

Second generation antipsychotics in the long-term treatment of schizophrenia

PhD thesis

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I. INTRODUCTION

Schizophrenia is a heterogeneous disease group with typically at early age onset and with significant effect on quality of life. The correct treatment of schizophrenia means adequate doses of acute and long-term maintenance therapy, started at the right time.

The cause of death in schizophrenic patients is suicide in about 10%. Clozapine is regarded as the prototype of second-generation antipsychotic agents. The clinical experiences, several studies and in particular the InterSept trial suggest that clozapine should be declared the first-line treatment of schizophrenia and schizoaffective disorders, especially for patients who are vulnerable in point of suicide. The unique pharmacological and clinical properties of clozapine have been investigated and reported upon by many authors. The most devastating complications of clozapine therapy are granulocytopenia and agranulocytosis, these abnormalities are reversible and curable with appropriate therapy. The long-term clozapine therapy plays a significant role in the rehabilitation of schizophrenic patients.

A growing number of literature data suggest that regular cannabis use may cause psychotic symptoms or even schizophrenia spectrum disorder. Experimental data suggest that exogenous cannabinoids can affect the endogenous cannabinoid system leading to a facilitation of dopamine release in the mesolimbic system and a deregulation of dopaminergic activity which is crucial in the pathomechanism of schizophrenia. There is an intensive discussion in the literature whether cannabis induced psychosis might be a distinct entity with special features or cannabis use can precipitate schizophrenia in those patients with genetic vulnerability. The issue is important to clarify the characteristics of cannabis induced psychosis in comparison with classic schizophrenia disease.

II. OBJECTIVES

Aim of study No.1.

The aim of the study was to describe experiences with clozapine administered maintenance therapy in one center during more than a 20-year period and to discuss the risk/benefit ratio of this treatment.

The following points were examined:

1. Comparison of the time of long-term maintenance treatment between clozapin and haloperidol therapeutic groups
2. Comparison of the therapeutic effect between the two therapeutic groups
3. Hematopoetic side effects of clozapine treatment mainly granulocytopenia and agranulocytosis
4. The effect of clozapin for lowering the suicidal behaviour

Aim of study No.2.

The aim of the study was to compare retrospectively the clinical characteristics between schizophrenic disorder with and without chronic cannabis use in a first-hospitalized population. An important point was the analysis of pharmacotherapy since relatively few data was found in the literature in this field.

I was looking for answers for the following questions:

1. What are the differences between the two subgroups in term of socio-demographic and anamnestic data?
2. The differences between the two subgroups in suicidal behaviour
3. The differences in psychotic symptoms between the two subgroups and characteristic conditions of patients
4. The characteristics of acute treatment and maintenance therapy in the two subgroups
5. An important question is to determine whether there are differences in therapeutic response to antipsychotics
6. Are second-generation antipsychotics correct therapies in special cases of schizophrenia?
7. Based upon these findings can we differentiate schizophrenic patients with and without cannabis use?

III. METHODS

Methods in study No.1.

Patients

During a 22-year period I analyzed retrospectively data of 1075 patients treated with clozapine. Among these patients 782 were diagnosed with schizophrenia and schizoaffective psychosis (according to the DSM-IV criteria).

Patients with long-term maintenance therapy for more than one year

181 schizophrenics had received clozapine and in the control group 152 schizophrenic patients had received haloperidol as monotherapy for more than 1 year.

I examined the daily dose and serum level of the antipsychotics used for more than one year from the start of the maintenance therapy, and comparison was made between the side effects in the two therapeutic groups. Side effects of both antipsychotics were also appraised.

Examination of the effectiveness of maintenance therapy according to the time of treatment discontinuation

I used treatment discontinuation to measure effectiveness, and to calculate this time in months. Starting-point of examination was one year after the start of long-term maintenance treatment. Discontinuation of periodic medical control means discontinuation of treatment.

Therapeutic effect of the maintenance treatment by CGIS score

The therapeutic effect of clozapine and haloperidol was quantified by using the Clinical Global Impression Scale (CGIS). The CGIS score was taken one year after the start of maintenance therapy.

Criteria for granulocytopenia and agranulocytosis caused by clozapine treatment

I examined the prevalence of granulocytopenia and of agranulocytosis during clozapine therapy. These abnormalities are subsets of leucopenia, defined as the reduction of peripheral WBC (white blood cell) count to $<4000/\mu\text{L}$. A granulocyte cell count below $1500/\mu\text{l}$ is identified as granulocytopenia, whereas the diagnosis of

agranulocytosis is established by a cell count lower than 500/ μ l. Neutropenia can result from the impaired production or increased margination of cells with redistribution in the systemic circulation.

Examination of suicidal behavior

Some evidence suggests that clozapine was found to dramatically reduce suicide rate in schizophrenia. Therefore some authors recommend that clozapine should be declared the first-line treatment of schizophrenia for patients who are vulnerable in point of suicide. For this reason it was also important to investigate suicidal behaviour during clozapine maintenance therapy.

Data analyses

In case of continuous variable F-test was accepted as significant if $p=0.05$. The statistical tests were performed by Microsoft Office Excel 2003 software.

Methods in study No.2.

Patients

Clinical data were processed retrospectively of 85 patients hospitalized with a schizophrenia spectrum disorder (ICD-10: F20.x, F23.x) for the first time during a 3-year period. Exclusion criteria were elder age than 35 years and earlier hospitalization at a psychiatric department before. Two subgroups were compared on the basis of diagnosis and anamnesis. Patients with psychotic episode without using any drug in the psychiatric history was categorized as Cnbs₀ (n=43), while Cnbs₁ subgroup was created by those psychotic subjects with anamnesis of daily consumption of cannabis for at least for a year (n=42). These patients reported app. 0.5- 1g cannabis use per day. Current cannabis use was verified by a urine test at admission to the department. Diagnosis was determined by psychiatrists based on clinical interview according to the DSM-IV criteria. Clinical data were collected from electronic medical documentation of patients about anamnesis, family history, social-demographic condition, symptoms and psychiatric state, acute and long-term therapy.

Psychotic symptoms

The literature shows conflicting results about cannabis-induced psychotic symptoms so we need further investigations to clarify differences in symptoms of the

two subgroups. Some studies have shown no difference and others have reported that cannabis users have fewer positive and negative symptoms but higher presence of visual hallucinations and incoherency. 8 symptoms were compared of the two subgroups: hallucination, incoherency, paranoid delusion, bizarre behaviour, derealization, aggression, psychomotorium, and negativism.

The state of patient at admission and emission was recorded with the Clinical Global Impression Scale (CGI-S) and the Clinical Global Improvement Scale (CGI-I), respectively.

Comparison of acute and maintenance therapy

I analyzed both acute and maintenance pharmacotherapy for each patient. I investigated the role of long-acting antipsychotics and their effect on compliance. I compared the oral and shorter parenteral doses of antipsychotics measured in daily doses, in case of long-acting treatment I calculated with 6 month's doses. For correct comparability I converted the different antipsychotic doses to the chlorpromazine equivalency table.

Data analyses

Comparison of categorical variables was computed with chi square test and odds ratios were estimated with binary logistic regression. In case of continuous variable t-test and ANOVA tests were performed adjusted by age and gender. Results were accepted as significant if p-value was less than 0.05 and as a trend between 0.05 and 0.08. All statistical tests were performed by SPSS 13.0 for Windows software.

IV. RESULTS

Results of the study No.1.

Patients with maintenance therapy for more than one year

Oral clozapine was administered once daily (at bedtime) in doses 50 to 200 mg, the serum clozapine-level was 24 to 78,5ng/ml. In the control group schizophrenic patients were treated exclusively with haloperidol. All patients in this subgroup took haloperidol once or twice a day in a mean daily doses 1.5 to 4.5 mg, the serum haloperidol-level was 2,1 to 3,2ng/ml..

During the maintenance clozapine therapy we used fixed dose. It was about half of the dose during the acute phase.

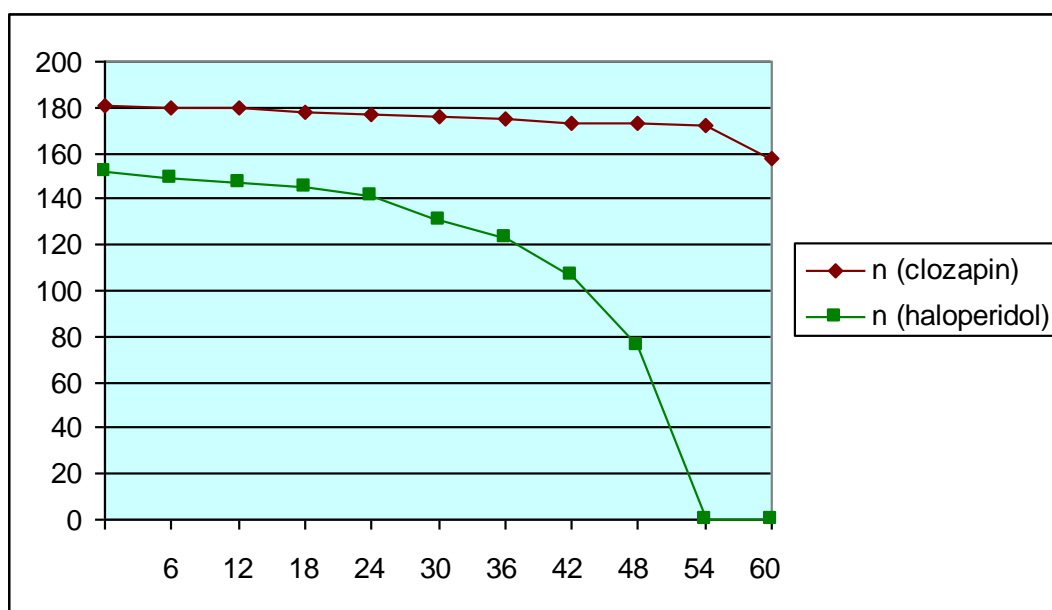
Effectiveness of maintenance therapy according to the time of treatment discontinuation

The time of the discontinuation of treatment was significantly longer in clozapine group than in haloperidol group (Table 1.). The minimum time was 3 months in clozapine group and 1 month in haloperidol group. The maximum time was 204 months in clozapine group and 54 months in haloperidol group. 87 % of patients were on clozapin treatment 5 years after the start of therapy (Figure 1.).

Table 1.: Data of time to treatment discontinuation in the two therapeutical groups

clozapin (n=181)		
mean:	x:	144,3757
	s:	42,92891
haloperidol (n=152)		
mean	x:	38,48684
	s:	10,67459
F=	16,17326	(p=0,05)

Figure 1.: Number of patients on maintenance therapy in months



Therapeutic efficacy of maintenance treatment by CGIS score

The mean value of CGIS was lower in clozapine group one year after the start of the maintenance therapy.

Both therapeutical groups were divided in 3 clinical subgroups according the CGIS score: symptom-free patients, patients with some symptoms, patients with markedly high psychiatric symptoms.

Table 2. shows the therapeutic efficacy of long-term clozapine treatment for more than one year.

Table 2.: Therapeutic effect of maintenance therapy with clozapine in schizophrenic patients (N=181)

	CGIS					
	symptom free		some symptoms		markedly symp.	
	N	%	N	%	N	%
Paranoid schizophrenia (N=112)	92	82.1	11	10.0	9	7.9
Catatonic schizophrenia (N=2)	2	100.0	0	-	0	-
Disorganized schizophrenia (N=16)	9	56.3	6	37.5	1	6.2
Residual schizophrenia (N=15)	9	60.0	5	33.3	1	6.7
Schizoaffective psychosis (N=36)	21	58.3	11	30.6	4	1.1

symptom free: 0-2; some symptoms: 3-4; markedly high symptoms: 5-7 (acc. CGIS)

The best results were accomplished in the subgroups of patients with paranoid or catatonic schizophrenia. In the former subgroup 82.1% of patients were symptom-free. In the latter three groups 6.2, 6.7 and 11.1% – that is rather small proportions – of patients relapsed. Mean serum clozapine level was 32.5 ± 10.87 ng/ml (range 24 to 78.5 ng/ml). It was lower than we realize in the literature but sufficient. Oral clozapine was administered 50-200 mg/day.

Table 3. shows the therapeutic efficacy of long-term haloperidol treatment for more than one year.

Table 3.: Therapeutic effect of maintenance haloperidol administration in schizophrenic patients (N=152)

	CGIS					
	symptom free		some symptoms		markedly symp.	
	N	%	N	%	N	%
Paranoid schizophrenia (N=109)	55	50.5	47	43.2	7	6.3
Catatonic schizophrenia (N=2)	1	50.0	1	50.0	0	-
Disorganized schizophrenia (N=12)	4	33.3	6	50.0	2	16.7
Residual schizophrenia (N=16)	5	31.2	9	56.3	2	12.5
Schizoaffective psychosis (N=13)	2	15.4	8	61.5	3	23.2

symptom free: 0-2; some symptoms: 3-4; markedly high symptoms: 5-7 (acc. CGIS)

Safety profile

The safety profile was much more favourable in the clozapine group, than in haloperidol-treated patients. The incidence of drowsiness, somnolence, delirium and postural hypotension was similar in the two groups. Only 1.1% of clozapine-treated patients complained about dry mouth compared to 26.9% in the haloperidol group. The incidence of extrapyramidal symptoms was also substantially different: 71.1 and 9.2% in haloperidol-treated patients and none in the clozapine group. Weight-gain and salivation was higher in clozapine group. Also these patients had no agranulocytosis and granulocytopenia during clozapine (and also haloperidol) administration.

Hematopoietic side-effects

Agranulocytosis developed in only two patients of 782 patients treated with clozapin, in the week 6. and 9. of treatment. With proper supportive therapy and administration of colony-stimulating factors this complications were reversible and non fatal.

Granulocytopenia developed in 7 patients. After discontinuation of clozapine treatment the patients fully recovered there was no need for administration of colony-stimulating factors.

In case of agranulocytosis hospitalization in hematological department is needed.

Suicidal behaviour

The incidence of suicidal attempt was 2.9% in case of clozapine treated schizophrenic patients. 23 patients of 782 clozapine treated patients attempted suicide during treatment. None of suicide attempts resulted in death. In general the incidence of suicide in schizophrenia is 20-40%. In this study clozapine reduced the suicidal behaviour with 90%. This significant reduction of suicidal behaviour is a very important factor mainly with patients of long term therapy.

The reduction of suicidal behaviour rate is of higher importance compared to rare incidence of hematopoetic side effects.

Results of the study No.2.

Analysis of anamnesis and socio-demographic characteristics

Age and gender was significantly different between Cnbs₀ and Cnbs₁ subgroups. Mean age of subjects with cannabis dependency was significantly lower ($p=0.0001$) (Figure 2.) and more men were presented among them compared to Cnbs₀ subgroup (OR=2.28, $p=0.007$) (Figure 4/a, 4/b).

Number of suicidal attempt was more than five fold higher in men without cannabis use (OR=5.25, $p=0.016$) (Figure 3).

Cannabis abuser were more qualified ($p=0.001$) and had better social status ($p=0.002$). The chance to smoke at least 10 cigarettes per day was higher among Cnbs₀ patients (OR=1.36, $p=0.047$).

Figure 2.: Mean age in two subgroups ($p=0,0001$)

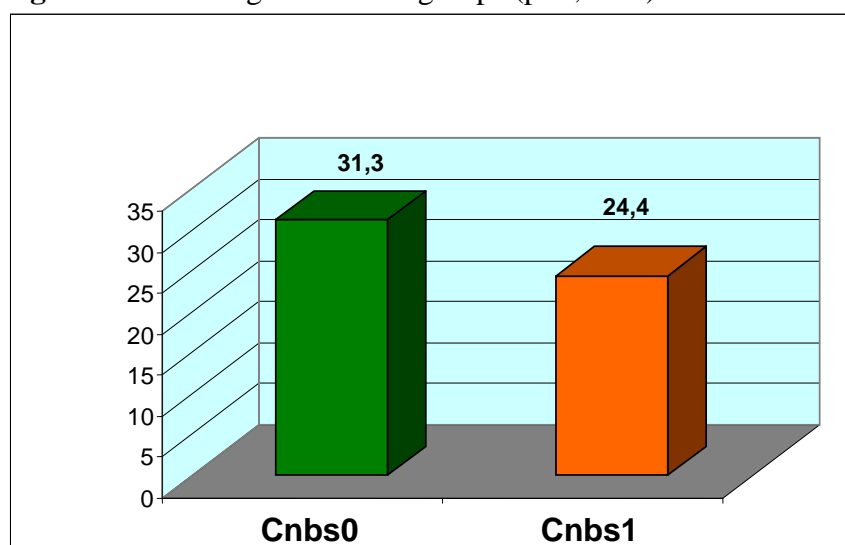


Figure 3.: Number of suicidal attempts in anamnesis of men (OR=5.25, p=0.016)

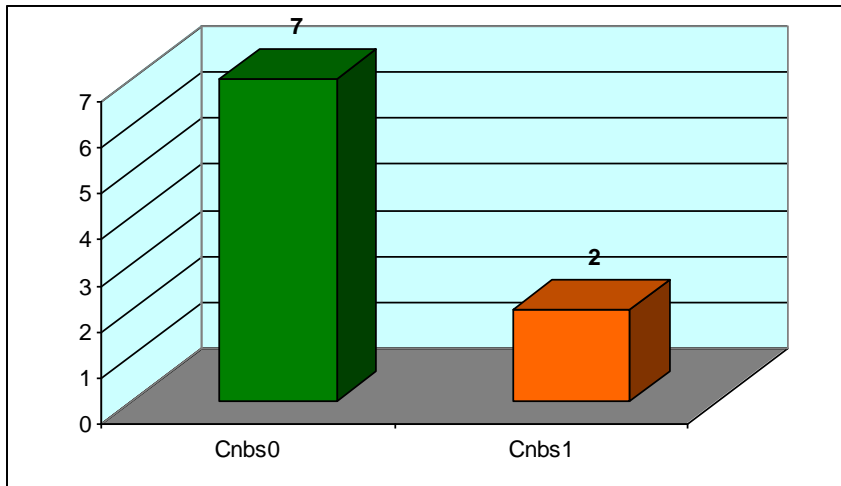


Figure 4/a.: Gender in Cnbs0 subgroup (n=43)

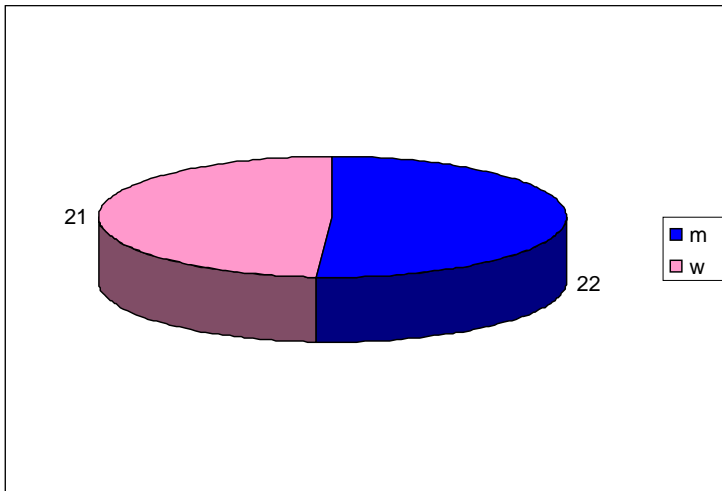
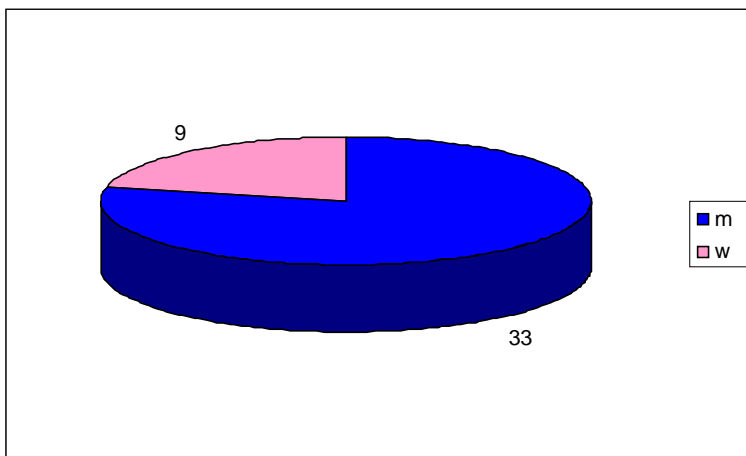


Figure 4/b.: Gender in Cnbs1 subgroup (n=42)



Comparison of symptoms in acute phase

Prevalence of psychotic symptoms did not differ significantly between the two subgroups. The most common symptom was incoherency in Cnbs₀ and hallucination in Cnbs₁ subgroup. Surprisingly similar prevalence of aggression was observed in the two subgroups. Mean scores of CGI-I and CGI-S were also similar in the two subpopulations.

Comparison of pharmacotherapies

I made comparison of acute and long term therapy between the two subgroups. In the sample aripiprazol and ziprasidon were not used for acute therapy of cannabis dependent patients at all. The chance to get olanzapine for acute therapy and aripiprazol for long term therapy was more than two fold higher in Cnbs₁ subgroup (OR=2.66, $p=0.048$; OR=3.67, $p=0.052$, respectively). Typical and atypical antipsychotics were applied at the same ratio in both populations ($p=0.78$).

Mean doses of admitted antipsychotics were higher in acute therapy of Cnbs₀ patients except in case of olanzapine and cisordinol. Higher dose was used of quetiapine at patients without cannabis dependency compared to Cnbs₁ subgroup with a strong trend ($p=0.053$). Although difference of mean dose of clonazepam was not significant between the two subgroups in the whole population men get higher dose with a strong trend in Cnbs₁ subgroup ($p=0.053$) compared to the men of Cnbs₀ subpopulation (Table 4., Figure 5.).

In case of long term therapy patients with cannabis dependency get higher dose of clozapine and alprazolam. Olanzapine was admitted to patients without cannabis use at a significantly higher dose compared to Cnbs₁ subgroup ($p=0.040$), although mean dose of alprazolam was higher in the latter subgroup with a trend ($p=0.076$) (Table 4., Figure 6.).

Table 4.: Acute and long term therapy of patients with (Cnbs₁) and without cannabis use (Cnbs₀)

	Cnbs ₀	Cnbs ₁	<i>p</i> -value
Acute treatment			
(mg/day)			
haloperidol	16.63±11.18 (n=8)	14.27±7.82 (n=13)	ns
risperidon	5.50±4.03 (n=10)	4.22±1.85 (n=9)	ns
olanzapine	24.38±15.45 (n=8)	26.50±33.23 (n=2)	ns
quetiapine	600.0±316.22 (n=8)	153.33±214.55 (n=3)	0.053
aripiprazol	30.0±0.00 (n=5)	-	-
clozapin	300.0±100 (n=3)	300±0.0 (n=1)	ns
ziprasidon	160.0±0 (n=2)	-	-
alprazolam	2.34±1.28 (n=7)	1.81±0.89 (n=4)	ns
clonazepam	3.33±1.83 (n=18)	4.25±2.01 (n=16)	ns
<i>in men</i>	2.94±1.89 (n=8)	4.69±1.88 (n=13)	0.053
diazepam	40.0±0.0 (n=2)	33.33±5.77 (n=3)	ns
Long term therapy			
(mg/day)			
aripiprazol	30.0±15.35 (n=6)	15.0±0 (n=1)	ns
clozapine	162.50±194.45 (n=2)	175.0±139.19 (n=3)	ns
olanzapine	19.29±1.89 (n=7)	13.61±6.96 (n=10)	0.040
quetiapine	633±239.79 (n=9)	440.0±341.23 (n=5)	ns
risperidon	3.88±1.35 (n=8)	3.38±1.19 (n=13)	ns
alprazolam	1.30±0.51 (n=11)	1.90±0.742 (n=5)	0.076
clonazepam	3.36±1.95 (n=11)	2.80±2.15 (n=10)	ns
Antipsychotic LAI			
(n)	15 (34%)	8 (19%)	ns
risperidon	578.57±56.69 (n=7)	430.00±178.88 (n=5)	0.063
(mg/6 months)			
<i>in women</i>	600±0.0 (n=2)	250±70.71 (n=2)	0.020
zuclopenthixol	1733.33±611.01 (n=3)	2400.0±0.0 (n=2)	ns
(mg/6months)			
flupenthixol	160.0±0.0 (n=1)	180.0±84.85 (n=2)	ns
(mg/6months)			
HPDC	480±164.31 (n=5)	-	-
(mg/6months)			
Hospitalization			
time (day)	35.72±26.96	23.02±19.28	0.026
CGI-S	4.98±0.55	5.22±0.51	ns
CGI-I	2.51±0.79	2.59±0.57	ns

LAI, long acting injection; CGI-S, Clinical Global Impression Scale; CGI-I, the Clinical Global Improvement Scale, HPDC, haloperidol-decanoate.

Figure 5.: Dose of antipsychotics during acute therapy in two subgroups

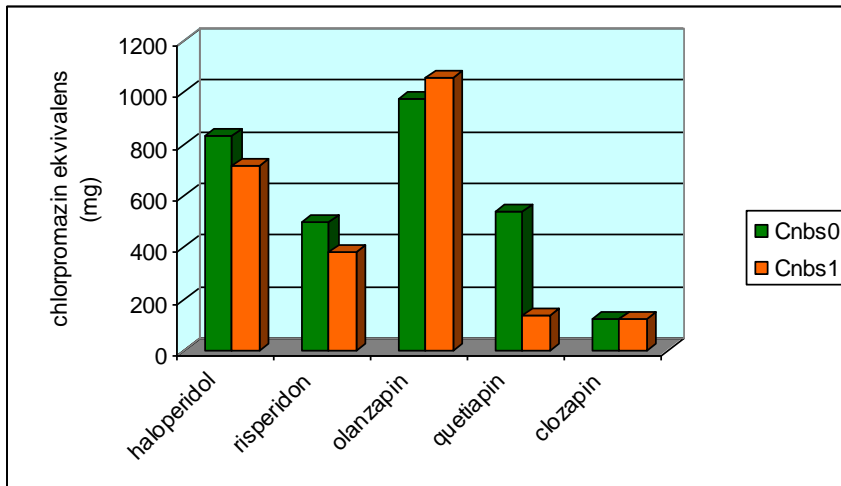


Figure 6.: Dose of antipsychotics during maintenance therapy in two subgroups

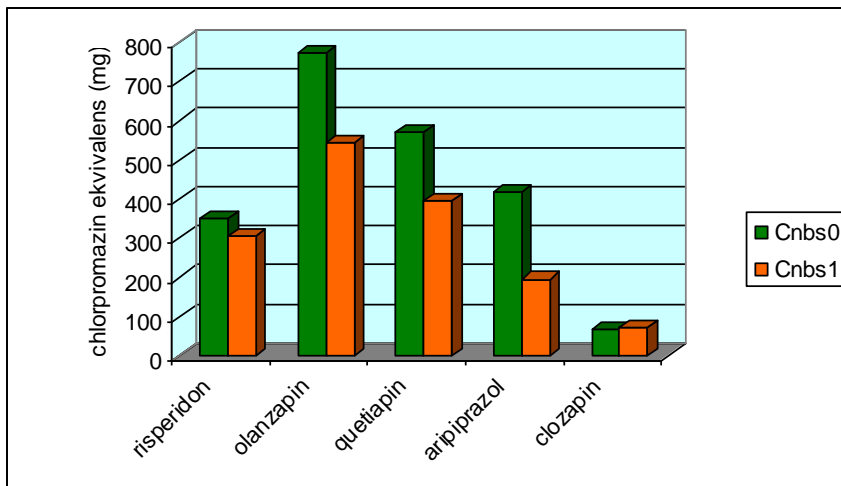
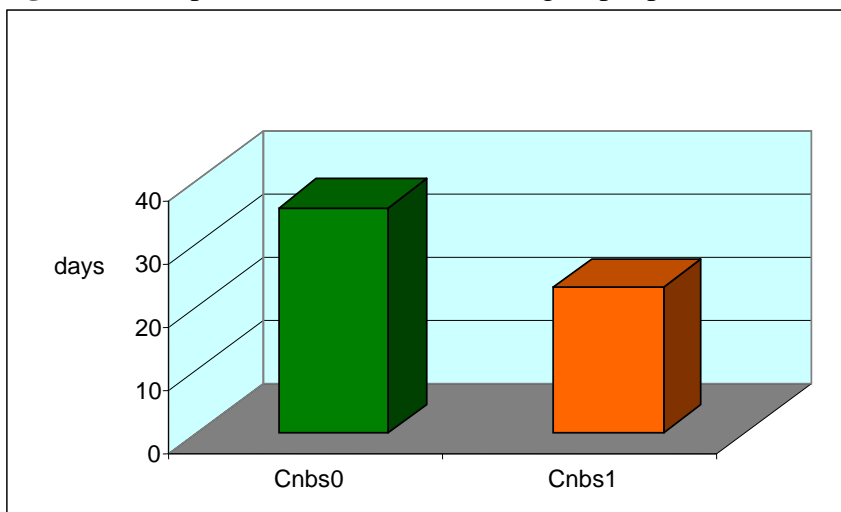


Figure 7.: Hospitalization time in two subgroups (p=0,026)



Antipsychotic LAI was applied with higher chance in Cnbs₁ subpopulation (OR=1.68, $p=0.042$) however haloperidol-decanoate depot injection was not used among them at all. There was no significant difference between usage of typical and atypical depot injections ($p=0.67$). Mean dose of risperidon (computed for 6 months) was almost significantly higher at patients without cannabis dependency ($p=0.063$) and significantly higher at women without cannabis dependency compared to women of Cnbs₁ subgroup ($p=0.020$). Hospitalization time was significantly longer in case of patients without cannabis dependency compared to Cnbs₁ subgroup ($p=0.026$).

V. CONCLUSIONS

Study No.1.

Due to on the recommendations of protocols the use of second-generation antipsychotics is preferred in the treatment of schizophrenia. Clozapin is regarded as the prototype of second-generation antipsychotic agents. The clinical experiences, several studies and in particular the InterSept trial suggest that clozapine should be declared the first-line treatment of schizophrenia and schizoaffective disorders, especially for patients who are vulnerable in point of suicide.

In my first study I concluded that:

1. In maintenance therapy clozapine is more effective than haloperidol. The time of the discontinuation of treatment was significantly longer in clozapine group than in haloperidol group. 87 % of patients were on clozapin treatment 5 years after the start of therapy
2. Long-term therapeutic effect of clozapine is better than haloperidol according to Clinical Global Impression Scale.
3. In case of catatonic and paranoid schizophrenic patients the clozapine maintenance therapy (lasting for more than one year) has proved very effective. Patients with severe symptoms responded better to the treatment.
4. Mean serum clozapine level was 32.5 ± 10.87 ng/ml in group of patients treated with clozapine maintenance therapy. It was lower than we realize in the literature but sufficient. One explanation is that the maintenance dose ranged between 50 and 200mg.

5. The hematopoetic adverse reactions to clozapine are not dose related in the study they occurred in the first two months of the treatment. These complications were always reversible and never fatal. The incidence of life-threatening complications range from 0.5-2% in the literature, in my data this was lower: 0,2%.
6. During clozapine treatment the suicide attempts occurred in 2,9 % of patients. In general the incidence of suicide is 20-40% in schizophrenia, so in the study the clozapine reduced the suicidal behaviour with 90%. This significant reduction in suicidal behaviour is a more important factor than the rare occurrence of agranulocytosis .

The results revealed that therapeutic efficacy of clozapin is satisfactory, relapse rate was low with lowering effect on suicidal behavior and treatment was characterized by a favourably safety profile and a good patient compliance. Agranulocytosis or granulocytopenia is a rare side effect which is reversible and curable with appropriate therapy.

Study No.2.

A growing number of literature data suggests that regular *cannabis use* may cause psychotic symptoms or even schizophrenia spectrum disorder.

The anamnestic, socio-demographic status and acute symptoms of cannabis-induced schizophrenia are of high importance and discussed in the literature. But the pharmacotherapy of acute condition and maintenance antipsychotic treatment is rarely discussed; the aim of my study was to compare the pharmacotherapy of schizophrenia spectrum disorder with and without cannabis.

In my second study I concluded:

- 1 earlier first onset of psychotic episode in cannabis abusers, and the higher rate of men was observed among them
- 2 cannabis related schizophrenic disorder was associated with lower occurrence of suicidal attempt among men compared to men suffering from schizophrenia
- 3 the lack of differences between positive and negative symptoms and aggression in acute psychotic period suggests that cannabis induced psychosis should be considered schizophrenia-spectrum disorder

- 4 I have observed shorter hospitalization time and lower doses of antipsychotics in the cannabis induced schizophrenia group and also that atypical antipsychotics were characterized by an improved response
- 5 the fact that long-acting antipsychotics in general were applied more commonly with cannabis abusers suggests that these patients are characterized by poor compliance.

These results revealed: certain clinical aspects were different of cannabis related schizophrenia spectrum disorder compared to schizophrenia. It is important to differentiate the schizophrenia spectrum disorders from addictive disorders based upon pathomechanism, clinical course and therapeutic consequence.

My results confirmed that second-generation antipsychotics are the correct therapy in special cases of schizophrenia disorder too.

VI. LIST OF PUBLICATIONS

List of publications related to the dissertation

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