a sense of uniqueness, identity and autonomy.

ANTIPSYCHOTICS = drugs that represent chemotherapy of choice in schizophrenia. Several methods are known of the neuroleptics. The most important current classification is the clinical-medical one.

NEUROTRANSMITTER = are substances released synaptic and provide the transmission of nervous impulse with the ability to trigger action potentials.

DOPAMINE = Neurotransmitter on synthesis ways of adrenaline and noradrenalin.

SEROTONIN = monoamine derived from an essential tryptophan amino acid, which under the influence of TRH passes in 5-hydroxytriptofan and this after decarboxylation generates 5-HT.

NORADRENALINE = mediator of vegetative sympathetic postganglionic nerve endings present in the peripheral vegetative effectors.

RECEPTORS = Membrane proteins specialized both in the identification and acceptance of the neurotransmitters and other molecules characterized by high specificity.

CLASSIC NEUROLPTICS = acts favorite on positive symptoms.

ATYPICAL NEUROLEPTICS = acts favorite and with superior efficacy on positive symptoms, negative primary and cognitive, with minimal or absent extra pyramidal effects, and the absence of increased secretion of prolactin after chronic administration.

CLOzapine = minimal positive and negative symptoms effective in schizophrenia, but also in tardive dyskinesia.

RISPERIDONE = establishes and maintains a satisfactory antipsychotic effect at a dose of 4 mg / day with minimal risks for extra pyramidal effects.

OLANZAPINE = increased affinity for the receptors rD2 and r.5-HT2A, but also for the receptors 5-HT2C and 5-HT6. Occupies majoritary the receptors D2 and 5-HT2A with the improvement of the post-schizophrenia depressive symptoms treated with Olanzapine.
SERTINDOLE = is effective in relieving the negative symptoms due to the affinity for the dopamine receptors D2.

QUETIAPINE = acts with predilection on rD4.

OMS = World Health Organization.

DISABILITY = disorder in minus and a deficiency of a human action that is based on one or more post-maladive deficiencies. For example: the difficulty of communication, walking, efficient resolution of some personal and community problems.

DEFICIENCY = persistent dysfunction of the human bio-psychological body, consequent to suffering a disease and based on violating (and/or disturbing) an organ or an individual functional system (deficiencies of vision, movement of legs, memory usage, etc.).

DISABLED = is the sum of the negative social consequences resulting from the deficiencies based on disabilities, consecutive to some chronic diseases or that leave defects. Thus, the disability can occur towards a profession, on the full manifestation socially or publicly, the support for the good of the family and household, etc.

SCALE = scale of measurement or evaluation of the symptoms or the clinical condition following the administration of the antipsychotic therapy.

GAF = Global Assessment of Functioning - global scale of assessment of the function.

PANSS = Positives and Negatives Symptom Scale - Scale of the positive syndrome and the negative syndrome in schizophrenia.

CGI = Clinical Global Impression - scale of the global clinical impression.

BECK = Depression Rating Scale.

BARS = BARNES scale of assessment of the drug-induced akathisia.

IMC = body mass index.

WHOQOL-BREF = abbreviated version of the scale WHOQOL-100 Rates the patients life quality that occur during the treatment.

Searching for other classes of drugs has become a constant concern of the psychiatrists and staff of psychopharmacological research in finding a common major secondary phenomenon in patients with long-term treatment with antipsychotics, including dyskinesias and cognitive disorders are the cause of the socio-professional invalidation. After Sertraki, the mental patients emissions can be grouped into four types:

- the patient gets back to work, is re-inserted into the family and society:
b. continuing the professional activity is made at a level below that previously had, inconsistent with the professional training; social and family reintegration is good;

c. the family reintegration is made with the family commitment on the part of its supervision: the patient can perform some tasks, as an occupational therapy;

d. The patient requires specialized institutional care as a result of the persistence of a symptom that makes impossible the reintegration into the family and society: the treatment plan includes the occupational therapy.

The clinical experience has shown that most remissions, under the treatment with classical antipsychotics are of type "c" and "d" (185).

The road to atypical antipsychotics started in America, where, in '70s, was introduced in the treatment of mental patients Clozapine, another kind of so-called "atypical"neuroleptic. Reports of some unwanted side effects in the patients treated with the new drug went, based on an awareness about health with rigorous standards, to the exclusion of the drug from the market. The drug, already manufactured in large quantities, is offered free to clinics in Europe. More pragmatic, the European psychiatrists are making the positive and negative effects balance, that tilts clearly for positive effects. The attempt to eliminate or mitigate the adverse effects of Clozapine led to the discovery of other antipsychotics, called "like cloze". After 1990 the therapeutic arsenal is enriched with new types of antipsychotics (95).

Undoubtedly, schizophrenia is the most devastating brain disease. The classic antipsychotics brought a ray of light for the patients affected by this disease (considered by some authors as a "destiny"). But it was not enough. Even if some bothersome symptoms are reduced or remitted under treatment, many problems remain unsolved related to the functioning of the patient, to the preservation of the cognitive function, etc., and also experience other disadvantages (unwanted side effects) (21).

Under these auspices, we proposed to examine the impact of the new generation antipsychotic medications on the life quality of the patients taking a prospective study of 192 patients, for a period of 5 years. To avoid bias, we studied patients treated with 3 atypical antipsychotics: Olanzapine, Clozapine, Risperdal and a classic neuroleptic - Haloperidol.

The study aims also to highlight the usefulness and the degree of approximation of various psychometric scales used today. By definition, the life quality is a highly subjective feature. Or, in patients with schizophrenia self-assessment can lead to incorrect results. This does not mean that there are not devices for measuring closer to the truth. The information obtained from the patient's entourage, first from the family, are particularly important.

At the beginning of the study, the clinical experience in managing the next generation antipsychotic medication did not exceed a decade, but some results were spectacular.

That was the challenge. What prove the 5 years of study?

The basic idea of the paper was a comparative study that spanned a period of five years, on groups of patients selected according to certain criteria. The patients selected were divided into four compartment groups, evaluated after a series of scales, then monitoring their clinical course periodically in administering the antipsychotic drugs: atypical versus typical.

In the first part of the paper is offered a perspective on the current orientation in schizophrenia, attempting a more exact definition of this disease, a disease short history following the presentation of the classification trials of the schizophrenia clinical types.

The difficulty of developing some diagnostic criteria for mental disorders versus the other diseases come from the absence, in most cases, of the etiological factor - essential feature of the mental disorders.
Currently are supported two major classification systems of mental disorders:

- International Statistical Classification of Disease and Related Health Problems (ICD) / WHO's International Statistical Classification of Diseases and Related Health Problems (ICD / CTM); this classification system is used in Europe.
- Diagnostic and Statistical Manual of Mental Disorders (DSM, Diagnostic and Statistical Manual of Mental Disorders).

Also, we follow considerations on the epidemiology and etiopathogenesis of schizophrenia.

The annual incidence is estimated between 0.1 and 0.5 per thousand inhabitants, and varies with age and sex - young men and women between 35 and 39 years showing higher rates of disease.

Regarding the etiopathogenesis and approach of this chapter based on the acceptance that the etiology of schizophrenia is still a great enigma for all professionals, even if in this direction is consumed the largest amount of research and scientific inquiry. Complex and recognized team of specialists have been limited to issue some "assumptions" and "concepts" and have identified "factors" favoring the disease.

The vulnerability-stress model accredits the idea of a specific biological vulnerability that is triggered by stress and leads to schizophrenic symptoms. Stress can have a genetic, biological and psychosocial or environmental nature.

Chapter 1 ends with some therapeutic considerations vis a vis the patient's clinical management and includes:
- Antipsychotic hospitalization and medication;
- Psychosocial treatments;

Chapter 2 provides an overview on current affairs in antipsychotic medication. The atypical antipsychotics apparition is related to the studies and research on elucidating the pathophysiological and etiological mechanisms of triggering and evolution of schizophrenia.

In terms of therapeutic effectiveness in treating schizophrenia, things are not yet sufficiently distinct, especially regarding the theory of "multifactorial" etiopathogenesis that supports the involvement of several levels of vulnerability, in a relative channeling. However, the biological – biochemical model that this theory was based on allows the development of new therapeutic and management strategies in schizophrenia.

The main etiopathogenic hypotheses developed based on the biochemical vulnerability are:
- The dopaminergic hypothesis of schizophrenia;
- The serotonin hypothesis;
- The noradrenergic hypothesis.
- The hypothesis of involving some complex systems of neurotransmitters.

Data provided by the psychopharmacological and neurobiological basic research and pouring the knowledge and clinical experience base the modern therapeutic strategies development that have precise objectives:

1) Early recognition of the onset of the disease by:
   - identifying the people with vulnerability for the disease;
   - Correlation of the clinical and anamnesis data of vulnerability with biological and biochemical indicators in objecting the high risk factors for schizophrenia.

2) Therapy with maximum efficiency of the acute episode of illness and prevention of rebounds. Two courses of treatment are differentiated:
   - Treatment of acute episode with predominantly positive symptoms;
   - Treatment of acute episode with predominantly negative symptoms;
   - Anticipating the therapy resistance and relapse by standardized assessments with high fidelity and validity correlated with biochemical and biological indicators;
   - Limitation of the neuroleptic medication induced adverse effects and the increase of adherence to long-term treatment.

Classifications of the antipsychotic substances:
- Chemical classification;
- Clinical classification;
- Classification based on clinical and pharmaceutical criteria

Chapter 3 focuses on the life quality in psychiatry by concept and systematization. There is evidence that frequent and prolonged hospitalization of mental patients adversely affect their ability to make decisions and auto-conduct in the social environment. The optimal psychiatric management should have as target the rehabilitation, re-education and resocialization of the mental patient after the acute episode of illness. In this enterprise, the medical team should also use people without medical training, but interested in the fate of the mental patient: family members, social workers, community support organizations (214). In this context emerged the concept of community psychiatry (14), which operates under terms that make up the concept of life quality: the personal interrelations, the social roles, the satisfaction of the vital needs, the personal happiness, the subjective well being.

Schizophrenia is the most devastating brain disease that affects 1-1.5% of the adult population of the world and represents more than half of psychosis (21). After most standards, the lives of the patients with schizophrenia lacks the satisfaction of the hard experience, interpersonal relations, social and welfare achievements, elements that generate the subjective feeling of satisfaction for the life quality.
So, the parts involved in mental health protection - psychiatrists, psychologists, nurses, sociologists, social workers - have received the "challenge" and cannot neglect the use of "construction" called "life quality" if they are to reach their goal: the provision of some quality services to the patient with mental problems.

The World Health Organization proposes for health problems in general, the following definition:

"The life quality is the people's perception about their position in life relative to the goals and values system that they have accepted and assimilated in the light of the decisions they have taken."

Lehman Model

Another definition, informal - quite simple if not simplistic - was provided by Lehman (1996): "... patient's perspective about what he has, what he does and how he feels his life stories. In short. QoL covers the understanding of the person on welfare ("well-being", includes also often, what they do (functional status), what they have (the access to resources and opportunities).

Katsing Model

The further theoretical systematizations and conceptualizations bring into question the three essential components of life quality, which Katschig (129) ranks as follows:

a. The subjective well-being ("well being", "bien être") from the interpretation of the emotional condition until the lasting satisfaction reported to the whole existence;

b. Operation in social roles;

c. Environmental factors, predominantly material: income, food, housing, heat; here are also included the social amenities, information and education opportunities, access to health and social services, personal security, relations with the neighbors.

Maslow Model

At one point, the life quality was assessed against the theories of Abraham Harold Maslow (American psychologist, 1908-1970) on "the basic human needs" ranked on several levels, as follows (162):

- physiological needs;
- protection and security;
- love and affection for those close;
- power, prestige and esteem;
- curiosity and the need for understanding;
- aesthetic needs;
- self-realization;
- transcendence, overcoming self;
The quality of life assessment is made by the BQOL scales (Beecham Life Quality Scale) and the Barry Model.

The systematization proposes a classification in terms of impairment, disability and handicap; considered as distinct of disease classification referring in principle to its consequences. In this sense, we describe:

a. The deficiency - persistent dysfunction of the human bio-psychological body, consequent to an unhealthy suffering and is based on the violating (and / or disturbing) of a functional organ or system of the individual (deficiencies of vision, movement of the legs, memory usage, etc.).

b. The disability - minus deficiency and a disorder of a human action, which is based on one or more post-maladaptive deficiencies. For example: the difficulty of communication, travel, efficient resolution of some personal and community problems.

c. The handicap - is a sum of the negative social consequences resulting from the deficiencies based on disabilities, consecutive to chronic diseases or that leave defects. Thus, the handicap can occur towards the profession, the full manifestation on social or public plan, the support in good conditions of the family and household, etc.

In light of the recent research conducted by O.M.S., the period of deficiency (disease) is more nuanced clarified, and:

- disability = weakness in specific human actions;
- handicap = deficiency in the functioning of social roles.

It appears to avoid the term of "handicap" that can be considered pejorative, to the terms "defective person" or "social integration".

Research purpose and objectives

The objective of this study is to compare the effectiveness of the long-term treatment with atypical antipsychotics (Olanzapine, Risperidone, Clozapine) compared with a classical antipsychotic (Haloperidol).

The alternative was pursued:
- impact on life quality;
- severity of the side effects;
- frequency and prevention of the decompensations;
- professional and social reintegration;
- the degree of preservation of the intellectual and social performances;
- changing the entourage attitudes towards the schizophrenic patient.

The goal of the research is to complete the data on the treatment with atypical antipsychotics accumulated so far to improve the management in the schizophrenic patient treatment.

Research hypotheses.

We hypothesized that the efficacy of the schizophrenic patient treatment with atypical antipsychotics should be considered in light of the long-term treatment related to the chronic disease development. The installing and maintaining of the therapeutic benefit involves the consistent
administration of the treatment, with the acceptance of some side effects for limited periods of time, inconveniences that can be corrected by adjusting the dosage or / and introducing an adjuvant medication.

The discontinuation of the treatment takes into account both the patient decision and the physician and must be made after assessing the therapeutic benefit and the use safety of the drug.

The clinical experience has shown the resurgence of the psychotic symptoms after discontinuation of the drug treatment (voluntary, based on an apparent "improvement", or involuntarily). In these circumstances is installed a "resistance" to the type of antipsychotic used which means that the restart of the treatment with the same antipsychotic means increasing the doses and introducing the additional medication (sometimes the pairing with another antipsychotic).

There are situations that require the interruption of the therapy due to ineffectiveness, adverse reactions aggression, of which the most difficult to tolerate: extra pyramidal symptoms, dyskinesia, weight gain, non-compliance (8).

The prospective study over a period of 5 years, since 2005, follows 198 patients with "Schizophrenia" diagnosed by the ICD X R and DSM IV criteria. The patients were selected from all the patients who were registered in the Mental Health Laboratory. The patients were distributed in 4 groups:

A. 53 patients receiving treatment with Olanzapine (10 mg / day);
B. 44 patients who received treatment with Risperidone (6 mg/day)
C. 51 patients receiving treatment with Clozapine (300 mg / day);
D. 50 patients who received treatment with Haloperidol (10 mg/day);

The choice of treatment was made during hospitalization, based on the clinical examinations and observations, laboratory tests, complex psychological assessments. In determining the treatment was considered the response to the treatment, the compliance, the treatments previously considered and their effectiveness.

Inclusion criteria for this study were:

- men or women aged between 18 and 65;
- informed consent, under signature, with knowledge of the procedures required by the Protocol;
- diagnosed with schizophrenia according to ICD 10 and DSM-FV;
- to have a score PANSS > 70;
- CGI-S > 10;
- capacity for understanding.

The exclusion criteria are listed below:

- History of allergy to haloperidol, risperidone, olanzapine, soflan or their ingredients,
- pregnant or lactating women;
• dependence on alcohol or other drug substances;
• history of positive results on serological tests for hepatitis B, C and HIV;
• hospitalized against their will;
• history of malignant neuroleptic syndrome;
• history of closed angle glaucoma;
• any unbalanced somatic disease;
• leukopenia;
• any cardiovascular, respiratory, neurological, kidney, liver, endo-crinological, hematological or immunological issues untreated;
• history of malignancy in the last 5 years;
• Moderate or severe dyskinesia during enrollment;
• suicidal thoughts or violent tendencies during the titration of the medication;
• The lack of efficacy of one of the substances investigated in the past.

Study design The study design was structured as follows:
• monthly visits, for medication administration;
• semester for evaluation GAF, PANSS, CGI, WHQOL;
• Annual, Beck assessment. BARS and adherence to treatment.

Screening: (duration 1 month)

For the subject to be able to continue the participation in the study, is necessary that all enrollment criteria are met. criteria for enrollment in the study. Given the large number of patients included in research at this stage required a longer period of time.

At this stage, considered also a prime visit, was proceeded to:
• inviting the patient to take part in this study and signing the informed consent;
• passport data record;
• diagnosis establishing;
• pathological personal history recording;
• collateral family history recording;
• socio-professional history;
• checking vital signs (T.A., pulse, temperature);
• measuring height and weight;
• pregnancy test (for women);
• scales application for the extra pyramidal effects - Barnes-Akathisia;
- scales implementation for the study efficiency (GAF, PANSS, CGI, Beck, WHOQOL)
- Body mass index calculation;
- Compliance index calculation.

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The above table has visualized the visit frequencies and their content.
Method, strategy and work material.

Investigation instruments:

The treatment efficacy will be assessed by applying the scales GAF, PANSS, CGI, BECK, OMS-QOL (BREF version), BARS (13) (25) (176) - according to the design. Will be calculated also compliance and body mass indexes, indexes that are constituted in important tools in assessing the effectiveness of the treatment. We kept these instruments, because we wanted to achieve comparisons with the moment when the treatment was started and because the patients were already familiar with the interview or self-evaluation procedures.

GAF (Global Assessment of Functioning - Global functioning scale) - records scores from 0 to 100; "0" defines a clinical picture characterized by severe psychotic symptoms, and "100" indicates an asymptomatic clinical picture, in a patient with superior social functioning (Appendix 1).

PANSS (Positive and Negative Syndrome Scale - Positive and Negative Syndrome Assessment Scale in Schizophrenia); the scale assesses 30 symptoms on 7 areas, totaling scores from 0 (asymptomatic) to 210 (extreme severity of symptoms) (Annex 2).

CGI (Clinical Global Improvement - Clinical Global Impression Scale). The symptom rating scales, including visual analog scales have witnessed a growing popularity in the controlled clinical trials with antipsychotics, while the interest in the global severity scales and overall improvement have decreased. In any case, it is advisable to include both types of global evaluation in the researches with antipsychotics. The most commonly used scale in psychopharmacology for measurement of overall disease severity is "Clinical Global Impression Scale" (Clinical Global Impression - CGI) - published by Guy in 1976. This scale has a score stretch from 1 (not depressed) to 7 (most severely depressed). (Annex 3).

BECK – scale that compiles the depressive symptoms, giving scores from 0 (no depressive symptoms) to 63 (severe depressive symptoms). (Annex 4).

WHOQOL-BREF (scale for assessing the life quality published by OMS, short form). Evaluates the patient's life quality changes that occur during treatment. Builds a profile on the quality of life on four areas: physical and mental health, social relations, environment. The score ranges from 0 to 100. (Annex 7).

BARS - (Barnes assessment scale of drug-induced akathisia). The scores for global assessment of akathisia were registered, scored from 0 (absent symptoms) to 5 (severe symptoms) (Annex 5).

The study aimed to evaluate the efficacy of the atypical antipsychotics treatment versus haloperidol (typical classical neuroleptic) in order to adapt the most appropriate therapeutic strategies in relation to the clinical progression shape and parameters of the disease.
The assessment tools used targeted a complex assessment of the patient and meant significant accumulation of massive amounts of data that could be ordered and analyzed using the SPSS statistical software. At the conclusion of the study were profiled the following conclusions:

1. The atypical antipsychotics are the medication that produce and maintain over time a real improvement in the life quality of the patient diagnosed with Schizophrenia by family, social and professional reintegration and the results of the evaluations and their comparison reveal that in the atypical antipsychotics, Olanzapine has a higher efficiency in the treatment than Risperidone and Clozapine.

2. Social functioning assessed with GAF (Global functioning assessment scale) records a substantial improvement after the first year of treatment, maintaining an upward trend for the coming years.

3. The psychotic symptoms (positive and negative) is more strongly influenced by the treatment with Olanzapine, the overall clinical impression (CGI) indicating a closer to normal behavior in patients treated with Olanzapine and registers acceptable scores in patients treated with Risperidone, the estimates indicating significant results for patients treated with Clozapine and Haloperidol.

4. After the first year of treatment the depression regresses in patients treated with Olanzapine, Risperidone and Clozapine and is maintained at the same level in patients treated with Haloperidol.

5. Akathisia and the discomfort are reduced in patients treated with atypical antipsychotics used in the study. Are noted, however, differences between the results obtained with atypical antipsychotics, the best results were recorded in group A (Olanzapine). The groups B (Risperidone) and C (Clozapine) record similar scores, significantly better for group C (Clozapine). In patients treated with Haloperidol these unwanted effects are installed after the first year of treatment and are maintained at the same level throughout the study.

6. The adherence and tolerance to treatment records values similar to atypical antipsychotics and conventional neuroleptics. The data from these assessments have not confirmed our expectations and differ from the data given in the specialty literature at the time of the study.

7. The mental decompensations during the treatment have required a large number of hospitalizations for the patients treated with Haloperidol and a net lower number for the patients treated with atypical antipsychotic drugs, that among the patients treated with Olanzapine are recorded fewer relapses requiring hospitalization.

8. The increase of the body mass index is recorded in all patients included in the study. The data from the study are not fully consistent with those cited by the specialized literature. If most studies show a
marked increase of IMC on Olanzapine particularly, our study reveals a more pronounced increase in IMC and with net upward trend in patients treated with Clozapine and Haloperidol.

9. Life quality assessment using the WHO-QOL BREF scale demonstrates efficacy of the atypical neuroleptics treatment compared to haloperidol:
   a. On the areas Q1 and Q2 are highlighted net changes (positively) to the final evaluation from the initial one for the patients treated with atypical antipsychotics.
   b. For D1 (physical health) are found increases in all groups, higher in group A (Olanzapine).
   c. For D2 (mental health) are found higher scores at the end, for the groups B (Risperidone), C (Clozapine) and D (Haloperidol) compared with relatively constant scores obtained in the group A (Olanzapine). Although these scores (initial and final) seem unfair, we think that this non-change shows a better evolution of group A patients (Olanzapine), expressing in fact the patient awareness of the disease or the psychic problems, issue found only in the group A (Olanzapine).
   d. For D3 (social relations) the assessments show a significant increase in the life quality of the patients in the group A (Olanzapine), moderate on the patients in the group B (Risperidone) and in the group C (Clozapine) and insignificant on the patients in the group D (Haloperidol).
   e. For D4 (environmental relationships) the scores obtained in the study show a significant improvement in the patients of the group A (Olanzapine), medium in the patients of the group B (Risperidone) and of the group C (Clozapine) and insignificant in the patients of the group D (Haloperidol).

10. All the initially selected patients participated in all stages of the study throughout its duration (5 years) and were not registered cases of intolerance or major adverse reactions to medication administration, both on classic antipsychotics and on atypical antipsychotics.

   By the combination of the objective data (GAF, PANSS, CGI, number admissions - with the subjective data (WHOQOL) I could make an assessment closer to the truth on the treatment efficiency with the atypical antipsychotics versus the conventional neuroleptics in the long-term treatment of patients with schizophrenia in study.

11. The treatment with atypical antipsychotic drugs should be included in the equation:

   Psychiatrist ➔ Patient ➔ Family.

   The psychiatrist is the main actor in a multidisciplinary therapeutic team.

12. The asylum type assistance decline of the patients with mental disorders brings into actuality the Mental Health Laboratories model, requiring their modernization and transformation in Mental Health Centers. The civil society offer, through the ONGs with activity profile in mental health completes the levers that can obtain and maintain specialized treatment effects.
13. The access to the treatment with atypical antipsychotics is hampered by the apparent high costs of the drugs. The evaluation of a long-term management reveals much lower costs by establishing in early stages of this type of treatment, by decreasing the number of hospitalizations and socio-professional integration.

14. The legislation on mental patient care must be completed in order to effectively ensure "the best treatments" for this category of patients, according to Law 487/2002 on the protection of the mental patient. The patient and family trust in the doctor and his informing whenever changes occur in the disease evolution.