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Comorbid Anxiety in Schizophrenia and Schizoaffective Disorder

Delia M. Podea, Aurora I. Sabau and Karol J. Wild

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Abstract

There is some evidence that antipsychotic medication (Quetiapine) is somewhat efficient in reducing anxiety in schizophrenic patients.

This study compared the efficacy of Olanzapine and Quetiapine versus Risperidone, Aripiprazole, and Haloperidolum in reducing the anxiety symptoms in patients diagnosed with schizophrenia and schizoaffective disorder hospitalized in the Psychiatry Department of Arad between 2013–2014.

Considering the treatment, 63 subjects were divided in two groups: T1 (treated with Olanzapine and Quetiapine) and T2 (treated with Haloperidolum, Risperidone, and Aripiprazol).

Anxiety is frequent in the course of schizophrenia and schizoaffective disorder with significant differences among the two groups. After treatment, the level of anxiety reduced with significant improvement of total score of PANSS; the effect is higher in group T2 compared to T1. Before treatment, anxiety is positively correlated with scores of PANSSN ($r=.285$; $p=0.010$), PANSST ($r=.260$; $p=0.040$), and HAM-D ($r=.455$; $p<0.0001$). YMRS is negatively correlated with negative items of PANSSN scale ($r=-.321$; $p=0.010$). IQ (intelligence quotient) was decreased posttreatment for both treatments, but T1 had had a higher effect on it.

Some antipsychotics have been reported to be successful in reducing the anxiety level in psychotic patients: in group T2 the treatment has a higher effect on anxiety and lower size effect on intelligence.

Keywords: Anxiety, Schizophrenia, Schizoaffective Disorder, Antipsychotics

1. Introduction

Anxiety disorders are serious, debilitating conditions, with wide discrepancies being found in the reports of the prevalence rates, in clinical and epidemiological studies.

Based on the literature, the rate of prevalence of anxiety disorder in patients with schizophrenia or schizoaffective disorder remains uncertain due to limiting factors: the definitions of the disorders themselves the sample size, the study procedures and the utilization of different measures and clinical assessments.

A meta-analysis by Achim et al., in 2011, found a prevalence rate for anxiety disorder of 38.3% in the schizophrenic population, compared with 28.8% reported for the general population [1].

Seedat et al., in 2007, in a study of hospitalized schizophrenic patients, found that 25% suffered from anxiety disorder [2]. In 2007, using a sample of inpatients, Ciapparelli et al. found anxiety disorders in 74% of the subjects [3].

In a study conducted by Braga et al., in 2004, 42% of schizophrenic outpatients presented anxiety disorders [4].

In schizoaffective disorder, the rates of anxiety disorders range from 32% in outpatients [3] to 45% in inpatients [5].

Schizophrenia is a common, chronic and severe mental illness defined by the presence of delusions, hallucinations, and disorganized behavior (positive symptoms); by the presence of apathy, social withdrawal, and involution (negative symptoms); and by cognitive disorganization [6].

It has long been known that anxiety has an important role in the psychopathology of schizophrenia. However, the nature of the development of anxiety disorder in psychosis is not well understood.

The presence of the comorbidity of anxiety in major psychotic disorders (schizophrenia, schizoaffective disorder) results in reduced cognitive functioning, increases the severity of comorbid medical conditions, increases the risk of reoccurrence, adds to internalized stigma, reduces functioning, and has a negative impact on the overall outcome for the patient.

Comorbid anxiety in schizophrenia and schizoaffective disorder is associated with the more positive symptoms: extrapyramidal symptoms suggesting more severe medication side effects [6], an increase in drug/alcohol abuse, a worsening of social and professional functioning, and in the quality of life [7].

Anxiety is common among patients with schizophrenia or schizoaffective disorder, and it may also manifest itself as a symptom during an acute psychotic episode [8], as a result of the side effects of medication or as a symptom of a comorbid anxiety disorder. Patients are generally discharged as soon as their psychotic episode is resolved, with little recognition of the presence of an anxiety disorder [9].

It is difficult to evaluate the relation of anxiety to psychotic symptoms since it is not clear which anxiety symptoms the disorder is associated with. Furthermore, the operational criteria

developed for the assessment of the level of anxiety found in the nonpsychotic population (Hamilton Anxiety Rating Scale, Yale Brown Obsession Compulsion Rating) may themselves be problematic. Extrapyramidal symptoms which develop secondary to neuroleptic treatment may coincide with anxiety symptoms [7].

Progress in understanding the etiology of comorbid anxiety in major psychotic disorders such as schizophrenia or schizoaffective disorder has been made. For example, in the field of genetics, two basic genetic strategies have been developed, enabling a better understanding of the etiology of anxiety: the linkage approach and the polymorphism or susceptibility allele, which associates different genes (e.g., dysbindin, the gene for the dystrobrevin-binding protein 1, located within the linkage peak on chromosome 6 p; or chromosomal regions, e.g., 6p22.3) with traits or illness [10].

Generally, anxiety disorders are relatively responsive to treatment so greater awareness should be paid to their comorbidity with psychosis in order to obtain clinical benefits.

Comorbid anxiety may have implications for treatment choice. Generally, anxiety is considered to be secondary to the psychotic condition and it is expected to improve simultaneously with an improvement in the schizophrenic symptoms. There is some evidence that antipsychotic medication (such as Quetiapine) has some degree of efficacy in reducing anxiety in schizophrenic patients [11].

The treatment for acute schizophrenia involves one of the newer generation antipsychotic drugs which is well-tolerated and can be used for maintenance therapy. In particular, it is desirable to use drugs with little sedative effect in order to optimize functioning and to preserve the quality of life [12,13]. However, lack of compliance with antipsychotics must be taken in consideration as it is known that nonadherence plays a significant role in psychotic relapse. In these cases, long-acting injectable antipsychotics (administered at two to four week intervals) are preferable as they may result in a lower risk of dose-related adverse effects (because of lower peak antipsychotic plasma levels) and lower rates of hospitalization due to acute exacerbations. These factors contribute to improving the individual quality of life.

A personalized treatment approach is necessary in the management of comorbid anxiety with schizophrenia which should be based on the pathogeneses and the clinical assessments.

In clinical practice, in those patients with significant agitation and anxiety, drugs with low sedative potential are not sufficient for the reduction of these symptoms. In these patients, anxiety may interfere with compliance to medication. So, benzodiazepines or sedative neuroleptics (levomepromazine) are often incorporated into the antipsychotic treatment [13].

In practice, two strategies are available to satisfactorily manage the severe anxiety associated with acute psychotic episodes: the use of sedative antipsychotic drugs (thioridazine, pipamperone, melperone, cyamemazine, a-flupenthixol, and levomepromazine) [14, 15, 16] or the use of adjuvant benzodiazepines therapy [17, 18, 19]. These sedative antipsychotics have been shown to have anxiolytic effects at low doses both in nonpsychotic patients and during acute psychotic episodes [18].

In order to prevent the risk of benzodiazepine dependence and rebound anxiety on the cessation of treatment, the use of benzodiazepines should be for as short a period as possible. Benzodiazepines should be prescribed in combination with nonsedative disinhibitory atypical antipsychotics.

Benzodiazepines used in psychotic episodes are drugs with potent anxiolytic action, a low propensity for pharmacokinetic drug interactions, and a long half-life to ensure uninterrupted cover [19, 20].

After the patient reaches a position where the symptoms are well-controlled, the treatment can be switched to a nonsedative antipsychotic for maintenance therapy.

Some atypical antipsychotics rely on the serotonin (5-HT) neurotransmitter system. The antagonism of 5-HT receptors permits the atypical antipsychotics to have a lower propensity to cause extrapyramidal symptoms and tardive dyskinesia.

The 5-HT actions may also result in improvements in the negative or cognitive symptoms of schizophrenia.

It has been proposed that the antagonism of 5-HT receptors and/or partial antagonism of 5-HT receptors and antihistaminic properties may play a role in the antianxiety effect of some atypical antipsychotics.

The literature indicates that Olanzapine and Quetiapine have a degree of efficacy in reducing anxiety in schizophrenic and schizoaffective patients [11, 19].

In order to explore the efficacy of atypical antipsychotics in reducing comorbid anxiety in schizophrenic and schizoaffective patients, we performed a study in our clinic.

We aimed to measure the efficacy of various antipsychotics in reducing anxiety levels in patients diagnosed with schizophrenia and schizoaffective disorder, who had been hospitalized in Arad between 2013-2014.

2. Methodology

2.1. Objectives

The aims of this study are: (a) to determine the relationship between anxiety and schizophrenia/ schizoaffective disorder, (b) to determine if the anxiety level is reduced under pharmacological treatment and to compare the efficacy in the two groups (T1- Olanzapine, Quetiapine; and T2- Haloperidolum, Risperidone, Aripiprazol), and (c) to estimate the effect of antipsychotic treatment on cognitive ability (intelligence level, IQ).

2.2. Sample

Sixty three patients diagnosed with schizophrenia, schizoaffective disorder, and anxiety were evaluated on admission and after 28 days of antipsychotic treatment. The patients were

hospitalized in the Psychiatry Ward of The County Clinical Emergency Hospital in Arad, between 2013–2014. The patients were divided in two groups: T1, who received antipsychotic treatment with Olanzapine or Quetiapine; and group T2, who received treatment with typical and atypical antipsychotics (Haloperidol, Risperidone, and Aripiprazole).

The diagnoses of schizophrenia, schizoaffective disorder and anxiety disorders were established according to the ICD-10²¹ and DSM-V-TM²² criteria.

GENDER	Females: 54%	Mean: 43.27		
AGE	Mean: 43.27	SD: 7.5		
EDUCATION	Secondary school: 9%	High school: 33.3%	Professional school: 46%	University: 7%
MARITAL STATUS	Never married: 7.9%	Married: 20.6%	Divorced: 20.6%	In a relationship: 7.9%
ALCOHOL USE	6.3%			

Table 1. Sample characteristics

The sample (Table 1) presented the following socio-demographic characteristics: (a) gender: 54% females, 46% males; (b) age: mean = 43.27, SD = 7.5; (c) education: 9% secondary school, 33.3% high school, 46% professional school and 7% university; (d) marital status: 7.9% never married, 20.6% married, 20.6% divorced, and 7.9% in a relationship; and (e) 6.3% alcohol use.

2.3. Measures

All subjects were evaluated using the following measures:

- The Hamilton Anxiety Scale (HAM-A;** Hamilton, 1959) [23] is a rating scale used to quantify the severity of anxiety symptomatology. It consists of 14 items, each defined by a series of symptoms. Each item is rated on a 5-point scale, ranging from 0 (not present) to 4 (severe).
- Positive and Negative Syndrome Scale (PANSS;** Kay SR, Fiszbein A, Opler LA. 1987) [24] is a semistructured clinical interview scale comprising 30 items and a seven point severity rating. There are seven psychiatric parameters belonging to a positive symptoms subscale, seven parameters belonging to a negative symptoms subscale and 16 parameters belonging to a general psychopathology subscale. The interitem correlations for PANSS were significant with a Cronbach's alpha between .71 to .83.
- The Hamilton Depression Rating Scale (HAMD - 17 items;** Hamilton M. A Rating Scale for Depression 1960) [25] is a scale that measures the symptoms of depression experienced over the previous week, and was originally developed for hospital inpatients. One limitation of the HAMD is that atypical symptoms of depression (e.g., hypersomnia, hyperphagia) are not assessed. A score of 0–7 is generally accepted to be within the normal

range (or in clinical remission), while a score of 20 or higher (indicating at least moderate severity) is usually required for entry into a clinical trial. HAMD have good internal consistency, between 0.77 to 0.91.

- d. **Young Mania Rating Scale (YMRS)** [26] is a rating scale used to evaluate manic symptoms in individuals with mania. The scale has 11 items and is based on the patient's subjective report of his or her clinical condition over the previous 48 hours. The studies regarding the psychometric characteristics of YMRS report a high degree of internal consistency ($\alpha = 0.91$).
- e. **Raven's Progressive Matrices** [27] is a nonverbal multiple choice measure of general intelligence; in each test item, the subject is asked to identify the missing element that completes a pattern. On the Romanian sample of 2755 subjects, RPM reported a high internal consistency ($\alpha = .91$).

2.4. Procedure and design

The participants of this study filled in the tests package presented at the section work instruments. For the protection of the participants, they only noted a code on the answer papers. We shall use the variance analysis (ANOVA factorial) considering that we shall observe the simultaneous influence of two interdependent variables on the dependent variable.

We have structured our research into three studies as follows:

- a. a correlation study—for which we have used Pearson correlation "r," in order to establish the relationship between all measurements in the pretreatment phase.
- b. a comparative study—between pre- and postintervention, respectively, between the two treatments on the dependent variables (anxiety, mania, depression, and positive versus negative psychotic symptoms); we have calculated **ANOVA 2 x 2 - General Lineal Model for Repeated Measurements** for the cases in which there was no initial (pretreatment) difference between the dependent variables means (e.g., HAMA, YMRS, PANSS-N).

ANOVA 2 x 2 as a statistical indicator is helpful to observe as well the evolution in time, as well the effect on the dependent variables of the interaction between treatment condition and evolution in time as independent variables.

We have calculated **ANCOVA - General Lineal Model Univariate Analysis of Variance** for the cases in which we have observed an initial difference between the dependent variables means (e.g., PANSS-P, PANSS-G, PANSS-T, HAMD).

ANCOVA as a statistic indicator helps to eliminate the initial difference (preintervention) from the end-results (postintervention) in order to see if at the end the difference is significant as a result of intervention and to estimate which would be the end-results means if we wouldn't had initial differences.

- c. a comparative study—on effect of the treatment on IQ as a dependent variable, for this propose we have used ANCOVA - Univariate Analysis of Variance, because we have observed a initial difference between the two groups regarding the IQ level.

3. Results

3.1. Correlations

Before treatment, anxiety is positively correlated with the total score of negative items on the PANSS scale (PANSSN: $r = .285$; $p = 0.010$); anxiety is also positively correlated with the total score on PANSS (PANSST: $r = .260$; $p = 0.040$) and the total score for depression assessed according to the Hamilton Depression Scale (HAM-D: $r = .455$; $p < 0.0001$).

The score on the YMRS is negatively correlated with negative items on the PANSSN scale ($r = -.321$; $p = 0.010$). In general, it is to be expected that a subject with negative symptoms will have a lower level of mania.

The IQ was positive correlated with the total score on the PANSS scale (PANSST: $r = .261$; $p = 0.036$) suggesting, in our study, that a higher level of intelligence represents possible a risk in the development of psychotic symptoms. The observed positive correlation between PANSST and IQ accounts for approximately 9% of the variation.

Pearson	IQ	PANSSP	PANSSN	PANSSG	PANSST	HAMA	YMRS	HAMD	No. Relapse	Age
IQ initial	1	.044	.162	.233	.261*	.108	-.015	.241	-.035	-.003
PANSS-P		1	.272*	-.052	.403**	.114	-.018	.053	.055	.082
PANSS-N			1	.174	.688**	.057	-.321*	.217	.286*	.352**
PANSS-G				1	.769**	.285*	.003	.304*	.027	.062
PANSS-T					1	.260*	-.155	.332**	.171	.242
HAMA						1	.001	.455**	.133	.240
Sample N	63	63	63	63	63	63	63	63	63	63

PANSS-P = positive items of PANSS scale; PANSS-N = negative items of PANSS scale; PANNS-G = general items of PANSS scale; PANSS-T = total score of PANSS scale; HAMA = Hamilton anxiety scale; YMRS = Young Mania Rating scale; HAMD = Hamilton Depression scale; *. Significant at the 0.05 level (2-tailed). **. Significant at the 0.01 level (2-tailed).

Table 2. Preintervention correlations between all measurements

Based on these results, there is a possibility that IQ can be a risk factor in 9% of the cases to stimulate the productivity of psychotic symptoms. Given this fact, we need to exercise a degree of caution with regard to the afore mentioned conclusion.

3.2. Comparing treatments

To assess the level of the anxiety disorders in both groups before and after 28 days of antipsychotic treatment, we used an ANOVA 2 x 2 design.

Because we expected that there would be initial differences between the two groups (T1 and T2), we also performed a t-test for independent samples (table 2) for the pretreatment values, in order to eliminate, if necessary, any initial differences from the postintervention results by calculating ANCOVA in such cases.

We obtained statistically significant difference for the PANSS-P, PANSS-G, PANSS-T, and HAM-D. To compare the efficacy of the treatment for these dependent variables between the two groups we used ANCOVA.

Pre-intervention measurments		<i>t-test for Equality of Means</i>						
		.t.	df	Sig. (2- tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
							Lower	Upper
PANSS-P	Equal variances assumed	-2.800	61	.007	-1.8589	.6638	-3.1862	-.5315
PANSS-N	Equal variances assumed	.578	61	.566	.6310	1.0926	-1.5538	2.8159
PANSS-G	Equal variances assumed	4.302	61	.000	6.1028	1.4187	3.2659	8.9397
PANSS-T	Equal variances assumed	2.206	61	.031	4.8468	2.1966	.4543	9.2392
HAMA	Equal variances assumed	1.025	61	.310	1.2319	1.2023	-1.1723	3.6360
YOUNG MANIA	Equal variances assumed	.181	61	.857	.3992	2.2024	-4.0047	4.8031
HAMD	Equal variances assumed	3.208	61	.002	3.4980	1.0903	1.3179	5.6781
PANSS-P = positive items of PANSS scale; PANSS-N = negative items of PANSS scale; PANNS-G = general items of PANSS scale; PANSS-T = total items of PANSS scale; HAMA = Hamilton anxiety rating scale; YMRS = Young Mania Rating SCALE; HAMD = hamilton depression rating scale;								

Table 3. Preintervention differences between the two groups (in order to see if it is necessary to use ANCOVA

As the main goal of this study was to evaluate the efficacy of antipsychotic treatment for anxiety, we compared the level of anxiety pre and postintervention, by using ANOVA because there were no initial differences observed (see table 3).

Results showed that there were differences in the level of anxiety reduction between the two groups: in group T2, the efficacy of the treatment was significantly higher than that of group T1. The result obtained was confirmed by the t-test for independent samples applied postin-tervention at T1 and T2 (t = 3.018; p =.004).

General Lineal Model – for Repeated Measurements for Anxiety					
Source	Sum of Squares	df	Mean Square	F	Sig.
Time (pre – post)	574.777	1	574.777	211.821	.000
Time * Treatments (T1 vs T2)	22.904	1	22.904	8.441	.005
Error (Time)	165.524	61	2.714		

Table 4. Comparing the level of anxiety pre and postintervention and between groups

The difference in anxiety reduction between the two groups (see table 4) was also measured, by comparing T2 with T1 with Cohen's $D = 0,7583$; $r = 0.3545$.

Using the t -test for paired samples t (T1) = -4.901, $p < 0.0001$ and t (T2) = -9.043, $p < 0.001$, the results obtained in our preliminary study revealed that both types of treatments are effective in significantly reducing the intensity of anxiety both for schizophrenic and schizoaffective patients.

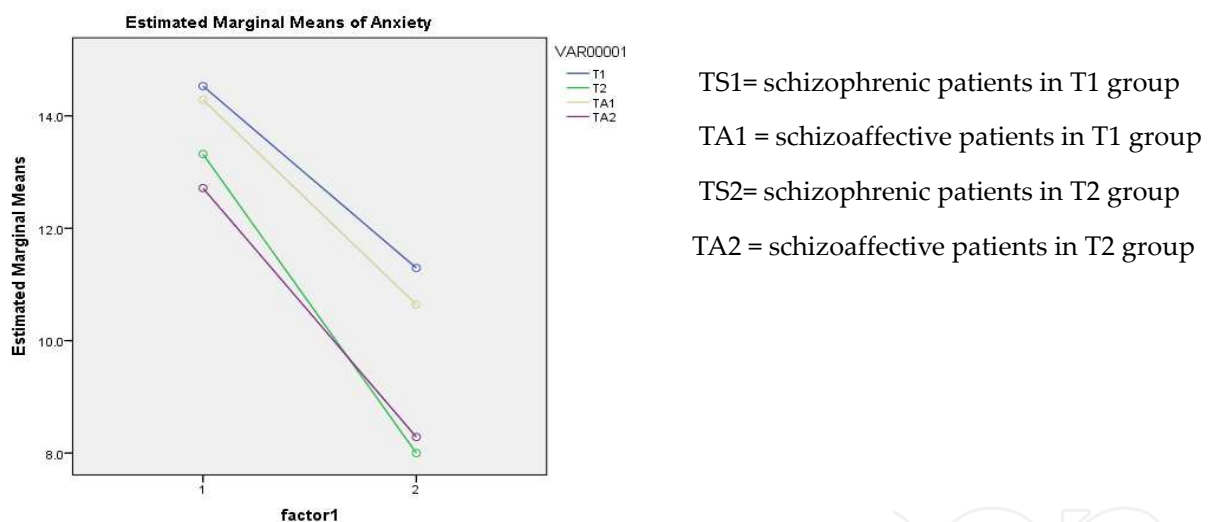


Figure 1. Pretreatment and posttreatment level of anxiety for both groups T1 (TS1 and TA1) and T2 (TS2 and TA2)

For both groups (Figure 1), the results showed that with regard to the efficacy of the treatments for the patients diagnosed with schizoaffective disorder compared to schizophrenic patients, there was no difference, t (T1) = -3.94, $p = 0.697$ and t (T2) = 0.212, $p = 0.933$.

3.3. Comparing IQ

To eliminate the initial preintervention IQ differences between groups ($t = 5,162$; $p < 0.0001$) we applied ANCOVA. In both groups of patients, antipsychotic treatment has a negative effect on cognitive functioning reducing IQ level, but the cognitive dysfunction was higher in group T1.

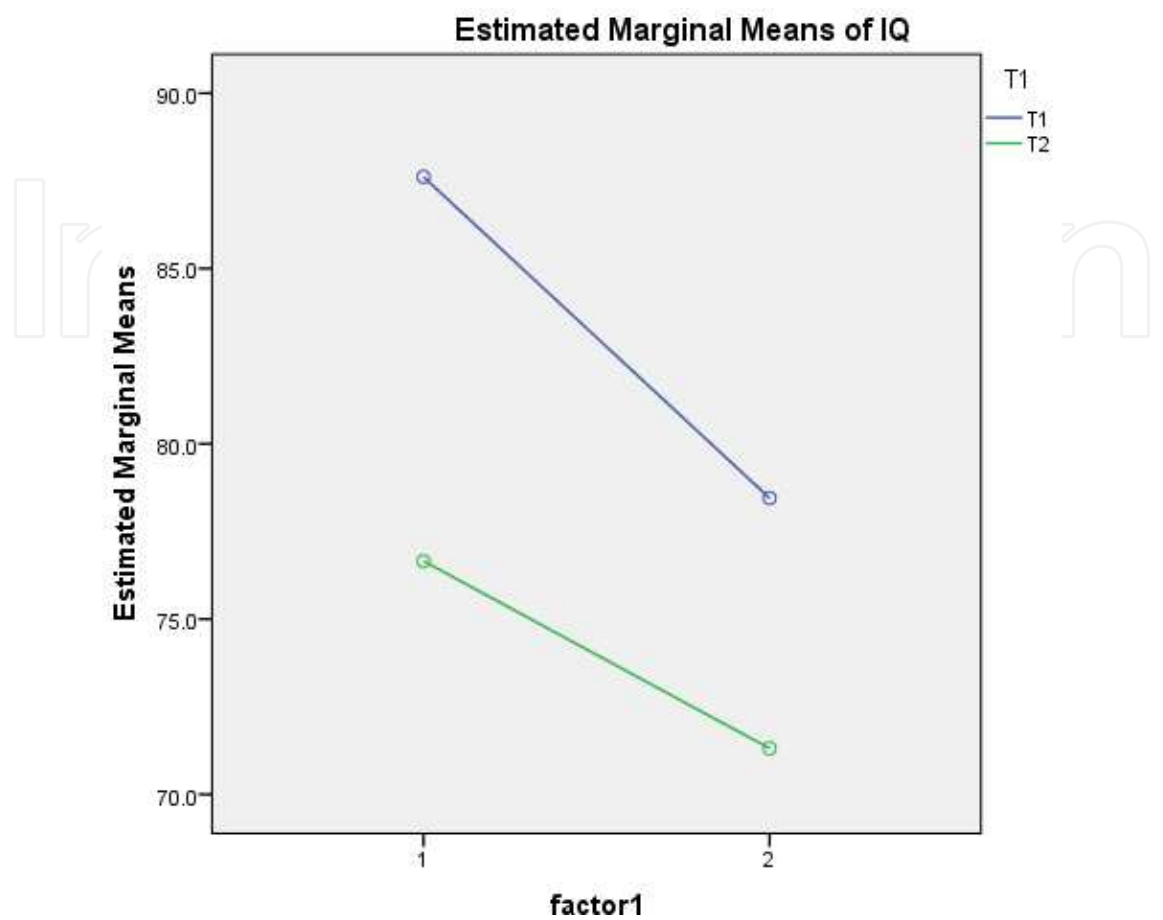


Figure 2. Evolution of the IQ levels in T1 and T2 group

The results obtained showed that in posttreatment (Figure 2) there were no statistically significant differences between the two groups, ANCOVA $F = 1.085$, $p = 0.302$. A possible explanation for these results is that the T1 treatment had a greater effect on cognitive functioning when compared with the T2 treatment, so that even if the T2 group initially had a lower intelligence level, after 28 days the difference was no longer significant (see Table 5).

Dependent Variable: IQ in evolution				
Pre-Post	Mean	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
T1 treatment	74.07 ^a	.93	72.21	75.93
T2 treatment	75.551	.91	73.72	77.37

Note: a.Covariates appearing in the model are evaluated at the following values: IQ initial = 82.048.

Table 5. Estimated marginal means after eliminating the covariance of the Initial IQ

4. Discussions and conclusions

The study's results proved that preintervention anxiety is positively correlated with the total score on PANSSN ($r = .285$; $p = 0.010$) and PANSST ($r = 0.260$; $p = 0.040$) and the total score on HAM-D ($r = 0.455$; $p < 0.0001$). Also the score on the YMRS is negatively correlated with the negative items on the PANSSN scale ($r = -0.321$; $p = 0.010$). Our results are corroborated by international studies [28, 29].

Based on the results of our study, the efficacy of Olanzapine or Quetiapine is lower than that of the typical and other atypical antipsychotics (such as Haloperidol, Risperidone, Aripiprazol). Olanzapine or Quetiapine have a greater negative effect on cognitive functioning than other antipsychotics.

These results are contrary to the international findings [11, 19, 30, 31].

In a study by Riedl et al., 2007 [19], both Quetiapine and Olanzapine improved cognition; however, the improvement in cognitive index scores was more marked in patients receiving Quetiapine. Quetiapine produce a significantly better improvement in reaction quality/attention than Olanzapine [11, 19].

Olanzapine, an atypical antipsychotic, has proved to be efficient in reducing the positive and negative symptoms of schizophrenia. Compared with conventional antipsychotics, it has greater affinity for serotonin 5-HT_{2A} than for dopamine D₂ receptors. In large, well-controlled trials involving patients diagnosed with schizophrenia, Olanzapine (5 to 20 mg/day) was superior to Haloperidol (5 to 20 mg/day) in the treatment of depressive and negative symptoms, comparable with effects on positive psychotic symptoms [28]. Contrary to these findings, in our study patients treated with haloperidol, Risperidone, and Aripiprazol (group T2) showed a greater reduction of symptomatology.

The 1-year risk of relapse of rehospitalisation was significantly lower with Olanzapine than with Haloperidol treatment [35].

In the first double-blind comparative study [28, 29, 33]) of Olanzapine 10 to 20 mg/day and Risperidone 4 to 12 mg/day, Olanzapine proved to be significantly more effective than Risperidone in the treatment of negative and depressive symptoms but not for overall psychopathological symptoms.

In contrast, preliminary results from an 8-week controlled study [34] suggested that Risperidone 2 to 6 mg/day was superior to Olanzapine 5 to 20 mg/day in the treatment of positive and anxiety/depressive symptoms, and that both agents demonstrated similar efficacy on overall psychopathology. These results are similar to our findings (Risperidone was superior to Olanzapine in reducing anxiety symptoms as confirmed by t-test for independent samples applied postintervention at T1 and T2: $t = 3.018$; $p = 0.004$).

However, preliminary results from an 8-week trial showed comparable cognitive enhancing effects for Olanzapine and Risperidone in patients with schizophrenia or schizoaffective disorder [30]. In our study, in both groups of patients, (T1, T2), antipsychotic treatment has a

negative effect on cognition with a larger effect on group T1 treated with Olanzapine and Quetiapine.

Olanzapine demonstrated superior antipsychotic efficacy when compared to Haloperidol in the treatment of acute phase schizophrenia, and in the treatment of some patients with first-episode or treatment-resistant schizophrenia [35].

The reduced risk of adverse events and the therapeutic superiority, compared with Haloperidol and Risperidone, in the treatment of negative and depressive symptoms support the choice of Olanzapine as a first-line option in the management of schizophrenia in the acute and maintenance phase of treatment response [36].

Aripiprazole, a 5-HT_{1A} partial agonist was found to have a considerable antianxiety effect which may concur with procognitive and mood-ameliorating effects [32, 37, 38]. These are similar to our results: when comparing T2 with T1 using effect size based on differences between means (Cohen's $D = 0.7583$; $r = 0.3545$), Aripiprazole is superior to Olanzapine and Quetiapine in reducing anxiety in schizophrenic and schizoaffective disorder patients. Regarding the cognitive dysfunction, posttreatment, in both groups of patients, we noticed a negative effect on cognition, although there was no statistically significant differences between the groups as determined by analysis of covariance (ANOVA $F = 1.085$; $p = 0.302$).

One hypothesis could be that this agonism of Aripiprazole is a mechanism contributing to antianxiety effects. Case reports and studies on the antipsychotic augmentation by Aripiprazole in partial responders to Clozapine found a considerable antianxiety effect [32].

However, this could be due to external factors or to the natural evolution of the illness. A randomized controlled study is required to evaluate the efficacy of the Clozapine-Aripiprazole combination in cases of treatment-resistant schizophrenia with a predominance of anxiety [39].

Risperidone's antianxiety action was demonstrated in the study by Blider et al. in 2002 [30], conducted on 62 patients hospitalized for acute exacerbations of schizophrenia, randomly assigned to receive Risperidone (a mean dose, 7.4 mg/day), Haloperidol (7.6 mg/day), or Methotrimeprazine (100 mg/day) for 4 weeks. The antianxiety effects were significantly greater in the Risperidone patients than the Methotrimeprazine patients. The difference between Haloperidol and Methotrimeprazine was not significant.

It is concluded that Risperidone is an effective antipsychotic and anxiolytic agent in schizophrenic patients. These results are confirmed by our findings in group T2 ($t = 3.018$; $p = 0.004$).

New Drug Perspectives

It is generally agreed upon that anxiety is a frequently occurring symptom of schizophrenia, strongly associated with an increased risk of relapse and more severe symptomatology. The effects of antipsychotics in reducing anxiety in psychotic patients remain controversial and the practice of prescribing adjuvants (benzodiazepines) is unsatisfactory [17, 18].

The next clinical trials for schizophrenia with comorbid anxiety perhaps will show the efficacy of some new compounds (the anticonvulsant/anxiolytic pregabalin and the atypical antipsychotic Quetiapine) [40].

Consequently, we think there is a need for more research in order to obtain a clear perspective of the efficacy of Olanzapine or Quetiapine. It should also be pointed out that our findings suffer from certain limitations: such as (a) the lack of a control group, (b) the small sample size, (c) the short treatment time, and (d) the lack of a follow-up evaluation after three and six months, and after one year. Our results can serve as a guide to future studies regarding the efficacy of psychopharmacological treatment on comorbid anxiety.

Limitations

The methodological limitations of this study will be addressed in a follow-up study: this was a preliminary study with a small sample size, lacking follow up evaluations at 3 months, 6 months and 1 year. Given that some of these patients will be inevitably lost to the follow up, a large sample size will need to be used in order to ensure that sufficient numbers are available to obtain meaningful repeat measures.

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