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MANAGEMENT OF PRIMARY NEGATIVE SYMPTOMS IN SCHIZOPHRENIA: AN ONE-YEAR OBSERVATIONAL STUDY

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SUMMARY

Negative symptoms represent a separate symptom domain, with respect to depression, neurocognition, and social cognition and have a strong direct and indirect impact on real-life functioning. Furthermore, negative symptoms that do not improve following antipsychotic treatment are an important diagnostic and therapeutic challenge. We conducted a 12-month-study open-observational study to evaluate the efficacy of some atypical antipsychotics on negative symptoms, according to the following recommendations of Consensus Development Conference Attendees. In our study, we evaluated in an open-label study the efficacy of some second-generation antipsychotics (clozapine, quetiapine, olanzapine, aripiprazole, paliperidone) in 42 patients with schizophrenia or schizoaffective disorder (DSM-5 criteria) with 'persistent negative symptoms'. We used different rating scales (PANSS, CDSs, BNSS, BPRS), but mainly we focused on the new Brief Negative Symptoms Scale (BNSS) for negative symptoms. Our total data indicate an overall statistically significant reduction in all scales, although not clinically relevant.

Key words: *negative symptoms – BNSS - schizophrenia*

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INTRODUCTION

Negative symptoms have long been recognized as a central feature of the phenomenology of schizophrenia (Kraepelin 1919, Bleuler 1908). They 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. Furthermore, negative symptoms that do not improve following antipsychotic treatment are an important diagnostic and therapeutic challenge. The presence of a significant decrease in behavioural or psychological function, including problems with motivation, social withdrawal, diminished affective responsiveness, speech and movement, contribute more to poor functional outcomes and quality of life for individuals with schizophrenia than to positive symptoms (Peralta 2014, Galderisi 2008). Effectively, negative symptom severity has been consistently linked to worse functional outcomes in schizophrenia, including specific relationships with impaired occupational functioning, household integration, social functioning, engagement in recreational activities, quality of life and finally, these symptoms lead to worse functional outcomes (Chan 2015, Strauss 2013, Rabinowitz 2012, Blanchard 2005).

PERSISTENT NEGATIVE SYMPTOMS

The current consensus definition of negative symptoms in schizophrenia includes symptoms of affective flattenig, alogia, avolition, asociality and anhedonia. Symptoms of inattention, poverty of speech, and inappropriate affect, traditionally included in some measures of negative symptoms, are seen to align more closely with clinical ratings of disorganization seen in schizophrenia (Foussias 2014). The term negative symptoms includes primary and secondary negative symptoms; the former refers to the symptoms that are intrinsic to schizophrenia, the later refers to symptoms caused by positive symptoms, affective symptoms, medication side-effects, environmental deprivation or other treatments (Ahmed 2015, Carpenter 1985). The term 'deficit symptoms' is used to refer to primary and enduring negative symptoms that represent the core aspect of a putative schizophrenia subtype (Kirkpatrick 2014, Buchanan 2007, Carpenter 1988). However, the categorization of subjects into deficit and nondeficit forms of schizophrenia may be difficult in the clinical context. The concept of persitent negative symptoms represent a broader concept than the deficit syndrome; the classification can be completed using any of the accepted and validated negative symptom scales (Galderisi 2013). 'Persistent negative symptoms' differ from deficit symptoms in several aspects. The most important differences are the duration and the severity (at least 12 months in deficit symptoms; at least six consecutive months with moderate or worse severity). "*In consequence, persistent negative symptoms identify a patient population with a clinically relevant symptomatology large enough to be targeted, selected, and studied*" (Buchanan 2007).

However, it was necessary to find assessment tools that could facilitate the study of this symptomatology. Based on these observations, in 2005 Carpenter co-chaired the Consensus Development Conference on Negative Symptoms sponsored by the US National Institute of Mental Health (Kirkpatrick 2006). The Conference resulted in a recommendation that a new instrument for quantifying negative symptoms be developed. Two instruments grew out of the recommendation: the Brief Negative Symptoms Scale (BNSS) (Kirkpatrick 2011) and the Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring 2013).

RESPONSE TO TREATMENT

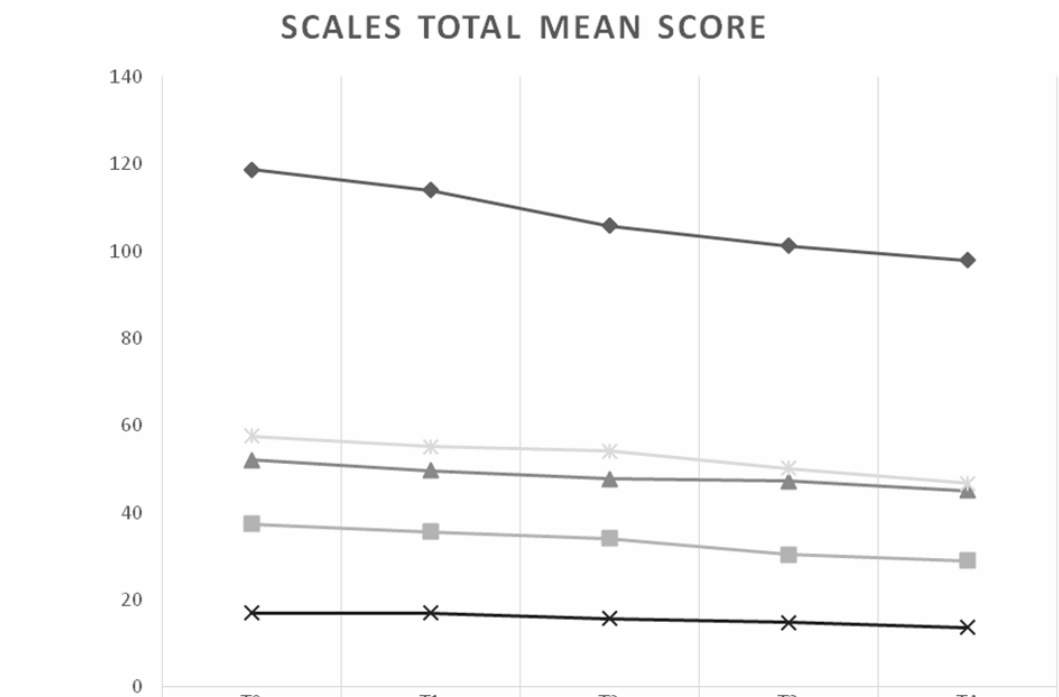
Convincing evidence is available that both old and new generation antipsychotics may act on secondary negative symptoms by removing, in part or completely, some of their causes, such as positive symptoms, depression or extrapyramidal symptoms. However, the efficacy of these drugs on primary and persistent negative symptoms has not yet been proven (Kirkpatrick 2008, Murphy 2006). There is no evidence that there is a difference between deficit and non-deficit patients in terms of the response of their positive psychotic symptoms to antipsychotics (Möller 2015). Any improvement of negative symptoms, obtained by treatment with antipsychotics, is very significant; nevertheless, there are few treatment trials focused on primary negative symptoms, and treatment of negative symptoms has remained unsatisfactory despite the advent of second generation antipsychotics (Schooler 2015, Chue 2014, Goff 2013).

PURPOSE OF THE STUDY

The aim of our study was to consider the impact of Second-Generation Antipsychotics (SGAs) in the treatment of primary negative symptoms, particularly in patients with persistent negative symptoms. While convincing evidence has been provided with the efficacy of second-generation antipsychotics on secondary negative symptoms, their impact on primary and persistent ones remains controversial (Galderisi 2008). The problem of an ambiguous interpretation of clinical trials focused on negative symptoms led to recommendations by *Consensus Development Conference Attendees* (Kirkpatrick 2006) of a specific study designed for negative symptoms. We conducted an open-observational study to evaluate the efficacy of atypical antipsychotics on negative symptoms, according to the following recommendations of *Consensus*: negative symptoms should be stable and persistent; this may be operationally defined using criteria for persistent negative symptoms (Buchanan 2007).

Table 1. Mean Scale Scores in 42 patients

	T0	T4	ANOVA (T0…Tn…T4)		
	Mean (±SD)		F	P	Eta Squared
PANSS					
Total	118.74±15.39	97.23±15.54	31.707	0.000	0.436
Clozapine	123.3±14.92	101.3±15.96	9.366	0.000	0.510
Olanzapine	118.33±6.59	105.33±8.89	8.582	0.000	0.632
Quetiapine	124.00±13.41	101.69±11.35	11.919	0.000	0.498
Paliperidone	120.67±15.81	90.50±11.11	16.678	0.000	0.769
Aripiprazole	101.14±14.82	86.14±22.81	0.291	1.321	0.180
PANSS Negative subscale					
Total	37.38±5.36	29.00±5.89	21.614	0.000	0.345
Clozapine	37.50±6.22	28.30±4.21	8.806	0.000	0.495
Olanzapine	39.17±4.177	29.00±6.11	9.647	0.000	0.659
Quetiapine	37.69±5.38	29.15±6.57	10.600	0.000	0.469
Paliperidone	34.84±5.50	31.00±6.07	0.252	0.905	0.048
Aripiprazole	37.28±6.26	28.00±7.55	5.847	0.002	0.494
BNSS					
Total	52.05±12.92	45.04±10.64	11.273	0.000	0.216
Clozapine	54.00±16.02	49.70±15.73	6.346	0.001	0.414
Olanzapine	57.67± 6.41	44.67±7.74	12.316	0.000	0.711
Quetiapine	49.54±12.21	42.92±8.92	5.010	0.002	0.295
Paliperidone	55.33±14.18	46.67±6.83	1.668	0.197	0.250
Aripiprazole	45.00±11.34	41.29±9.46	1.466	0.244	0.196
BPRS					
Total	52.05±12.92	45.05±10.64	11.273	0.000	0.216
Clozapine	54.90±16.02	49.70±15.73	6.346	0.001	0.414
Olanzapine	57.67± 6.41	44.67±7.73	12.316	0.000	0.711
Quetiapine	49.39±12.21	42.92±8.92	5.010	0.002	0.295
Paliperdidone	55.33±14.18	46.67±6.83	1.668	0.197	0.250
Aripiprazole	45.00±11.34	41.29±9.45	1.466	0.244	0.196
CDSs					
Total	16.95±3.75	13.81±2.85	15.367	0.000	0.273
Clozapine	17.70±2.67	13.00±1.49	9.496	0.000	0.513
Olanzapine	18.17±4.67	15.17±3.6	2.726	0.001	0.307
Quetiapine	17.07±3.59	14.14±2.82	5.309	0.001	0.307
Paliperdidone	14.00±4.24	12.83±4.26	1.278	0.0312	0.204
Aripiprazole	17.14±3.89	14.00±2.45	1.218	0.329	0.169



	T0	T1	T2	T3	T4
PANSS Tot	118,7380952	114,047619	105,8333333	101,2619048	97,92857143
PANSS Neg	37,38095238	35,5952381	34,14285714	30,45238095	29
BNSS	52,04761905	49,66666667	47,73809524	47,23809524	45,04761905
CDS	16,95238095	16,96875	15,78125	14,875	13,6875
BPRS	57,5952381	55,14285714	54,11904762	50,23809524	46,78571429

Figure 1. Scales Total Mean Scores in 42 Patients

METHODS USED

In this study, we evaluated in an open-label 12-month-study the efficacy of second-generation antipsychotics in 42 patients (12 females; 30 males) with schizophrenia or schizoaffective disorder (DSM-5 criteria). Inclusion criteria were at least one persistent negative symptoms of moderate or higher severity, for 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.

All patients were treated with some SGAs (clozapine; quetiapine, olanzapine; aripiprazole, paliperidone) and evaluated at baseline (T0) and after 1 (T1), 3 (T2), 6 (T3), and 12 (T4) months with following scales: Positive and Negative Syndrome Scale (PANSS) (Kay 1987) for typological and dimensional assessment; Calgary Depression Scale for Schizophrenia (CDSS) (Addington 1990) for depressive symptoms; Brief Negative Symptoms Scale (BNSS) (Kirkpatrick 2011) for negative symptoms; Brief Psychiatric Rating Scale (BPRS) (Overall 1988) for psychopathological assessment. At the baseline mean age, gender distribution, rating scale scores we collected. The overall analysis consisted of the comparison of the upper bound of the 95% confidence interval (CI) of the mean Clinical Global Impression-Improvement (CGI-I) score to 5 (no change) at the end of the study and of mean other scales of evaluation. Data were collected in excel format and evaluated by EZAanalize/Excel, version 3.0.

RESULTS

Demographic and clinical characteristics of subjects included in the present study (N=42) at baseline presented a large percentage of males (76.19%). Subjects included in the study had a PANSS mean total score of 118.74 (±SD: 15.39) and a CGI total score of 4.23 (±SD: 0.81). Total mean age was 45.64 (±SD: 11.73) years; in females: 43.75 (±SD: 11.90) years; males: 46.40 (±SD: 11.78) years. Significant data from any scales showed in following table 1 and figure 1. ANOVA results on PANSS total scores indicate that at least two of repeated measures differed significantly ($F=31.707$; $p<0.00001$). After one year (T0 vs T4) the clozapine and quetiapine and paliperidone groups showed higher significant statistically differences (respectively, $F=9.366$, 11.919, 16.678). For the BNSS, ANOVA also resulted in a significant difference in the total scores ($F=21.614$; $p<0.00005$) and more evident differences in olanzapine and clozapine groups (respectively, $F=12.316$ and 6.346). In CDSs data, the differences were less significant than in other scales. Interestingly, although not statistically significant for the small number of patients, paliperidone and aripiprazole have been shown to be effective in larger part of the scales. Data obtained with BNSS and PANSS

negative subscale show significant differences in following SGAs: clozapine; olanzapine; quetiapine. Instead, clozapine-treated patients had a significant reduction in overall PANSS negative subscale score ($F=8.806$; $p<0.00005$) and particularly in asociality and avolition subscales. Although no significant difference was found in the PANSS and BNSS total scores in paliperidone and aripiprazole groups, these antipsychotics showed significant symptoms reduction in the PANSS and BNSS alogia subscale. Finally, our total data indicate an overall statistically significant reduction in all scales, although not clinically relevant.

CONCLUSIONS

The therapeutic management of negative symptoms of schizophrenia is currently a major challenge for clinicians in psychiatry. While psychotic or positive symptoms are generally, treated effectively, cognitive and negative symptoms have been posited to play a more important role in functional recovery (Remington 2015). There are not studies that show a superiority of a drug over another. However, results emerging show that some antipsychotics act preferentially on some specific items of this complex group of symptoms. Currently pharmacological studies are focusing on new brain systems (for example, glutamatergic system (Balu 2015, Zink 2015, Iasevoli 2014, Nunes 2012), or on new augmentation therapeutic strategy (for example, with high dose creatine augmentation (Levental 2015). Beyond pharmacologic interventions, there have been some promising results for cognitive behavioural therapy for negative symptoms (Velligan 2015, Keshavan 2014). The Consensus and the subsequent international meetings have stressed the importance of relying on best instrument for therapeutic trials and the meaning of improvement in a subdomain (Marder 2011). In past decades, advances in our understanding and measurement of negative symptoms have led to important explanation and symptomatological reconceptualizations. While, before the SANS and then PANSS negative subscale have represented the most important instruments for the assessment of negative symptoms, the development of two instruments of "new generation" rating (BNSS and Cains) testifies to the growing interest in our understanding of negative symptoms (Foussias 2014).

In this small study, we used the new BNSS scale, along with other scales, to evaluate the efficacy of some SGAs on negative symptomatology. Our total data indicate an overall reduction in all scales. Reducing overall scores in each scale used is present and this is a different aspect than in previous studies. It must be underscored, however, that the data obtained may have been distorted by several variables: compliance, adherence therapy, combination with other drugs, cognitive deficit, etc. Therefore, our work represent with many critical issues a perspective observational study that it has the need to be developed and deepened.

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