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# EXTRAPYRAMIDAL SYNDROME INDUCED BY ANTIPSYCHOTIC MEDICATION. CLINICAL TRIAL

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## **ABSTRACT:**

### **1. INTRODUCTION**

Approximately 50 – 74 % of the patients that receive antipsychotics present extrapyramidal secondary effects (ESP).

The extrapyramidal secondary effects are caused by the excessive blockade r.D2.

They represent an important indicator of reducing the neuroprotection, significantly correlated with chronic deficient evolution.

ESP also represents a major cause of therapeutic compliance reduction.

The atypical antipsychotics associate with a reduced risk of ESP towards the typical ones, due to the effects over other neurotransmitters.

The ESP risk differs according to the atypical antipsychotic administered, the dose and the patient's vulnerability.

### **2. THE PRIMARY OBJECTIVE OF THE STUDY**

The evaluation of the incidence and severity of the adverse extrapyramidal effects in the administration of 8 of the atypical antipsychotics and an atypical antipsychotic (haloperidol).

### **3. STUDY DESIGN**

A clinical, longitudinal prospective, open comparative study was done regarding the differences of security and tolerance between the atypical antipsychotics and the latter *versus* haloperidol.

The study had been carried on for 1 year, on a group of 180 patients diagnosed with schizophrenia, according to the DSM IV-TR criteria.

Groups of 20 patients were administered one of the atypical antipsychotics and a group of 20 patients was administered haloperidol.

The patients were selected according to the eligibility criteria and were psychiatrically, somatically and paraclinical evaluated, initially and subsequently according to the monitoring protocol.

#### 4. RESULTS

The extrapyramidal syndromes that occurred during the treatment were of acute type: parkinsonian disorder, acute dyskinesia, pseudo-akathisia or akathisia.

Their severity was quantified with the help of the specific scales of measuring the extrapyramidal syndrome.

Within each group of 20 patients who received a certain antipsychotic, were calculated:

- the percentage rate of mild ESP, that did not impose the stopping of the study;
- the percentage rate of severe ESP, that impose the stopping of the study.

The statistical processing and interpreting of the study data was realised with a specialized program IBM SPSS Statistics – 19.

The percentage rates of mild and severe ESP occurred after the administration of each atypical antipsychotic was analyzed. These were compared with the percentage rates of ESP determined by haloperidol.

#### 5. CONCLUSIONS

- the atypical antipsychotics determine less ESP than the haloperidol does;
- there are differences of tolerance within the atypical antipsychotics;
- there were no cases of DT or SNM registered.

**Keywords:** parkinsonian disorder, acute dyskinesia, akathisia

#### REZUMAT:

##### 1. INTRODUCERE

Aproximativ 50 – 74 % dintre pacienții care primesc antipsihotice tipice prezintă efecte secundare extrapiramidale (ESP).

Efectele secundare extrapiramidale sunt cauzate de blocada excesivă a r.D<sub>2</sub>.

Acestea reprezintă un indicator important de scădere a neuroprotecției, corelabil semnificativ cu evoluția deficitară cronică.

De asemenea, ESP reprezintă o cauză majoră de scădere a complianței terapeutice.

Antipsihoticele atipice se asociază cu un risc redus de ESP față de cele tipice, din cauza efectelor asupra altor neurotransmițători.

Riscul de ESP diferă în funcție de antipsihoticul atipic administrat, de doză și de vulnerabilitatea pacientului.

##### 2. OBIECTIVUL PRIMAR AL STUDIULUI

Evaluarea incidenței și severității efectelor adverse extrapiramidale la administrarea a 8 antipsihotice atipice și a unui antipsihotic tipic (haloperidolul).

##### 3. DESIGNUL STUDIULUI

A fost efectuat un studiu clinic longitudinal, prospectiv, deschis, comparativ, privind diferențele de siguranță și tolerabilitate dintre antipsihoticele atipice și dintre acestea și haloperidol.

Studiul s-a desfășurat pe o perioadă de un an, pe un lot de 180 pacienți diagnosticați cu schizofrenie, conform criteriilor DSM IV–TR.

Loturi de 20 pacienți au primit unul dintre antipsihoticele atipice, iar un lot de 20 pacienți a primit haloperidol.

Pacienții au fost selectați conform criteriilor de eligibilitate și au fost evaluați psihiatric, somatic și paraclinic, inițial și ulterior, conform protocolului de monitorizare.

##### 4. REZULTATE

Sindroamele extrapiramidale care au apărut pe parcursul tratamentului au fost de tip acut: tulburare parkinsoniană, diskinezie acută, pseudoakatisie sau akatisie.

Severitatea lor a fost cuantificată cu ajutorul scalelor de măsurare specifice sindromului extrapiramidal.

În cadrul fiecărui lot de 20 pacienți care a primit un anumit antipsihotic, s-a calculat:

- rata procentuală a ESP ușoare, care nu au impus stoparea studiului;
- rata procentuală a ESP severe, care au impus stoparea studiului.

Prelucrarea și interpretarea statistică a datelor studiului s-a efectuat cu un program specializat IBM SPSS Statistics – 19.

Au fost analizate ratele procentuale ale ESP ușoare și severe apărute după administrarea fiecărui antipsihotic atipic. Acestea au fost comparate cu ratele procentuale ale ESP determinate de haloperidol.

## 5. CONCLUZII

- antipsihoticele atipice determină mai puține ESP decât haloperidolul;
- în cadrul antipsihoticelor atipice, există diferențe de tolerabilitate;
- nu au existat cazuri de DT sau SNM.

**Cuvinte-cheie:** tulburare parkinsoniană, diskinezie acută, akatisie

## 1. MOTIVATION OF THE STUDY

The conventional antipsychotics are molecules with different chemical structure, which, from a psychopharmacological point of view, have as main action the blocking of the D2 receptors on the subcortical level, with the deafferentation of the mesolimbic way, action amplified by the interactions that these substances exert over the receptors of other neuromediators.

These psychopharmacological effects determine the diminution of the positive symptomatology, the psychomotor agitation and psychotic anxiety, accompanied, however, by the occurrence of some important secondary effects which determine the decrease of therapeutic compliance, especially the extrapyramidal secondary effects.

New antipsychotics, atypical or from the second generation block both the dopamine and the serotonin receptors.

The absorbing degree of the r.5HT is significantly larger in the atypical antipsychotics than the typical antipsychotics.

If a degree of absorption of r. D2 of 78 – 85% predisposes the occurrence of ESP, the blockade r.5HT would make a diminution in the risk of these effects occurrence.

The secondary extrapyramidal effects represent an important indicator of the neuroprotection decrease, significantly correlated with the deficient chronic evolution.

## 2. THE PRIMARY OBJECTIVE OF THE STUDY

The evaluation of the incidence and severity of the adverse effects of the atypical neuroleptics towards the haloperidol.

## 3. STUDY DESIGN

A clinical, longitudinal prospective open comparative study was realised regarding the differences of security, tolerance and efficacy between the atypical neuroleptics and the latter *versus* haloperidol.

8 medicines were used belonging to the neuroleptics of the second generation: risperidone, amisulprid, olanzapine, clozapine, quetiapine, ziprasidone, aripiprazol and sertindol.

The haloperidol was the only conventional neuroleptic administered.

The administered doses varied between 6 – 20 mg / day haloperidol, 200 – 1000 mg / day amisulprid, 4 – 8 mg / day risperidone, 120 – 160 mg / day ziprasidone, 400 – 600 mg / day clozapine, 10 – 20 mg / day olanzapine, 400 – 1000 mg / day quetiapine, 12 – 16 mg / day sertindol, 15 – 30 mg / aripiprazol.

Groups of 20 patients received one of the enumerated antipsychotics.

A group of 20 patients received haloperidol.

The study had been carried on for 1 year, on a group of 180 patients diagnosed with schizophrenia, according to the DSM IV-TR criteria.

The periodic control was varied on every 2 weeks in the first month, once a month in the following 5 months and every 2 months in the next 6 months.

The patients signed the consent deliberately.

The 180 patients registered in the study, diagnosed with schizophrenia according to the DSM IV-TR criteria, were selected from the patients examined at the Emergency Room of the “Voila

Hospital” – Câmpina, Prahova county and / or hospitalized in the Section II and Section III of the hospital, during 2008 – 2010.

Inclusion criteria:

- the patients diagnosed with schizophrenia according to the DSM IV-TR;
- the patients situated in the first 4 years of illness evolution in its debut;
- the patients who did not previously receive the prescribed antipsychotic;
- the patients aged between 18 – 40 years old;
- the patients from schools.

The evaluation of the patients registered in the study:

- longitudinal and transversal psychiatric evaluation;
- somatic evaluation;
- para-clinic investigations.

In order to evaluate the extrapyramidal adverse reactions, the following scales were used:

- The abnormal involuntary movements scales AIMS  
(Abnormal Involuntary Movement Scale)
- The extrapyramidal syndrome rating scale ESRS  
(Extrapyramidal Symptom rating Scale)
- The scale for BAS, BARS Akathisia  
(Barnes Akathisia Scale)
- The scale for the SAS Parkinson symptoms  
(Simpson Angus Scale)

#### **4. THE OPERATION METHOD AND THE STATISTIC ANALYSIS USED**

The analysis and statistic interpretation (graphic representation included) of the study data were realized on with the help of a specialized program IBM SPSS Statistics – 19.

The evaluation of the extrapyramidal adverse effects of the antipsychotics administered to the 9 groups of patients was made as it follows:

A. The percentage rate of the extrapyramidal adverse effects which did not impose the stopping of the study was calculated by reporting the number of patients who presented these effects to the total number of patients, of which the non-compliant ones were excluded.

B. The percentage rate of the extrapyramidal adverse effects that impose the stopping of the study was calculated by reporting the number of patients that presented these effects to the total number of patients, of which the non-compliant ones were excluded.

The non-compliant patients were considered those who have not follow the treatment or abandoned the treatment for other reasons than the adverse effects.

#### **5. RESULTS**

5.1. The group of patients treated with HALOPERIDOL: 20 patients, 5 non-compliant patients.

A. The percentage rate of the extrapyramidal adverse effects which did not impose the stopping of the study: 26.66 %.

3 patients presented mild parkinsonian disorders, occurred at 10 – 14 days after the beginning of the treatment, a dose of 10 mg/day.

1 patient of male gender presented akathisia, 14 days after the beginning of the treatment, to the dose of 10 mg/day.

B. The percentage rate of the extrapyramidal adverse effects which impose the stopping of the study: 33.33 %.

3 patients presented a parkinsonian syndrome occurred after 14 days from the beginning of the treatment to a dose of 12 mg/day.

1 patient presented acute dystonia, 8 days after the beginning of the treatment to a dose of 10 mg/day.

1 patient presented akathisia, 4 weeks after the beginning of the treatment to a dose of 10 mg/day.

5.2. The group of patients treated with AMISULPRID: 20 patients, 3 non-compliant patients.

A. The percentage rate of the extrapyramidal adverse effects which did not impose the stopping of the study: 11.76 %.

2 patients presented parkinsonian disorders, 10 days after the beginning of the treatment to a dose of 800 mg/day.

B. The percentage rate of the extrapyramidal adverse effects that impose the stopping of the study: 11.76 %.

1 patient presented akathisia, about 3 months after the beginning of the treatment to the dose of 800 mg/day, followed by a suicidal attempt by ingesting 30 tb. of amisulprid.

1 patient presented acute dystonia, 7 days after the beginning of the treatment to a dose of 600 mg/day.

5.3. The group of patients treated with RISPERIDONE: 20 patients, 2 non-compliant patients.

A. The percentage rate of the extrapyramidal adverse effects which did not impose the stopping of the study: 16.66 %.

1 patient presented parkinsonian disorders, 10 days after the beginning of the treatment to a dose of 6 mg/day.

2 patients presented mild dyskinesia movements, 7 days after the beginning of the treatment to a dose of 6 mg/day.

B. The percentage rate of the extrapyramidal adverse effects that impose the stopping of the study: 16.66 %.

1 patient presented a parkinsonian syndrome occurred after 4 weeks from the beginning of the treatment to the dose of 8 mg/day.

1 patient presented akathisia, 2 weeks after the administration of risperidone to a dose of 8 mg/day.

5.4. The group of patients treated with ZIPRASIDONE: 20 patients, 4 non-compliant patients.

A. The percentage rate of the extrapyramidal adverse effects which did not impose the stopping of the study: 6.25 %.

1 patient presented parkinsonian syndrome after the increase of the dose to 160 mg/day, 3 weeks after the beginning of the treatment.

B. The percentage rate of the extrapyramidal adverse effects that imposed the stopping of the study: 6.25 %.

1 patient presented severe parkinsonian syndrome 6 weeks after the beginning of the treatment to a dose of 160 mg/day.

5.5. The group of patients treated with CLOZAPINE: 20 patients, 1 non-compliant patient.

There were no patients presenting mild or severe extrapyramidal effects.

5.6. The group of patients treated with OLANZAPINE: 20 patients, 1 non-compliant patient.

A. The percentage rate of the extrapyramidal adverse effects which did not impose the stopping of the study: 26.31 %.

4 patients presented mild extrapyramidal effects of parkinsonian type, after 4 – 5 weeks from the beginning of the treatment to the dose of 20 mg/day.

1 patient presented pseudoakathisia, 14 days after the beginning of the treatment to the dose of 10 mg/day.

B. The percentage rate of the extrapyramidal adverse effects that impose the stopping of the study: 5.26 %.

1 patient presented acute dystonia, 10 days after the beginning of the treatment to a dose of 10 mg/day.

5.7. The group of patients treated with QUETIAPINE: 20 patients, 2 non-compliant patients.

A. The percentage rate of the extrapyramidal adverse effects which did not impose the stopping of the study: 5.55 %.

1 patient presented mild parkinsonian disorder, 4 weeks after the beginning of the treatment to the dose of 800 mg/day.

B. The percentage rate of the extrapyramidal adverse effects that impose the stopping of the study: 5.55 %.

1 patient presented akathisia, accompanied by anxiety, dysphoria, irritability and insomnia. The akathisia occurred 6 weeks after the beginning of the treatment to a dose of 1000 mg/day.

5.8. The group of patients treated with SERTINDOLE: 20 patients, 5 non-compliant patients.

A. The percentage rate of the extrapyramidal adverse effects which did not impose the stopping of the study: 6.66 %.

1 patient presented pseudoakathisia, 4 weeks after the beginning of the treatment to the dose of 16 mg/day.

B. The percentage rate of the extrapyramidal adverse effects that impose the stopping of the study: 6.66 %.

1 patient presented akathisia, 8 weeks after the beginning of the treatment to a dose of 16 mg/day.

5.9. The group of patients treated with ARIPIPRAZOLE: 20 patients, 5 non-compliant patients.

A. The percentage rate of the extrapyramidal adverse effects which did not impose the stopping of the study: 13.33 %.

2 patients presented mild dyskinesia movements, occurred after increasing the doses of aripiprazole to 30 mg/day, 3 weeks after the beginning of the treatment.

B. The percentage rate of the extrapyramidal adverse effects that impose the stopping of the study: 6.66 %.

1 patient presented acute dystonia, to the dose of 30 mg/day, occurred 14 days after the beginning of the treatment.

## 6. THE BIOSTATICS ANALYSIS OF THE STUDY RESULTS

To compare the rates of extrapyramidal adverse reactions between haloperidol (the medicine with the highest percentage of subjects experimenting RA extrapyramidal) and atypical neuroleptics, we have used the *Fisher 2-sided exact test*; the reason is being to the small number occurred in each cell (under 10), situation in which it is not recommended the comparing by the classic test Pearson squared-chi. We made the comparisons both for the population per protocol (PP), i.e. excluding the abandons caused by the lack of compliance, and for the population intending to be treated (ITT), including the non-compliant patients. For the security of the analysis, we will consider the PP analysis as being stronger.

The PP analysis excluding the non-compliant patients obtained the following results:

| <i>Fisher 2-sided exact test between...</i> |                              |                                      |
|---------------------------------------------|------------------------------|--------------------------------------|
| <b>Haloperidol</b>                          | <b>Atypical neuroleptics</b> | <b>p<br/>Fisher's<br/>exact test</b> |
| <i>Haloperidol</i>                          | <i>Clozapine</i>             | <b>0.0001</b>                        |
| <i>Haloperidol</i>                          | <i>Sertindole</i>            | <b>0.021</b>                         |
| <i>Haloperidol</i>                          | <i>Amisulprid</i>            | <b>0.070</b>                         |
| <i>Haloperidol</i>                          | <i>Ziprasidone</i>           | <b>0.009</b>                         |
| <i>Haloperidol</i>                          | <i>Aripiprazole</i>          | <b>0.060</b>                         |
| <i>Haloperidol</i>                          | <i>Risperidone</i>           | 0.170                                |
| <i>Haloperidol</i>                          | <i>Quetiapine</i>            | <b>0.008</b>                         |
| <i>Haloperidol</i>                          | <i>Olanzapine</i>            | 0.165                                |

Table I: Rates of extrapyramidal adverse reactions between haloperidol and atypical neuroleptics, using the Fisher 2-sided exact test; for the population per protocol (PP), i.e. excluding the abandons caused by the lack of compliance

The ITT analysis including non-compliant patients:

| <i>Fisher 2-sided exact test between...</i> |                              |                                      |
|---------------------------------------------|------------------------------|--------------------------------------|
| <b>Haloperidol</b>                          | <b>Atypical neuroleptics</b> | <b>p<br/>Fisher's<br/>exact test</b> |
| <i>Haloperidol</i>                          | <i>Clozapine</i>             | <b>0.0001</b>                        |
| <i>Haloperidol</i>                          | <i>Sertindole</i>            | <b>0.015</b>                         |
| <i>Haloperidol</i>                          | <i>Amisulprid</i>            | <b>0.088</b>                         |
| <i>Haloperidol</i>                          | <i>Ziprasidone</i>           | <b>0.015</b>                         |
| <i>Haloperidol</i>                          | <i>Aripiprazole</i>          | <b>0.041</b>                         |
| <i>Haloperidol</i>                          | <i>Risperidone</i>           | 0.257                                |
| <i>Haloperidol</i>                          | <i>Quetiapine</i>            | <b>0.015</b>                         |
| <i>Haloperidol</i>                          | <i>Olanzapine</i>            | 0.257                                |

Table II: Rates of extrapyramidal adverse reactions between haloperidol and atypical neuroleptics, using the Fisher 2-sided exact test; for the population having the intention to be treated (ITT), including the non-compliant patients

## 7. DISCUSSIONS CONCERNING THE PRIMARY OBJECTIVE OF THE STUDY

### 7.1. THE EXTRAPYRAMIDAL ADVERSE EFFECTS WHICH DID NOT IMPOSE THE STOPPING OF THE STUDY

The haloperidol presented the highest percentage of ESP which did not impose the interruption of the treatment (26.66 %), followed by olanzapine (26.31 %), risperidone (16.66 %), aripiprazole (13.3 %), amisulprid (11.76 %), sertindol (6.66 %), ziprasidone (6.25 %) and quetiapine (5.55 %).

Clozapine presented no extrapyramidal adverse effect.

The high percentage of extrapyramidal adverse effects occurred at the administration of haloperidol corresponds to the data from the specialized literature, which underlines that these adverse effects are more frequent in the administration of the neuroleptics from the first generation with registered antidopaminergic effect and low anticholinergic effect (1).

The extrapyramidal adverse effects represent the consequence of the antagonization of the r.D2 dopaminergic in a proportion of more than 75 – 80 % (2).

To a dose of 4 – 6 mg/day of haloperidol, the degree of r.D2 absorption is of 75 – 89 %, so the risk for the occurrence of ESP is high.

The studies have shown that it is very difficult to settle the haloperidol dose to confer both tolerance and clinic efficiency (3).

The mild extrapyramidal adverse effects occurred at the administration of haloperidol were reversible to the diminution of doses, according to certain specialized literature studies (1).

The occurrence of ESP to olanzapine corresponds to the data from the specialized literature, which shows that doses between 10 – 20 mg/day determine a degree of absorption of r.D2 of 65 – 80 %.

ESP were signalled to these doses there (4).

In our study, the mild extrapyramidal adverse effects occurred in percentage high enough to olanzapine is explained by the difference of plasmatic concentration between men and women of the olanzapine (30 % increased in the case of women) and through the slow elimination to the non-smokers. (Mc Grat, J., 2004; Desai, H. D., 2001) (5, 6).

These effects occurred to 3 persons of feminine gender, non-smoking, with heredo-colateral psychiatric case history and coffee and cola addiction.

2 patients of the 5 which presented mild ESP to the administration of olanzapine were alcohol consumer, substance which raise the absorption of olanzapine and could aggravate ESP.

A female patient was under treatment with cimetidine of 800 mg/day, for an illness of oesophageal reflux; cimetidine (H<sub>2</sub> antagonist) inhibits the olanzapine metabolism, resulting in an increase of plasmatic concentration.

After 2 weeks, the female patient interrupted the treatment with cimetidine, and the ESP disappeared.

The occurrence of ESP at the administration of risperidone corresponds to the data from the specialized literature, which showed that this atypic neuroleptic determines, to the dose of 2 – 4 mg/day, an absorption of 95 % of r.HT2A (7) and the dose of 6 mg/day of 79 % of r.D2. (8).

This mechanism explains the possibility of ESP occurrence, but also the efficacy on the positive symptomatology efficacy in schizophrenia.

The occurrence of mild ESP at the administration of amisulprid, to the increase of the doses, is explained by the degree of absorption of r.D2. / D3.

The results of the study correspond to the evaluation by brain imaging made to patients with schizophrenia who received 600 mg/day of amisulprid and who manifested a 56 % degree of absorption of r.D2. / D3 from the striated ganglions, 75 % of thalamus and 82 % of the striated cortex (9).

The low percentage of mild ESP occurred at sertindole, ziprasidone and quetiapine corresponds to the data from the specialized literature (10). (11). (12).

Regarding the aripiprazol, this medicine presents a great similarity for r.D2. / D3, as well as for 5 HT 1A and 5 HT 2 A.

The occurrence of mild ESP to the administration of the aripiprazol comes with the data from the specialized literature, which underline that the occurrence of reduced secondary effects is explained by combining a partially agonistic activity on r.D2 and 5 HT 1A with an antagonistic activity on 5 HT 2A. (13).

The lack of any extrapyramidal effect to the administration of clozapine corresponds to the data from the literature, which underlines that their profile of pharmacologic action, justifies the low incidence of ESP. (4).

The most frequent extrapyramidal adverse effects were the disorders belonging to the parkinsonian syndrome.

These extrapyramidal disorders did not impose the stopping of the treatment from the following reasons:

- their low amplitude;
- their fast remission to the diminution of the dose or to the administration of anticholinergics;
- did not influence the therapeutic compliance;
- the patients presented a good clinical evolution.

## 7.2. EXTRAPYRAMIDAL ADVERSE EFFECTS THAT IMPOSED THE STOPPING OF THE STUDY

A number of 15 patients of the 152 compliant patients presented severe extrapyramidal reactions of acute type.

The haloperidol presented the highest percentage of severe ESP reactions (33.33 %) and is followed by risperidone (16.66 %), amisulprid (11.76 %), aripiprazol (6.66 %), sertindol (6.66 %), ziprasidone (6.25 %), quetiapine (5.55 %) and olanzapine (5.26 %).

At the antipode, stands the clozapine which presented no severe extrapyramidal effect.

The highest percentage of extrapyramidal secondary effects at the administration of haloperidol correlates with the data from all the comparative studies between the classic and atypical neuroleptics (14, 15).

Risperidon and amisulprid had the highest percentage of adverse effects ESP from atypical neuroleptics.

This situation corresponds to the data from the specialized literature (16).

Thus the meta-analysis of the antipsychotics of the second generation efficacy, published in 2003 (J. M. Davis et al.), concludes that some new antipsychotics, respectively the risperidone and amisulprid, determine ESP directly proportional with the dose (16).

The EUFEST study also concluded that the haloperidol and amisulprid had the highest probability to be prescribed anticholinergic agents (14).

The low percentage of severe at the administration of aripiprazole, sertindole, ziprasidone, quetiapine and olanzapine corresponds to the results of the studies of the specialized literature, which shows that these atypical antipsychotics induce so few ESP that their incidence is comparable with the placebo (16).

Clozapine presented no severe ESP effect, resulted in concordance with the studies from the specialized literature, which underlines the extreme low incidence of ESP, tardive dyskinesia included at the administration of this neuroleptic (17, 18).

The most frequent extrapyramidal effect was represented by akathisia (6 patients), followed by the parkinsonian syndrome (5 patients) and acute dystonia (4 patients).

The studies show that the high doses of risperidone, olanzapine and ziprasidone are associated with the high risk of ESP occurrence (Gerlach, J., 2002) (19).

In our study, on the first places after haloperidol, is situated the risperidone followed by amisulprid.

It was ascertained that the risperidone to a dose of over 10 mg/day determines an incidence of ESP comparable to the haloperidole (Owens, D. G., 1994) (20).

To the maximum dose used in our study – 8 mg/day – the ESP percentage was almost 2 times lower than haloperidole.

The data from the specialized literature suggest that to doses between the posology interval, the sertindole, quetiapine, aripiprazole and clozapine do not differ from placebo from the ESE incidence point of view (Lublin, H., Eberhard, J., Levander, S., 2005) (21).

In our study also, these medicines were associated with a reduced percentage of ESP.

The studies showed that the akathisia could occur during the treatment, at almost all the antipsychotics, including the clozapine (Gardner, D. M., Baldessarini, R. J., Waraich, P., 2005) (22).

In our study, the clozapine presented no ESE.

Although the studies show that the amisulprid, to doses between 200 – 1200 mg/day has an ESE profile similar to that of the olanzapine (5 – 20 mg/day) and risperidone (4 – 10 mg/day) (Mortimer, A. and collab., 2004) (23), in our study the amisulprid presented less ESP than risperidone and more than olanzapine.

The atypical antipsychotics administration was associated to the anticholinergic medication administration in a reduced number of cases, according to the data from the specialized literature (Gedes, J., 2000) (24).

In our study, the olanzapine presented the lowest percentage of severe extrapyramidal secondary effects, except for the clozapine, which presented no ESP.

This fact corresponds to the data from the specialized literature which underlined the olanzapine property to diminish the neurotoxic effects of r.NMDA, of facilitating the activity of neurotrophic factors (Marx, C. E. and collab., 2003) (25) and to stimulate the neurogenesis (Wang, H. D. and collab., 2004) (26).

The meta-analysis carried out by Corell, C. U. and collab., 2004 (27) show that the use of atypical antipsychotics is associated with an inferior risk for the occurrence of tardive dyskinesia.

In our study, there was no case of tardive dyskinesia.

The malignant neuroleptic syndrome was quoted as a severe complication after the use of clozapine, risperidone and olanzapine (Caroff, S. N. and collab., 2000) (28).

In our study, there was no case of malignant neuroleptic syndrome.

## 8. CONCLUSIONS

- The extrapyramidal adverse effects medicamentously induced could occur after the administration of any neuroleptic, but they have a lower frequency after administering the atypical neuroleptics;
- The highest percentage of extrapyramidal adverse effects was presented by haloperidol, respectively a percentage of 33.33 % from the number of 15 patients compliant to haloperidol;
- From the atypical neuroleptics, the risperidone and amisulprid presented the most severe extrapyramidal effects, respectively 16.66 % and 11.76 % from the total number of patients compliant to these medicines;
- The lowest percentage of the severe extrapyramidal effects was presented by olanzapine – 5.26 %, quetiapine – 5.55 %, aripiprazol and sertindol – 6.66 % and ziprasidone – 6.25 %;
- The clozapine was the only atypical neuroleptic that presented no ESP adverse effect;
- Inside the group studied, 180 patients, severe ESP occurred to a number of 15 patients, respectively a percentage of 9.86 % compliant patients;
- The male gender patients presented the highest percentage of severe ESP effects (12 men; 7.89 %) comparatively to the female gender (3 women; 1.97 %);
- Although it is recommended the avoidance of antiparkinsonians in the severe ESP syndrome, they were administered, due both to the distress provoked to the patient and to the negative impact it had on the other patients and/or the caregivers;
- The big number of adverse ESP reactions occurred at the administration of haloperidol suggests that the use of classic neuroleptics should be restricted to limited time periods, when the positive symptomatology, the hostility and aggressiveness are marked;
- The severe ESP represents major factors of therapeutic non-compliance, indicates the decrease of neuroprotection and could favour the occurrence of tardive dyskinesia and chronic akathisia;
- The periodic control of the patients who are administered classic neuroleptics is compulsory, both for noticing the acute ESP effects and for noticing the tardive ESP, which may occur after months and years of treatment, especially if the medication is reduced or discontinuously;
- The occurrence of severe adverse effects determined the reduction of the therapeutic benefit on conditions of stopping the administered neuroleptic, even in the case of good clinic evolution;
- The treatment of the severe adverse effects led to the pathologic upload by accumulation of adverse reactions produced by the introduction of other medicines in therapy;
- The occurrence of a severe adverse effect required the conversion to another antipsychotic, conversion carried out, as a rule, slowly in order to avoid the relapse risk; the set up of another neuroleptic action presupposed the extension of the hospitalizing period and thus of the costs.

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