NEUROCOGNITIVE MANAGEMENT OF THE PRIMARY NEGATIVE SYMPTOMS OF SCHIZOPHRENIA: A ROLE OF ATYPICAL ANTIPSYCHOTICS

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SUMMARY

Patients with schizophrenia have profound and disabling cognitive deficits while negative symptoms represent a separate symptom domain, with respect to depression, neurocognition, and social cognition. Particularly, primary negative symptoms of schizophrenia represent a diagnostic and therapeutic challenge, In this study we try to evaluate the cognitive symptoms in 51 primary negative schizophrenic inpatients by the administration of simple, fast and understandable scales (MMSE, DSST, EpiTrack, PANSS cognitive factor). We also evaluate the correlation with some SGAs (aripiprazole, quetiapine, olanzapine, paliperidone). Our results support the evidence of the use of simple, rapid and acceptable scales for cognitive evaluation in clinical practice. Overall data indicate no statistically significant variations of the negative symptomatology in all the examined sample, although a reduction of the statistical averages in each group is observed (paliperidone and olanzapine, particularly).

Key words: negative symptoms schizophrenia – atypical antipsychotics – cognitive deficits – effectiveness

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INTRODUCTION

A common feature in schizophrenia is the cognitive impairment which, in turn, is associated with reduced functional outcomes and quality of life (Byrne 2015). Cognitive symptoms have for a long time been recognized as a central feature of the phenomenology of schizophrenia (Kraepelin 1919, Bleuler 1908). The view that cognitive symptoms are the core of the disease is growing. Negative symptoms represent a separate symptom domain, with respect to depression, neurocognition, and social cognition (Foussias 2014, Kirkpatrick 2014), and have a strong direct and indirect impact on real-life functioning. The relationship between cognition and positive and negative symptoms in schizophrenia has been studied in several works. While the relationship with the positive symptoms does not appear to be related to cognitive dysfunction (Rund 2016, Ventura 2013, Ventura 2009), the relationship between negative and cognitive symptoms is less clear. In fact, data in recent work supports the relative independence of cognitive performance and negative symptoms in patients with schizophrenia (Bagney 2015, Harvey 2006); however, in other studies, this association has been confirmed (Mosiołek 2016, Fakra 2015, Bozikas 2004).

THE DEFINITIONS AND INSTRUMENTS OF COGNITIVE AND NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

Several definitions and tools for the assessment of negative and cognitive symptoms of schizophrenia have

been proposed, such as for example, the Scale for *Scale for the Assessment of Negative Symptoms* (SANS) or the original negative scale of the *Positive and Negative Syndrome Scale (PANSS)* (Kay 1987). Some researchers have highlighted the possibility of using specific items of these scales. In fact, several factorial analyses studies of these scales have shown a 5-factor subscale, which include "Cognitive/Disorganized factor", and "Negative factor" (Lehoux 2009, Lindenmayer 1996). More recently, the use of a PANSS negative factor derived from factorial analysis has been recommended rather than original PANSS negative subscale (Marder 2011).

For studying cognitive dysfunction in schizophrenia different instruments are used, and a wide range of instruments have been developed to aid clinical assessment of cognitive assessment. The most widely used scales are the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein 2008, Kern 2008) which includes ten tests that measure seven cognitive domains; EUFEST (Fleischhacker 2005), CATIE (Lieberman 2005), BACS (Keefe 2004). However, the complexity and the time used for compiling these scales make them difficult to use in daily clinical practice. Thus, the use of instruments for cognitive assessment in schizophrenic patients is very low.Only 12% of new patients diagnosed with schizophrenia receive a cognitive assessment (Belgaied 2014). Therefore, there is the need to apply an assessment of cognition that can try to achieve the objective in a simple and effective manner (Svendsen 2012), and the availability of simple and handy tools can be crucial for good clinical practice (Russo 2015) especially tools which are well accepted by the patients.

For this reason, recent studies have begun to evaluate tests that are simple, easy and quick, too (Ong 2016). These are some texts that have the above characteristics: Mini-Mental State Examination (MMSE) (Folstein 1975), BACS; Digit Symbol Substitution Test (DSST) (Wechsler 1981) designed to assess attention, psychomotor speed, and executive function; Perceived Deficits Questionnaire 5-Item Version (PDQ) (Fehnel 2016; Sullivan 1990) that assesses self-perceived cognitive difficulties; EpiTrack® (Lutz 2005) a tool designed to assess and track changes in cognitive function in people with epilepsy. This screening tool uses a short list of critical questions and visual indicators to assist healthcare professionals (HCPs) in detecting problems with attention and executive function. Following on our previous study in which we evaluated the efficacy of some antipsychotics in the negative symptoms of schizophrenia (Franza 2015), in this study we try to evaluate the cognitive symptoms in primary negative schizophrenic inpatients with administration of simple, fast and understandable scales.

METHODS

In 24-month-study we evaluated the effects on cognitive symptoms of second-generation antipsychotics in 51 patients (11 females; 40 males) with schizophrenia or schizoaffective disorder (DSM-5 criteria), recruited in the Neuropsychiatric Centre "Villa dei Pini" of Avellino, Italy. Inclusion criteria were at least one persistent negative symptoms of moderate or higher severity, according to the recommendations by Consensus Development Conference Attendees (Galderisi 2008; Kirkpatrick 2006): more than 6 months with adequate antipsychotic treatment and clinically stable and minimal psychotic symptoms, depression/anxiety, extrapyramidal side effects, or other significant cause of secondary negative symptoms. The study was conducted in patients hospitalized from 2013 to 2016, and evaluated for 24 consecutive months. Discharged patients were observed in subsequent clinical interviews in normal clinical practice. The data collected were: age, gender, educational level, number and type of episodes, age at onset, number of hospitalizations, age of illness.

All patients were treated with some SGAs (quetiapine, olanzapine; aripiprazole, paliperidone) and evalua

ted at baseline (T0) and after 1 (T1), 6 (T2), 12 (T3), and 24 (T4) months with following scales: Negative factor and Cognitive Factor on Positive and Negative Syndrome Scale (PANSS)(Kay et al. 1987) for typological and dimensional assessment; Brief Negative Symptoms Scale (BNSS) (Kirkpatrick et al. 2011) for negative symptoms; Brief Psychiatric Rating Scale (BPRS)(Overall 1988) for psychopathological assessment. All inpatients were administered with following psychopathological scales at baseline (T0), after 3 (T1), 6 (T2), 12 (T3), 24 (T4) months: MMSE; Digit Symbol Substitution Test (DSST); EpiTrack® tool.

All the relevant data were analysed using EZAnalyze Version 3.0, Microsoft Excel Add-In (Suffolk University in Boston, Massachusetts, USA). Chi-square test was used for analysing categorical data (age, gender, etc.). Score Data was analysed using ANOVA Test. $P<0.05$ was taken as statistically significant.

RESULTS

The patient groups were comparable to each other in terms of age, sex, gender, SGAs, and DSM-5 episode disorders (Table 1). Table 2 shows data of Cognitive and Negative Factor PANNS, BNSS, BPRS, scales at baseline and T1, T2, T3, T4 times. Overall data indicate no statistically significant variation of the negative symptomatology in all the examined sample (see Franza 2015). However, some small changes in mean scores in some scales were observed. In fact, interesting data obtained with the PANSS Cognitive Factor scale, in which in the total values we did not find statistically significant differences ($p=0.278$; Eta Squared 0.025) while statistically significant differences were observed in the olanzapine group (T0 vs T4: $p=0.034$; T2 vs T4: $p=0.022$; T3 vs T4: $p=0.026$) and the paliperidone group ((T0 vs T4: $p=0.004$; T1 vs T2: $p=0.044$; T2 vs T4: $p=0.000$).

The data of the other scales used (Table 3) for the assessment of cognition of the analysed patients (Table 3) indicate that there are statistically significant differences in the overall results (for example, in EpiTrack total data: T0 vs T4: $p=0.019$; T3 vs T4: $p=0.011$ P - Unadjusted), while in each analysed group, no statistically significant differences were observed. The data obtained with the MMSE scales is interesting. The overall data indicates a statistically significant difference

Table 1. Demographic and other data of patients

Patient characteritics	ARZ	OTP	OLZ	PAL	
No. of cases	12	12	12	15	
Age (years) mean ± SD	39.75±12.58	38.66±13.95	39.64±9.8	38.67±11.1	0.676
Gender male:female	10:2	9:3	9:3	12:3	0.787
Age of illness (ys) mean ± SD	9.2±2.7	8.56±8.2	7.3±7.8	8.9±7.9	0.501
Number hospitalizations	5.4	6.3	6.3	4.1	0.438
BPRS 18 items (baseline)	63.33±14.88	66.17±13.16	58.33±12.24	57.07±14.41	
Married: 27% Separated: 16% Single: 51% Widower: 6%					

ARZ - aripiprazole group; QTP - quetiapine group; OLZ - olanzapine group; PAL - paliperidone group

Table 2. Data BNSS, Negative factor PANSS scales

SGAs group	Scale	T0 (mean±SD)	T1 (mean±SD)	T2 (mean±SD)	T3 (mean±SD)	T4 (mean±SD)	P value	Repeated Measures ANOVA Variables differed significant
	BNSS							
Total		52.6±12.86	50.4±13.24	48.3±12.8	47.64±4.66	44.961±10.59	0.000	at least two
	Negative factor PANSS							
Total		24.667±4.435	22.451±6.001	24.588±4.428	24.255±4.625	20.314±7.863	0.000	at least two

Table 3. Data EpiTrack®, MMSE scales

SGAs group	Scale	T0 (mean±SD)	T1 (mean±SD)	T2 (mean±SD)	T3 (mean±SD)	T4 (mean±SD)	P value
	EpiTrack						
Total		23.60±6.68	22.92±6.81	22.68±6.54	23.11±6.58	22.27±6.12	0.046
The ANOVA results indicate that at least two of the repeated measures differed significantly:							
						T0 vs T4	0.019
						T1 vs T4	0.021
						T3 vs T4	0.011
Aripiprazole		23.33±6.99	22.75±6.51	22.5±6.113	23.33±6.77	22.83±6.103	0.877
Quetiapine		24.41±7.24	23.00±7.097	22.917±7.62	22.833±6.926	21.667±6.972	0.086
Olanzapine		22.917±4.994	23.34±5.187	22.667±4.942	22.250±4.673	21.833±4.019	0.340
Paliperidone		23.73±7.713	22.933±8.464	22.66±7.650	23.867±7.918	22.667±7.287	0.582
	MMSE						
Total		16.137±5.355	15.824±5.226	15.824±4.966	15.333±4.533	14.961±4.377	0.048
						T0 vs T4	0.030
Aripiprazole		14.417±4.358	14.583±5.680	13.917±5.468	13.00±4.88	13.667±6.344	0.331
Quetiapine		14.583±5.823	14.083±5.485	15.917±5.616	15.156±5.524	15.333±5.069	0.284
Olanzapine		14.333±4.677	14.583±4.252	14.333±3.676	15.083±3.630	14.583±3.232	0.814
Paliperidone		20.200±4.313	19.200±4.109	18.267±4.217	17.533±3.226	16.000±2.360	0.000
The ANOVA results indicate that at least two of the repeated measures differed significantly:							
						T0 vs T3	0.002
						T0 vs T4	0.001
						T1 vs T4	0.032
						T2 vs T4	0.028
						T3 vs T4	0.009

difference in comparing T0 vs T4 (P=0.030), and particularly in the paliperidone group (T0 vs T4: P=0.000; T0 vs T3: P=0.002; T3 vs T4: P=0.003 P - Unadjusted). In all other groups analysed with MMSE, although no statistically significant differences are highlighted, it is observed that there is a reduction of the statistical averages in each group. Finally, we have reported a trend of the data where there has been observed a gradual improvement in the overall averages until the time T3 and then observed an increase in the mean to indicate an overall worsening of cognitive symptoms.

CONCLUSIONS

In a sample of 51 inpatients with negative symptoms in schizophrenia, this study examined the cognitive changes and the role of atypical antipsychotics. Our results support the evidence of the use of simple, rapid and acceptable scales for cognitive evaluation in clinical practice. In fact, all inpatients accepted and concluded the administration of the test. Unlike most structured and comprehensive tests, but, which require a greater execution time (EUFEST, CATIE, MATRICS, BACS: 40, 90, 60, 35 minutes, respectively), those ones used in this study were simpler to administrate in daily clinical practice. It should be stressed that their use can be even more important in the group of patients suffering from negative symptoms, in patients where it was not possible to use the most complete test batteries. Several limitations in our study deserve consideration. Firstly, the sample size was small. There were more males than females. Secondly, this is an observational study conducted during the routine clinical practice in psychiatric wards and with all the influences of daily activities. Thirdly, some scales, MMSE and EpiTrack, were built to evaluate other pathologies and in particular for the latter these are no comparative studies, so far.

In conclusion, the main aim of our study has been to evaluate the possibility to use other more practical scales, in order to evaluate the effect on cognition of antipsycho-

tics in inpatients groups. For a more complete assessment, the patient may be subjected to more specific cognitive rehabilitation strategies such as remediation and compensatory approaches. These programs can improve functioning and cognitive deficits, and can lead to lasting improvements in cognition and daily functioning.

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