**UNIVERSITY OF MEDICINE AND PHARMACY
OF CRAIOVA**

THERAPEUTIC AND EVOLUTIVE ASPECTS IN SCHIZOPHRENIA

ABSTRACT

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Key words: schizophrenia, long evolution, cognitive impairment, functioning

GENERAL PART

CHAPTER I
SIGNIFICANCE OF THE ISSUE. DISSERTATION MOTIVATION.

Schizophrenia is a severe psychic disorder that has high direct and indirect, financial and human costs, and affects about 1% of the world population. Being one of the main causes for disabilities worldwide, causing increasing costs and affecting individuals of any culture or origin, schizophrenia has remained one of the priorities of the world psychiatry. Schizophrenia is characterized by the traditionally described symptoms, a significant functional deficit and cognitive impairment.

The majority of researches have focused on the debut of the illness and the etiopathogenic hypotheses in schizophrenia, while the population of old patients has been investigated less.

CHAPTER II
SCHIZOPHRENIA. EPIDEMIOLOGICAL DATA. ETHIOPATOGENESIS.

Comparing to other mental disorders, schizophreina displays a relatively low rate of incidence (annual average of 15.2/100,000 people) but, at the same time, it is one of the main causes for disease burden worldwide, according to the estimates made by the World Health Organization, due to the impact that it has on the community because of the costs generated by severe social functioning disabilities causing a dependancy on the assistance services, the long term evolution with numerous episodes and the debut at an early age.

The meta-analyses have indicated an average annual prevalence of 4.6 out of 1,000 people, and a prevalence for the whole lifespan of 4.0 out of 1,000 people.

The etiopathogenetic models of schizophrenia range from the genetic inheritance to the role of stress or the environment factors, with variants leading to the dynamics of neurotransmitters or the changes of neural circuits.

One of the most valid theories which tries to explain the etiopathogenesis of schizophrenia is the *stress-vulnerability model*, that places schizophrenia at the unfortunate conjunction of a vulnerable biological background and a living context filled with psycho-stress significant to the subject.

CHAPTER III
SCHIZOPHRENIA. DIAGNOSIS. CLINICAL. TREATMENT.

Nowadays, there are two widely accepted major classification systems of mental disorders:

- ICD (*International Statistical Classification of Diseases and Related Health Problems*).
- DSM – (*Diagnostic and Statistical Manual of Mental Disorders*).

The two systems are based on some similar diagnosis criteria but also present some conceptual differences.

The clinical stages of schizophrenia refer to the whole life: the prodromal stage, the clinical debut stage, the stable stage. After the resolution of the psychotic symptoms, affective demodulations occur in the clinical picture, then there is a stage in which the psychotic symptoms are calmed down but can relapse powerfully.

The clinical management of the schizophrenic patient includes medicinal and non-medicinal treatment. The non-medicinal treatment refers to hospitalization (indicated for the duration of acute de-compensations, for dealing with comorbidities or clinical-therapeutic assessment), the psychotherapeutic approach (supportive, cognitive-behavioral, family or group psychotherapy; rehabilitation of cognitive and vocational abilities; reality testing through short therapies; improvement of social abilities), actions of community psychiatry and social re-integration.

CHAPTER IV
SOCIAL-ECONOMICAL COSTS OF SCHIZOPHRENIA

For schizophrenia, the disease burden as indicated by the parameters of the World Health Organization, namely *Disability-Adjusted Life Years* – DALYs, *Years of Life Lost because of premature death* – YLL and *Years Lived with Disability* – YLD, place this disorder worldwide as the eighth major disability cause for the 15-44 age group, and within the first 25 disability causes in 2013, ahead of other pathologies with significant debilitating potential such as paraplegia or cecity because of dependency level and need of daily care. Expressed by the aforementioned indexes, schizophrenia cumulates 1.1% of total DALYs and 2.8% of total YLD.
In economical terms, according to the statistics of World Health Organization, schizophrenia involves costs between 1.6% and 2.6% of the total expenditures generated by medical systems. There are costs of hospitalization, pharmacological treatment, ambulatory treatment, home care or community centers care, direct non-medical costs generated by protected homes, transport, food, social service or concerning suicide and indirect costs concerning informal care, low work productivity caused by absenteeism and presenteeism, professional inactivity, premature mortality, judicial costs, accidents and damage caused.

SPECIAL PART - OWN RESEARCH

CHAPTER V
HYPOTHESIS. OBJECTIVES. MATERIAL AND METHOD

Schizophrenia is a debilitating disorder with chronic evolution, having a severe impact on patient's functioning and his/her family, as well as important costs on a long run. Studying the evolution of schizophrenic subjects for a long period of time, we better learn the importance of therapeutic approaches, adequate therapeutic management and the optimum way of achieving remission and functioning.

RESEARCH OBJECTIVES

1. To determine the pattern and the evolution particularities in patients with long term schizophrenia;
2. To highlight the cognitive, biological, symptomatological and functional status of the patients in the research batch;
3. To assess the comorbidities and their impact;
4. To highlight the risk factors linked to the negative evolution;

5. To suggest improvements of services and medical care addressed to old schizophrenic patients.

REGISTERED INDICATORS

- *Social-demographic indicators:* current age, residence, marital status, educational level, origin background when included in the research;
- *Clinical indicators:* somatic comorbidities, evolution period of the disorder (the time between the disorder debut and the current evaluation), age at the disorder debut, risk behavior (smoking), assessment of negative and positive symptomatology made by the psychiatric therapist by applying *The Positive and Negative Syndrome Scale (PANSS)*, the evaluation of the cognitive impairment made by the therapist using the *Mini Mental State Examination (MMSE)* scale, the global clinical assessment of the psychopathologic severity made by the therapist using the *Clinical Global Impressions Scale – Severity (CGI-S)*, the therapist's evaluation of the tardive dyskinesia by employing the *Abnormal Involuntary Movement Scale (AIMS)*, the assessment of akathisia by the psychiatrist using the *Barnes Akathisia Scale (BAS*, the evaluation of medication induced parkinsonism, made by the psyhiatrist, by using the *Simpson Angus Scale (SAS)*, the assessment of the current global state (made by the psychiatric therapist by applying the *Global Assessment of Functioning Scale – GAFS*);
- *Indicators concerning the past five years treatment:* treatment with typical antipsychotics; treatment with atypical antipsychotic substances; pharmacological treatment associated with medication other than antipsychotic; treatment associated with trihexyphenidyl hydrochloride (Romparkin®)
- *Paraclinical indicators (done for all patients in the same laboratory and same imagistic center),* hematologic lab tests, electrocardiogram (ECG), cat scan (native)

Inclusion criteria: diagnosed schizophrenia (paranoid, affective, undifferentiated forms) according to ICD-10 and/or DSM IV TR criteria; date of first diagnosis of schizophrenia at least 20 years ago; permanent residence in Galati city or Galati county; proper filling of data in patients observation charts from "Elisabeta Doamna" Psychiatric Hospital, Galati; patients' consent and of the family member(s) or the person in charge of the patient's care to participate in the research.

Exclusion criteria: diagnosis of schizoaffective disorder; patients with accidental current schizophrenia diagnosis who had been hospitalized before with other diagnoses more recent than the schizophrenic one; patients with a history of mainly schizoaffective disorder (more than 50% of the number of diagnoses); patients with a history of affective bipolar disorder; patients with a history of epilepsy or organic cerebral disorders caused by a cerebral disease or other general medical condition; incomplete data in the observation charts; refuse of the patients and the family member(s) or the person in charge of the patient's care to participate in the research.

CHAPTER VI
RESULTS

PANSS Scores

	PANSS
Minimum	83
Quartile 1	101
Median	106
Quartile 3	109
Maximum	131
Average	105.35
standard deviation (n-1)	8.79

AIMS scores

	AIMS
Minimum	1
Quartile 1	2
Median	3
Quartile 3	4
Maximum	6
Average	2.98
standard deviation (n-1)	1.24

BAS scores

Statistic	BAS
Minimum	0
Quartile 1	0
Median	1
Quartile 3	1
Maximum	2
Average	0.70
standard deviation (n-1)	0.76

SAS scores

Statistic	SAS
Minimum	1
Quartile 1	3
Median	4
Quartile 3	5
Maximum	7
Average	3.83
standard deviation (n-1)	1.62

Distribution according to the GAF score

Statistic	GAF
Minimum	16
Quartile 1	24
Median	29
Quartile 3	37
Maximum	59
Average	30.87
standard deviation (n-1)	10.24

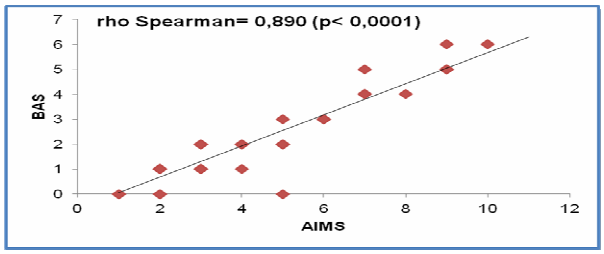
CHAPTER VII
DISCUSSIONS

Since most of the scores for the clinical scales used are more ordinal variables than numerical variables, we further used the Spearman correlation coefficient to analyze the existent relations between these clinical scales. Calculating the matrix of correlation coefficients, we identified multiple correlations between the scores, as displayed and described in detail below:

There is a very strong and direct correlation between the BAS and AIMS scores, statistically proved by rho=0.890 (direct correlation) and by $p<0.001$ (high, statistically significant). These results are the ones expected, since both scales measure extra-pyramidal phenomena secondary to long term antipsychotic medication.

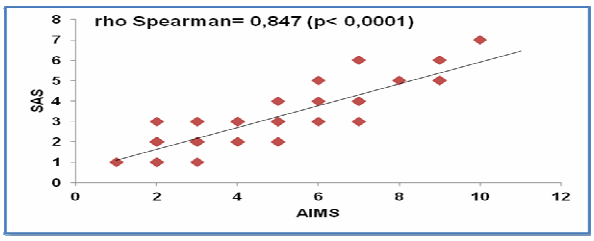
Rho Spearman correlation coefficients (value p)

	PANSS	AIMS	BAS	SAS	GAF	MMSE	CGI-S
PANSS		0.014 (0.926)	0.003 (0.987)	0.080 (0.594)	0.009 (0.955)	0.026 (0.863)	0.016 (0.917)
AIMS	0.014 (0.926)		**0.890 (< 0.0001)**	**0.848 (< 0.0001)**	**-0.614 (< 0.0001)**	**-0.313 (0.034)**	**0.370 (0.012)**
BAS	0.003 (0.987)	**0.890 (< 0.0001)**		**0.824 (< 0.0001)**	**-0.636 (< 0.0001)**	-0.161 (0.285)	**0.423 (0.004)**
SAS	0.080 (0.594)	**0.848 (< 0.0001)**	**0.824 (< 0.0001)**		**-0.560 (< 0.0001)**	**-0.321 (0.030)**	**0.460 (0.001)**
GAF	0.009 (0.955)	**-0.614 (< 0.0001)**	**-0.636 (< 0.0001)**	**-0.560 (< 0.0001)**		0.144 (0.337)	-0.249 (0.095)
MMSE	0.026 (0.863)	**-0.313 (0.034)**	-0.161 (0.285)	**-0.321 (0.030)**	0.144 (0.337)		**-0.342 (0.021)**
CGI-S	0.016 (0.917)	**0.370 (0.012)**	**0.423 (0.004)**	**0.460 (0.001)**	-0.249 (0.095)	**-0.342 (0.021)**	



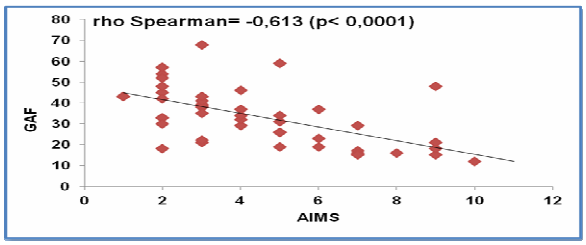
Correlations between BAS and AIMS scores

Similar to the previous comparison, there is also a very strong and direct correlation between the SAS and AIMS scores, proved statistically by rho=0.847 and by p<0.001 (statistically significant).



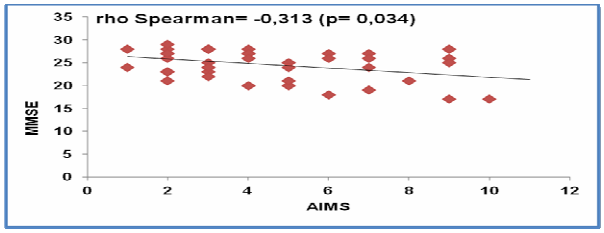
Correlations between SAS and AIMS scores

Between AIMS and GAF scores there is a statistically high significant correlation (p<0.001), but the relation is inversely proportional (rho=-0.613), that is high AIMS values are associated with low GAF values and low AIMS values are associated to high GAF values.



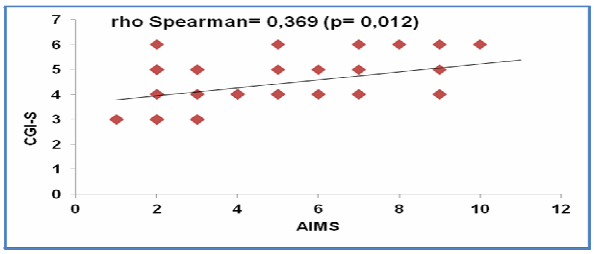
Correlations between AIMS and GAF scores

Although the relation between the AIMS and MMSE scores is weaker, among the values on these two scales, there is a statistically significant association (p=0.034<0.05) and displays an inverse correlation (rho=-0.313) which means high AIMS scores correlated with low MMSE scores and vice versa. We notice again a particular pattern in which patients with low MMSE score (meaning serious cognitive deterioration) associate high AIMS scores, meaning stressed extrapyramidal phenomena, according to literature data.



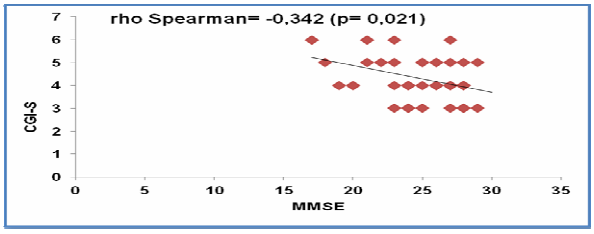
Correlations between MMSE and AIMS scores

The relation existent between the AIMS score and the CGI-S score is weaker than other correlations presented in the current study, but it is stronger than the relation between AIMS and MMSE. The AIMS CGI-S correlation still remains statistically significant (p=0.012<0.05) and is directly proportional (rho=0.369). The clinical and evolutional explanation of this directly proportional correlation resides in the fact that higher AIMS scores (that means belonging to the same sub-group with negative evolution) correspond to higher CGI-S scores, meaning moderate-severe stage of disorder.



Correlations between AIMS and CGI-S scores

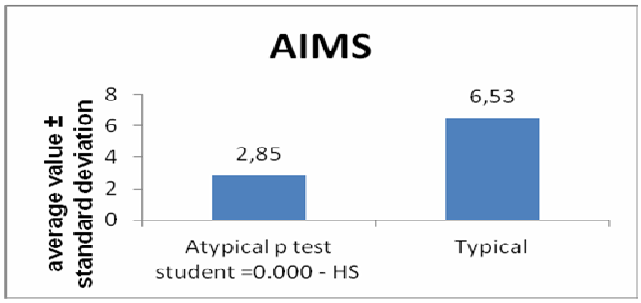
There is an inverse correlation between the MMSE and CGI-S scores (rho=-0.342), significant from a statistical point of view (p=0.021<0.05). This highlights the fact that the patients with cognitive impairment (low MMSE score) were in a moderate-severe stage of evolution of the disorder, which correlates with data from literature that identify the cognitive impairment as the main factor to differentiate patients' functionality.



Correlations between MMSE and CGI-S scores

Correlations between the type of antipsychotic treatment and the AIMS scores

AIMS	Atypical	Typical
No	54	38
Average	2.85	6.53
Standard deviation	1.17	2.17
p test Student	0.000	- HS



Correlations between the kind of antipsychotic treatment and the AIMS scores

Comparing the average values of the BAS scores of the patients treated with atypical antipsychotics with those of the patients treated with typical antipsychotics, we observed the existence of a statistically high significant difference (p Student<0.001), the ones treated with atypical antipsychotics having much lower BAS scores.

Correlations between the kind of antipsychotic treatment and the BAS scores

BAS	Atypical	Typical
No	54	38
Average	1.11	3.63
Standard deviation	0.70	1.46
p test Student	0.000	- HS

Correlations between the kind of antipsychotic treatment and the SAS scores

SAS	Atypical	Typical
No	54	38
Average	2.07	4.05
Standard deviation	0.78	1.47
p test Student	0.000	- HS

Correlations between the kind of antipsychotic treatment and the MMSE scores

MMSE	Atypical	Typical
No	54	38
Average	25.48	23.42
Standard deviation	2.67	3.66
p test Student	0.004	- S

Correlations between the kind of antipsychotic treatment and the GAF scores

GAF	Atypical	Typical
No	54	38
Average	39.41	26.11
Standard deviation	12.03	12.57
p test Student	0.000	- HS

CHAPTER VIII
CONCLUSIONS

1. In the research batch N=92, between January 1st and December 31st 2015, in *Elisabeta Doamna* Psychiatric Hospital from Galati, the gender ratio was favorable to women (82.61% vs. 17.39%), 43.48% of patients coming from urban areas, while 56.52% were coming from rural area, having an average age of 64.74±7.56, mainly high-school graduates (41.30%), whereas 29.35% finished 8 years of school and 20.65% finished only primary school, the majority not having a life partner (63.04%).
2. The debut of the mental illness occurred after the age of 30 (89.13%), with an evolution lasting for more than 30 years (73.91%), in family environment 56.52%, institutionalized 43.48%.
3. The antipsychotic treatment involved atypical substances in 58.70% of the cases, in addition to antidepressants (43.48%), benzodiazepine (78.26%), disposition stabilizers (32.61%), anti-parkinson agents (43.48%), while somatic comorbidities were present in 28.26% of the patients. The ECG diagram showed a normal aspect for 65.22% and the anemia occurred in 65.22%.
4. The active symptoms (positive and negative) were identified in all patients (PANSS scores >80), tardive dyskinesia of medium intensity (AIMS>2) for 89.13%, akathisia (BAS>2) for 52.17%, and global extrapyramidal phenomenology (SAS) in all patients.
5. Patients with long term evolution schizophrenia need keeping the active social-familial support (GAF 30.87±10.24) in the context of cognitive impairment present (MMSE 25.37±2.58) and a global clinical impression which suggests seriousness of the condition (CGI 4.22±0.84).
6. The types of extrapyramidal phenomena encountered in batch patients (akathisia, dyskinesia, extrapyramidal signs) and evaluated using the clinical scales (BAS, AIMS, SAS) correlated highly significantly from the statistical point of view ($p<0.001$), the same level of statistical significance being observed for the negative influence that the presence of extrapyramidal phenomena had had on the global functioning of the patients (AIMS vs. GAFS, $p<0.001$; BAS vs. GAFS, $p<0.001$), on the severity of the cognitive impairment (AIMS vs. MMSE, $p<0.05$; SAS vs. MMSE, $p<0.001$) and on the global clinical impression (AIMS vs. CGI-S, $p<0.05$; BAS vs. CGI-S, $p<0.001$; SAS vs. CGI-S, $p<0.001$).
7. The treatment with atypical antipsychotics is associated to a lower frequency of the presence and severity of the whole range of extrapyramidal phenomena assessed by the working instruments comparing to the therapy with antipsychotic substances of first generation ($p<0.001$), the psychotropic treatment with substances of the second

generation having, similarly, a positive influence on the cognitive impairment ($p<0.01$), on patients' global functioning ($p<0.001$) and on global clinical impression ($p<0.001$), comparing to neuroleptics.

8. As far as the gender distribution is concerned, it was noticed that tardive dyskinesia, akathisia and secondary drug-induced parkinsonism are less frequent in women ($p<0.001$), while the level of global functioning ($p<0.05$) and the clinical impression ($p<0.01$) is also favorable for women.
9. From the patients' social background point of view (institutionalized versus the ones in communities), the extrapyramidal phenomena were more frequent and more severe in institutionalized patients ($p<0.05$) who also displayed low social functioning ($p<0.001$).
10. The current research restates the validity of some literature data regarding similar batches, but, at the same time, highlights certain particularities. As far as the evolution of long term schizophrenia patients is concerned, the particularity of the batch resides in the overwhelming number of women, while the men are far fewer and have a more unfavorable clinical picture as well as more important adverse effects in relation to antipsychotic medication. Moreover, the correlation between the occurrence of extrapyramidal phenomena, the poor functioning, the cognitive impairment and the severity of schizophrenia suggests that actually, the patients with negative evolution coagulated all the negative evolution factors.

Beyond the traditional belief regarding the negative importance of institutionalization and the cognitive impairment as an indicator of functionality, we noticed that patients with unfavorable evolution were considered as such in the old history. In other words, although the patients follow an evolutional continuum, some of them started in the debut period with a drawback (behavioral or cognitive) which later reflected into the psychosocial area (loss of social-familial support, institutionalization) or prolonged incisive treatment triggering a whole range of secondary effects.