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PhD THESIS

**SOCIO-COGNITIVE DEFICITS AND ASPECTS REGARDING
TREATMENT IN NEUROPSYCHIATRIC PATHOLOGY**

ABSTRACT

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Keywords: theory of mind, cognitive dysfunctions, Parkinson's disease, schizophrenia, long-acting antipsychotics, hyperprolactinemia, metabolic syndrome

1. INTRODUCTION – MOTIVATION

Socio-cognitive abilities are regarded as essential components for an effective social functioning. Social cognition is a multidimensional construct that reflects the manner in which a person processes, preserves and utilizes information about complex social relationships.

Social and cognitive impairments, often described in neuropsychiatric conditions, usually have a major negative impact on patients' quality of life, progressively leading to social isolation. In complex psychiatric disorders such as schizophrenia, schizoaffective or bipolar disorder, these deficits are most evident during acute episodes, but are also present in varying degrees during remission phases, which further diminishes patients' social rehabilitation. Studies evaluating social cognition in neurodegenerative diseases have shown significantly impaired socio-cognitive abilities in Parkinson's disease (PD), with a severely negative impact on patients' prognosis.

Nevertheless, to be able to recognize own and others' mental states requires an intact cognitive performance, mainly regarding domains such as attention, memory, language and problem solving. However, which cognitive processes have the most impact on social cognition is still for debate.

Antipsychotic medication is used for treating many psychiatric disorders, both acute and chronic psychoses. Atypical or second-generation antipsychotics introduced a new era for psychiatric pharmacology, as they were highly efficient and significantly more well tolerated, with fewer side-effects than conventional neuroleptics. In the last few years, antipsychotic treatment was again improved with the long-acting injectable (LAI) antipsychotics, exhibiting less oscillating serum concentrations and thus, affording a more "giving" administration rhythm (once or twice a month, or even every three months). However, atypical antipsychotics' secondary effects (which include metabolic, neurologic and cardiovascular disturbances), although not as frequent or severe than those of conventional neuroleptic, are still a cause for concern, as they can lead to treatment non-adherence and multiple hospital admissions.

This thesis has addressed two important topics in the neuropsychiatric field. The first objective of this research was to evaluate socio-cognitive deficits and to analyze the relationship between cognitive performance and the affective dimension of ToM in neurologic (Parkinson's disease) and psychiatric (schizophrenia, schizoaffective and bipolar disorder) pathologies, as socio-cognitive impairments are known to greatly affect patients' quality of life and independent living. The second objective was to explore two major complications following antipsychotic treatment (hyperprolactinemia and the metabolic syndrome) and the factors that can influence clinician's choice for antipsychotic medication when prescribing LAI antipsychotics. The subject of the thesis is even more important because there is not enough information about it neither regionally or worldwide in the specialized literature.

2. GENERAL PART

Social cognition refers to the ability to understand and infer others' mental states (actions, intentions, emotions, desires, beliefs), needing efficient cognitive functions.

Patients with chronic neuropsychiatric conditions tend to progressively lose this fundamental ability together with other cognitive functions, which can lead to social isolation, with a tremendous negative impact on their global functioning and quality of life.

In recent years there has been an increasing interest in studying cognitive and social deficits in non-demented patients with PD. There are studies showing impaired emotion recognition skills in patients suffering from PD, such as the capacity to recognize anger, sadness, fear, disgust. Studies focusing on theory of mind (ToM) abilities in PD have revealed, generally, deficits in the cognitive domain, impairments that evolve in a negative manner throughout PD' evolution. However, literature data regarding affective ToM in PD has yielded inconsistent results, certain authors also finding deficits in this area, whilst others not finding impairments in affective ToM abilities. When affective ToM deficits were found, they were associated with certain cognitive impairments (which regard visuospatial abilities, executive functions), apathy, and a lower quality of life.

There is evidence that in patients with schizophrenia, schizoaffective disorder and bipolar disorder, social cognition deficits, more so than neurocognition deficiencies, interfere with social and professional functioning, independence of living, as well as the development of meaningful interpersonal connections. In patients with schizophrenia, ToM deficits (cognitive and affective) are found both during the early stages, as well as throughout evolution, where are significantly associated with negative symptoms. Some studies have been suggesting that ToM deficiencies in patients with schizophrenia may be linked to deficits in several cognitive domains: attention, memory, language, and executive functions. By contrast, other researchers appear to endorse the theory that ToM is independent of other cognitive processes in patients with schizophrenia, schizoaffective and bipolar disorder.

Nowadays, psychiatrists have a multitude of antipsychotics to choose from. Their efficiency has been granted by numerous randomized and controlled multicentric clinical studies and by clinical practice. Conventional antipsychotics have a strong antagonism on dopaminergic D2 receptors, therefore being highly efficient in controlling psychotic symptomatology. But because of this strong blockade, they also generate serious side-effects such as extrapyramidal syndrome, hyperprolactinemia, cardiovascular, metabolic and cognitive impairments. By contrast, atypical antipsychotics, by antagonizing both dopaminergic and 5HT2A serotonergic receptors, lower the risk of developing extrapyramidal symptoms and hyperprolactinemia. However, the risk exists even with these improved formulations. Hyperprolactinemia is the consequence of the dopamine (DA) receptor blockade in the

tubero-infundibular pathway, which releases prolactin under the influence of DA, leading to sexual dysfunctions (amenorrhea-galactorrhea syndrome in women; gynecomastia and sexual impairments in men). Metabolic syndrome (MS) is another frequent complication of antipsychotic treatment and may lead to serious somatic complications. Studies suggest that certain antipsychotics have a higher impact on these metabolic complications (for example clozapine, olanzapine, quetiapine), other agents influence them in a minor manner (aripiprazole, risperidone), whereas most antipsychotics have a moderate effect. Nevertheless, MS and its components must be carefully monitored during the course of any antipsychotic treatment in order to prevent life-long complications.

3. SPECIAL PART

3.1 PURPOSE AND OBJECTIVES

This thesis included 5 studies, which had the following objectives:

- The first objective was to assess socio-cognitive deficits and analyze the connection between cognitive performance and the affective dimension of social cognition in neuropsychiatric pathologies. This aspect was examined in two clinical studies, one study involving patients diagnosed with PD, and another study involving patients diagnosed with schizophrenia, schizoaffective and bipolar disorder.
- The second objective of this thesis was to analyze two major complications, which can appear during antipsychotic treatment (hyperprolactinemia and the metabolic syndrome), and to identify factors that may influence physician's choice for antipsychotic medication when prescribing LAI antipsychotics. This objective was assessed in three clinical studies performed on patients suffering from chronic psychoses.

3.2 MATERIALS AND METHODS

3.2.1 The first study included 116 participants recruited from the Timisoara County Hospital (Neurology and Psychiatry Departments) and from neurologic and psychiatric ambulatories: 65 patients diagnosed with idiopathic PD and 51 healthy controls (HC) matched for gender, age and educational levels. Only subjects without somatic and psychiatric illnesses that could negatively impact on cognitive functioning, without dementia and without hearing and visual impairments were included in the study. The following neuropsychological assessment scales were used: the reading the mind in the eyes – RMET (to measure affective ToM), the Montreal Cognitive Assessment – MoCA scale (to evaluate cognitive performance and several of its sub-domains), the Brief Psychiatric Rating Expanded – BPRS-E (to assess the presence and severity of psychiatric symptomatology).

3.2.2 The second study included two samples: 37 outpatients diagnosed following ICD-10 diagnostic criteria with schizophrenia, schizoaffective disorder and bipolar disorder (with minimum 2 episodes accompanied by psychotic symptoms) in remission upon study entry (PAT sample), and 40 healthy participants, matched for gender and age (HC sample). The PAT sample included patients that were registered at “Pius Brînzeu” County Clinic Emergency Hospital, Timisoara. Exclusion criteria for both samples: a history of organic mental conditions and a history of psychoactive substance use (other than alcohol and tobacco). From the PAT sample were also excluded patients that were in the acute phase of the disorder at study entry. Psychiatric assessment: empathy was measured with the Empathy Quotient (EQ); affective ToM abilities were evaluated with RMET; cognitive performance was measured using MoCA; and the BPRS-E scale was utilized to assess any residual psychiatric symptomatology.

3.2.3 The third study included 77 outpatients diagnosed with schizophrenia and schizoaffective disorder, receiving treatment in specialized ambulatory settings from Timisoara and Cluj-Napoca. For an ensured treatment adherence, only patients receiving LAI antipsychotics for at least two months were involved in this research. For each patient the following data were collected: age, gender, age at disorder onset, the total duration of the psychosis – DP (the time interval from disorder onset to present assessment, in months), the duration of LAI treatment (the time interval of LAI treatment, in months), the duration of pre-LAI treatment (the time interval from disorder onset to LAI treatment introduction, in months), smoking habits, adjunctive medication, systolic and diastolic blood pressure. The BPRS-E scale was used to assess the presence and severity of psychiatric residual symptomatology. Fasting blood glucose, HDL cholesterol, and triglyceride serum levels were measured for each participant using the PalmLab SC-101 glucometer, and the LipidPro ILM-0001A lipid meter.

3.2.4 The fourth study included 170 inpatients with psychosis, admitted in the Timisoara Psychiatric Clinic over a period of 6 months. Participants were included randomly, as they were admitted in the psychiatric unit. Patients were diagnosed following ICD-10 criteria with: schizophrenia (F20), persistent delusional disorder (F22), acute and transient psychotic disorder (F23), schizoaffective disorder (F25), and bipolar disorder (F31) – depressive or manic episode with psychotic symptoms. The presence and intensity of psychiatric symptomatology were evaluated using the BPRS. Serum prolactin levels were measured after 2 days of hospital admittance and under antipsychotic treatment, in the morning (8:00 a.m), 12 hours after the last

dose of antipsychotic. Blood samples were processed by the Timisoara Emergency County Hospital using the activated chemo-luminescence method. To exclude renal and liver failure, liver enzymes (aspartate aminotransferase—ASAT, alanine transaminase—ALAT) and serum creatinine were also measured. Hyperprolactinemia was considered when plasma prolactin levels exceeded 25 ng/ml in women (not pregnant or lactating), and 20 ng/ml in men.

3.2.5 The fifth study included 111 outpatients treated with LAI antipsychotics (olanzapine, risperidone, paliperidone, and aripiprazole) in specialized ambulatory settings from Timisoara and Cluj-Napoca, diagnosed with schizophrenia or schizoaffective disorder, according to ICD-10 diagnostic criteria, and on LAI treatment for at least 3 months. Patients during acute episodes, pregnant or lactating, treated with oral antipsychotics, presenting severe somatic comorbidities or with hepatic/renal failure, and patients with a history of substance abuse were excluded from the study. Participants were divided into three groups according to dosage equivalence: low dosage group (LDG) – group I, middle dosage group (MDG) – group II, and high dosage group (HDG) – group III.

3.3 RESULTS

3.3.1 PD patients presented significantly lower RMET scores, MoCA total scores, MoCA sub-scores for EF (executive functions), VSA (visuospatial abilities), AT (attention) and MEM (memory), and significantly higher BPRS-E total scores, compared to HC. Significant differences were present between the PD group and HC group in the following BPRS-E specific items: somatic concerns, anxiety, depression, guilt, suicidality, self-neglect, motor retardation, and tension (symptoms of depression-anxiety syndromes). Significant differences between HC subjects, H&Y mild PD patients and H&Y moderate PD patients were observed regarding the following scale scores: BPRS-E total scores ($H=57.0$, $p<0.0001$), BPRS-E sub-scores for depression-anxiety symptoms ($H=45.29$, $p<0.0001$), RMET scores ($H=36.57$, $p<0.0001$), MoCA total scores ($H=64.71$, $p<0.0001$), MoCA sub-scores for EF ($H=15.59$, $p<0.0001$), VSA ($H=52.66$, $p<0.0001$), AT ($H=15.05$, $p=0.001$), and MEM ($H=32.35$, $p<0.0001$). MoCA total scores were significant predictors of affective ToM ($R^2=0.50$, $F=28.07$, $\beta=1.004$, $p<0.0001$), deficits in cognitive functioning predicting impairments in affective ToM. A multiple regression analysis model comprising all of the three cognitive domains with distinct influence on affective ToM (AT, EF and VSA) explained 64% of the variance and was a significant predictor of RMET scores ($F=32.004$, $p<0.0001$). The presence of disease (PD) was an independent predictor of deficits in affective ToM ($\beta=-0.27$, $p<0.0001$), but also in global cognitive performance ($\beta=-1.88$, $p=0.001$). A simple mediation test was conducted to test the impact of disease (PD) on

affective ToM abilities (RMET scores) through the mediator effect of global cognitive status (MoCA total scores). Lower MoCA total scores were significantly related to the presence of PD ($a=-4.07$; $p<0.0001$), and deficits in MoCA total scores were subsequently related to lower RMET scores ($b=1.08$; $p<0.0001$). To assess which cognitive domain might be driving this mediation, another model was next constructed, using VSA, AT and EF. The long-way mediation (PD \rightarrow AT scores \rightarrow EF scores \rightarrow VSA scores \rightarrow RMET scores) was significant (indirect effect: -0.66 , 95% CI: -1.41 ; -0.12), as was the specific path PD \rightarrow VSA scores \rightarrow RMET scores (indirect effect: -3.88 , 95% CI: -5.77 ; -2.19). The total effect of the model was significant (total effect: $c=-3.63$; $p=0.001$, 95% CI: -5.74 ; -1.51).

3.3.2 The PAT sample presented significantly lower EQ ($p=0.02$) and RMET ($p<0.0001$) scores than HC. Education had a significant influence only on RMET scores ($H=23.07$, $p<0.0001$), subjects with superior education presenting higher scores than those with medium educational levels ($p<0.0001$), and low educational levels ($p=0.04$). In both samples, female participants presented higher scores for empathy ($U=480.5$, $Z=-2.08$, $p=0.04$), and better affective ToM abilities ($U=479$, $Z=-2.09$, $p=0.04$) compared to males. In the PAT sample, no significant differences in scale scores (RMET, EQ, MoCA, BPRS-E) were found with respect to psychiatric diagnosis, the antipsychotic treatment (olanzapine, clozapine, quetiapine, risperidone, paliperidone or aripiprazole), or the associated medication for affective symptoms (mood stabilizers or antidepressants). RMET scores positively correlated with MoCA total scores ($r=0.35$, $p=0.03$) and MoCA sub-score for AT ($r=0.04$, $p=0.01$). To assess the relationship between the relationship between the psychiatric disorder, RMET and EQ scores, a logistic regression was performed. The model was statistically significant ($\chi^2=27.74$, $p<0.0001$), explaining 40% of the variance in the case of presence of the psychiatric disorder, and correctly classifying 75.3% of cases. Lower RMET scores correlated with a higher probability for the presence of a psychotic spectrum disorder ($\beta=0.25$, Wald=11.34, $p=0.001$). EQ scores ($\beta=0.02$, Wald=0.56, $p=0.45$), gender ($\beta=0.22$, Wald=0.13, $p=0.71$), age ($\beta=0.03$, Wald=1.53, $p=0.21$), and educational levels ($\beta=0.39$, Wald=0.42, $p=0.51$) had no significant contribution to the regression model.

3.3.3 A number of 45 patients (58.4%) fulfilled the criteria for MS. Patients treated with risperidone LAI, compared to patients on olanzapine LAI, presented significantly more frequent hypertension ($\chi^2=4.383$, $p=0.036$). Both their systolic ($Z=-2.716$, $p=0.007$) and diastolic ($Z=-2.517$, $p=0.012$) values were significantly higher. Although hypertensive patients were significantly older than non-hypertensive patients ($Z=-2.956$, $p=0.003$), age at study entry was not significantly different in patients on risperidone LAI than in those on olanzapine LAI. There were no significant differences between the two samples (risperidone vs. olanzapine) regarding the presence of hyperglycemia, hypo-HDL cholesterol and hypertriglyceridemia. Patients on risperidone LAI had a significantly increased abdominal circumference ($Z=-2.191$, $p=0.028$) than those on olanzapine LAI. Patients with MS presented a longer DP ($Z=-2.215$, $p=0.03$) and a longer LAI treatment duration ($Z=-4.122$, $p<0.0001$).

than patients without MS, but no significant differences were found between patients with MS and those without MS regarding pre-LAI treatment duration. Gender, age, adjunctive medication, and tobacco use did not influence the presence of the MS or its components.

3.3.4 Hyperprolactinemia was found in 120 (70.6%) participants, 80 (66.7%) females and 40 (33.3%) males. The mean increase in prolactin levels was 2.46 times the normal value in female subjects, and 1.59 times the normal values in male subjects. We found no significant association between hyperprolactinemia and antipsychotic treatment (atypical/conventional/combinations). Antipsychotic medication had no significant influence on patients' gender, age, diagnosis, or DP. Patients treated with prolactin raising antipsychotics presented significantly more frequent hyperprolactinemia than those treated with prolactin sparing antipsychotics ($p=0.004$). Patients with a DP over 10 years had significantly lower prolactin levels when compared with those with DP less than 5 years (Wilcoxon's Signed Rank test, $Z=-2.243$, $p=0.025$). Prolactin levels were not significantly different between patients with DP ranging from 5 to 10 years and those with DP less than 5 years, or over 10 years. A multivariate regression analysis including variables that might have an influence on prolactin serum levels was performed: gender, type of antipsychotic medication—prolactin sparing/raising, DP (divided into the aforementioned subgroups), BPRS total scores. Age, diagnosis, and antipsychotic category were entered as controls. The overall model was significant, $F(13;156)=3.75$, $p<0.0001$, and explained 24% of the variance. Gender, type of antipsychotic medication – prolactin sparing/raising, and DP significantly predicted prolactin serum levels when the other variables were controlled for. Female gender was associated with an increase in serum prolactin levels ($\beta=0.27$, $p<0.0001$). Prolactin sparing antipsychotics ($\beta=-0.23$, $p<0.003$) and a DP over 10 years ($\beta=-0.15$, $p=0.04$) were associated with lower prolactin levels.

3.3.5 There were no significant differences between patients treated with olanzapine, risperidone, paliperidone and aripiprazole regarding gender, age, age at disorder onset, number of smokers, number of cigarettes smoked per day, DP and pre-LAI treatment duration. Significant differences were found as regards BPRS-E scores and LAI duration treatment. The Dunn-Bonferonni post-hoc test revealed that patients on risperidone had significantly shorter a LAI treatment duration than those on paliperidone ($p<0.0001$) and aripiprazole ($p=0.04$). Patients on aripiprazole had lower BPRS-E scores than patients treated with paliperidone ($p=0.01$). Patients in the LDG – low dosage group had lower BPRS-E scores than those in MDG – middle dosage group ($p=0.04$) and HDG – high dosage group ($p=0.02$). No significant differences were observed between MDG and HDG, regardless of the antipsychotic. 69 (62.2%) patients of the entire sample received a mood stabilizer, regardless of the type of the antipsychotic. BPRS-E scores were significantly higher in patients receiving adjunctive treatment with a mood stabilizer ($U=1806.5$, $p=0.03$), regardless of the antipsychotic type. Mood stabilizers were used significantly more frequent in HDG subjects, by comparison to MDG and LDG patients ($\chi^2=10.23$, $p=0.006$).

3.4 DISCUSSIONS AND CONCLUSIONS

The thesis's objectives were entirely attained, and the positive findings were consistent with those found in the specialized literature.

3.4.1 Similar to other studies, we found that early PD patients have preserved affective ToM abilities, by contrast to moderate PD patients, which might suggest a decline in affective ToM performance throughout PD's evolution. Affective symptomatology (depression, anxiety) had no significant influence on these deficits. More important, we have demonstrated that cognitive functions mediate the relationship between affective ToM and PD, as a consequence of the combined effect of three cognitive sub-domains (attention, executive functions and visuospatial skills): PD generates attention deficiencies; an impaired attention produces negative effects on executive functions, which impact negatively on visuospatial abilities, which ultimately cause deficits in affective ToM performance. Moreover, we have shown that PD has a direct negative effect on affective ToM through visuospatial deficiencies, without the involvement of attention and executive functions.

3.4.2 In the second study, our results showed a significant impairment of empathic response and affective ToM abilities in these patients when compared to healthy controls, which is consistent with literature data. These impairments were not significantly influenced by patients' diagnosis, or medication (type of antipsychotic and adjunctive treatment). Furthermore, we found that the disorder was a significant predictor of impaired affective ToM. Affective ToM abilities were negatively impacted by symptom severity and deficits in overall cognitive performance.

3.4.3 The prevalence of metabolic syndrome (MS) in patients with schizophrenia spectrum disorders is significantly higher than that of the general population. In these patients, MS can appear as the result of a cumulus of factors, including the disorder itself (which impacts negatively on patients' everyday activities and diet) and antipsychotic treatment. In our sample, MS was present in more than half of the patients, and we found no statistically significant differences between patients treated with olanzapine LAI and risperidone LAI regarding the presence of MS. Patients with MS had a longer duration of psychosis (DP) and a LAI treatment duration, a fact that endorses the idea that MS can be considered the consequence of both the disorder and antipsychotic medication. In our patients, hyperglycemia was the only MS component significantly associated with the antipsychotic treatment.

3.4.4 By conducting a study on inpatients diagnosed with chronic psychoses, we found that the majority of these patients (70.6%) presented hyperprolactinemia, which was significantly more frequent in female participants. The increase in prolactin levels was also significantly higher in women. As

expected, the use of prolactin “sparing” antipsychotics associated with lower prolactin serum levels. Even more important, we observed that the increase in prolactin levels induced by the antipsychotic treatment depends on the duration of the disorder, with a critical change after 10 years of disorder evolution (we found a progressive decline in prolactin response after 5 years of psychosis evolution, with a major change after 10 years). According to our research, the increase in prolactin levels following the start of antipsychotic treatment may be a reliable sign of treatment resistance.

3.4.5 There are numerous factors that could influence the choice of an antipsychotic over another and its dose in clinical practice. We have found that clinical symptoms, anticipated side-effects and antipsychotic dosage were factors with significant impact regarding antipsychotic choice. Patients that presented milder clinical symptoms received more frequently antipsychotics such as aripiprazole, with a reduced profile of adverse effects, or decreased doses of the other three analyzed antipsychotics. Higher doses of antipsychotic medication and/or the addition of an adjuvant mood stabilizer were necessary to overcome treatment resistance, revealed by the presence of residual symptoms. This study reveals what actually occurs in clinical practice, where patients with serious and complex conditions or with multiple comorbidities must be managed.