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Mentalizing Skills Deficits in Schizophrenia as a Clue for Drug Choice: Clozapine Versus Other Antipsychotics on Keeping Outpatients Stable

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1. Introduction

Despite the proven the efficacy of antipsychotic drugs approximately 10-30% of all schizophrenic patients show poor response or remain resistant to antipsychotic medications, and up to an additional 30% of patients have partial responses to treatment, meaning that they exhibit improvement in psychopathology but continue to have mild to severe symptoms (Barnes, 2011; Miyamoto et al., 2005). The proportion considered to be 'treatment resistant' varies according to the criteria used (Barnes et al., 2003; Barnes, 2011: Conley and Kelly, 2001; Pantelis and Lambert, 2003). A minority (around 10%) of patients receiving conventional or atypical antipsychotics do not achieve remission even after the first episode (Crow et al., 1986; Lambert et al., 2008). More commonly, treatment resistance develops as the illness becomes progressively more unresponsive to medication (Barnes 2011; Wiersma et al., 1998). Kane et al. (1988) defined treatment refractoriness as lack of periods of good functioning for 5 years, no response to two different classes of neuroleptics and presence of moderate to severe symptomatology including positive and negative symptoms, as well as disorganized or violent/aggressive behaviour, thought disorder and suicidal ideation. Predictors associated with an unfavourable response to treatment are cognitive functioning deficits (Rabinowitz et al., 2000), poor premorbid functioning (Crespo-Facorro et al., 2007; Duñó et al., 2008), earlier age of onset (Gogtay et al., 2011), duration of untreated psychosis (Farooq et al., 2009) and male gender (Caspi et al., 2007). It remains uncertain whether treatment resistant schizophrenia should be considered simply as the more severe end of the illness spectrum or as a distinct subtype of schizophrenia for which neurocognitive markers of resistance should be explored (Barnes, 2011).

Social cognition generally refers to mental operations that underlie human transactions, including perceiving and interpreting social stimuli as well as responding to socially relevant inputs, such as dealing with intentions and behaviours of others. Theory of Mind (ToM) or mentalizing, a subdomain of social cognition, is defined as the ability to think

about people in terms of their mental states (Green et al., 2008a). The bulk of evidence has shown consistent social cognitive impairments in schizophrenia (Green et al.,2008b), that can be present at early phases (Brüne et al., 2011; Chung et al., 2008; Couture et al., 2008) and persist trough different phases of the illness (Green et al., 2011), and several reviews and meta-analysis have established that patient-control differences on mentalizing skills are large and persistent across the chronic phase of illness (Bora et al., 2009; Brüne 2005).

Clozapine is the only antipsychotic that has been found to show superior efficacy for treatment-resistant patients when compared to conventional and atypical antipsychotic drugs. Clozapine is the most effective antipsychotic for severe refractory schizophrenia (approximately 30-60% of patients who fail to respond to other antipsychotics may respond to clozapine), and moderately refractory illness (Barnes, 2011), Further, there are other important benefits with clozapine, including improvement in cognitive function (Bilder et al., 2002; Machado de Sousa and Hallak, 2002; Purdon et al., 2001), reduction in suicidality (Meltzer et al., 2003) and an anti-hostility action or improvement in persistent aggression and behavioural disturbance (Krakowski et al., 2006; Volavka and Citrome, 2008; Volavka et al., 2004). Despite of the abundance of findings about social cognitive deficits in schizophrenia, only a few reports have related these handicaps to the clinical improvement obtained with antipsychotic treatment. Mizrahi et al. (2007) and Harvey et al. (2006) offered some evidence that the atypical risperidone and olanzapine enhanced performance on particular social cognition abilities (Kee et at., 1998; Littrel et al., 2004). Accordingly, Savina and Beninger (2007) found that olanzapine and clozapine but not typical neuroleptics or risperidone may either improve ToM ability or protect against its decline, probably by restoring or improving neural activation at the mPFC. Another study in the same line carried out by Lund et al. (2002) cohered with these results. Contrary to that, Sergi et al. (2007) and Penn et al. (2009) found no differences among medications or within each medication group over time, on these measures. In remitted schizophrenics anomalies in social cognition were worse in the more severe patients (Sprong et al., 2007) and some of the abovementioned studies reported reductions of social cognitive dysfunctions with a specific antipsychotic drug. In this context, the present study attempted to determine which pharmacological treatment (conventional, atypical antipsychotics or clozapine) exhibited superior efficacy to improve ToM skills and whether the deficits on ToM might be linked with resistance to antipsychotic treatment in stable schizophrenic patients. Given that abnormalities in mentalizing are particularly severe in patients with poor premorbid adjustment (Duñó et al., 2008), and that poor premorbid adjustment is considered a factor of refractoriness to treatment, we expected to find a link between the degree of ToM deficit and an increased risk of antipsychotic drug resistance.

2. Method

Fifty-eight schizophrenic patients fulfilling diagnostic and statistical manual (DSM) IV criteria were recruited in a consecutive fashion during the years 2001–2005. Subjects who did not give their consent to participate and those with a visual or auditory disability limiting test application, neurological disease, or another chronic/acute condition that could interfere with cognitive performance were not recruited. Patients with additional DSM-IV diagnosis on Axis I/II were also not recruited. Participants showing an IQ below 70 (Blyler et al., 2000) were excluded from the study. All subjects were on clinical remission at 5 months after discharge from the Day Hospital of the Psychiatry Unit, Parc Taulí University

Hospital (Sabadell-Barcelona, Spain). Clozapine treatment was prescribed only to patients who met the criteria for antipsychotic treatment resistance (Kane et al., 1988).
The schizophrenic group was compared to a control group of forty-eight patients with no psychiatric diagnosis who had been admitted to the Orthopedics and Surgery Department of the same hospital. Control subjects were recruited at the same time as the group with schizophrenia and were matched by sex, age and educational level. The exclusion criteria for this group included a history of psychiatric disorders, the presence of psychopathology and distress at the time of the evaluation according to the three global indices of the Symptom Checklist-90-Revised scale (SCL-90-R) (Positive Symptom Total, Global Severity Index, Positive Symptom Distress Index) (Martinez-Azumendi et al., 2001) medical prescription of psychoactive drugs and an IQ score below 70 (Blyler et al., 2000). Sociodemographic factors of this group are described in Table 1.

2.1 Assessment

Patient's symptom severity was assessed with the positive and negative syndrome scale (PANSS) (Kay et al., 1987). Premorbid adjustment with the Premorbid Adjustment Scale (PAS) (Cannon-spoor et al., 1982; Silverstein et al., 2002). Four false belief ToM tasks were applied: two first-order tasks, "the cigarettes" (Happé, 1994) and "Sally and Anne" (Baron-Cohen, 1989) and two second-order tasks, "the burglar" (Happé and Frith, 1994) and "the ice-cream van" (Baron-Cohen et al., 1985). Stories were read aloud by the examiner and subjects had to listen and answer two questions. The first one (a ToM question) had to be answered on the basis of the mental state of one of the characters and concerned that character's false belief within the situation. The second one (control question) reflected the subject's comprehension of the story. These tasks were rated according to the following:

- correct ToM (task score = 1): correct answers in both ToM and control questions;
- ToM deficit (task score = 0): failure in ToM question and correct answer in control question;
- comprehension error: correct answer in ToM question and failure in control question or failure in both (data in this category omitted from the analysis).

Patients were excluded from the study if they showed comprehension errors in more than two ToM tasks. If the comprehension error was in a second-order ToM task, none of the second-order ToM tasks were considered for analysis, while first-order ones were. The same criteria were applied when comprehension errors appeared in first-order ToM tasks. Subsequently, three categorical subgroups of ToM performance were established for both first- and second-order tasks by adding up scores as follows: 0=two tasks with scores of 0 (severe ToM deficit); 1=one task scoring 1 and the other scoring 0 (low ToM performance); 2=scoring of 1 in both tasks (good ToM performance). Neurocognitive measures were grouped into several domains, from basic to high-level processing according to Nuechterlien et al. (2004) criteria: Speed processing (Trail Making Test A (TMT-A) (Reitan, 1993), Working Memory (Digit Span Backward) (Wechsler, 1999), Executive functions (Stroop Color-Word (Golden, 1994), Trail Making Test B [TMT-B] (Reitan, 1993), Block Design (Wechsler, 1999).
Antipsychotic treatment included 3 groups of drugs: conventional, atypical (olanzapine, risperidone aripiprazol) and clozapine. Drug doses for each group were converted to haloperidol equivalents (mg/day). Patients were assessed on these all measures at 5 months

after discharge from hospital, except PANSS scale, which was further administrated at start and end of hospitalization.

Long-term Follow-up: 6-10 years later these patients were contacted again through telephone calls. All were retraced except 3 who were dead, 4 who had changed address and 2 who were hospitalized. From the remaining, 21 patients refused to collaborate and 24 accepted and were re-examined. Symptom severity was assessed with the positive and negative syndrome scale (PANSS) (Kay et al., 1987) and ToM tasks were assessed applying the same tasks and methodology as stated above.

2.2 Statistical analysis

Socio-demographic data as well as neuropsychology and social cognition measures were compared in patients and controls by means of either the X^2-test (for categorical variables) or t-tests. Relations among antipsychotic treatment and haloperidol equivalents doses with PANSS scale were studied through descriptive analysis. Comparative analysis between social cognition and dosage of haloperidol equivalents were carried out through U Mann-Whitney tests. Relations between first- and second-order ToM tasks scores and antipsychotic treatment were studied by the X^2-tests. Ordinal regression models were employed to analyze the association between the results of first-order and second-order ToM tasks with socio-demographic variables, premorbid adjustment, neuropsychological scores and antipsychotic treatment as possible explanatory variables of treatment resistance. Starting with regression models including gender and PAS for social isolation, further explanatory variables were included if they significantly improved the model fit and yielded maximum R-square values. Several links for ordinal regression models were considered and those that yielded maximum R-square values were chosen. Finally, it was proved that the models for first- and second-order ToM tasks held the assumption of parallel lines (Chen and Meharry, 2004). Statistical analysis was performed with the statistical software packages SPSS, version PASW 18 version 18.0.0 and R, v. 2.11.1, in particular using the contributed package "exact RankTests" (Hothorn and Hornik, 2011). P-values below 0.05 were considered statistically significant. For the long term follow-up measures only a descriptive analysis was carried out.

3. Results

Sociodemographic and clinical data of schizophrenic patients and controls are shown in Table 1, as well as, neuropsychological and social cognition measures in Table 2. Clear differences between patients and controls appeared in independence, paternity and occupational status. Premorbid adjustment in the patients was poor, worsening from childhood into late adolescence. Patients scored significantly lower in Trail Making Test A, Stroop word-colour and Trail Making Test B. Table 3 displays changes over time in PANSS scale in relation to antipsychotic drugs and dosage haloperidol equivalents at discharge and follow-up study. Total PANSS scores improved over time in all groups. Patients on clozapine had higher scores at each PANSS subscales at baseline and lesser scores at the end of assessment. At the long-term follow-up these scores in general decreased slightly, being more pronounced for atypical and clozapine. First- and second-order ToM tasks performance relations to mean dosage of haloperidol equivalents are shown in Table 4. Dosage haloperidol equivalents were inferior in category 2 on both measures.

	Schizophrenia group (N=58)	Control group (N=48)	p-value
Males	41 (70.7%)	36 (75.0%)	
Age	31.4 (8.1)	33.9 (8.6)	
Years of education =< 8 years	42 (72.4%)	37 (77.1%)	
Living with own family	15 (25.9%)	35 (72.9%)	**χ^2=23.336; p<0.001**
Children	8 (13.8%)	26 (54.2%)	**χ^2=19.650; p<0.001**
Employed	12 (20.7%)	41 (85.4%)	**χ^2=44.014; p<0.001**
Age of illness onset	21.6 (4.9)		
Psychiatric diagnosis (DSM-IV)			
Paranoid schizophrenia	39 (67.2%)		
Non-paranoid schizophrenia	8 (13.7%)		
Schizofreniform disorder	6 (10.3%)		
Schizoaffective disorder	5 (8.6%)		
Global activity (DSM-IV)	61.6 (11.7)		
SCL-90-R[1]			
Positive Symptom Total		24.9 (11.2)	
Global Severity Index		0.27 (0.12)	
Positive Symptom Distress Index		1.19 (0.20)	
PAS			
Childhood	0.27 (0.2)		
Early adolescence	0.39 (0.2)		
Late adolescence	0.44 (0.2)		
Years of illness evolution	9.6 (7.7)		
Drugs			
Mean dose haloperidol equivalents (mg/day)	8.7 (7.3)		
Conventional antipsychotic	**14 (24.1%)**		
Atypical antipsychotic	**35 (60.3%)**		
Mixed antipsychotic	**6 (10.3%)**		
Clozapine[2]	**17 (29.3%)**		
None[3]	**3 (5.2%)**		
Anticholinergic	**8 (13.8%)**		
Antidepressant	**15 (25.9%)**		

Results are presented as mean (standard deviation) in case of continuous variables and as frequency (%) in case of categorical variables. Gender, age, and educational level were matching variables; hence, no statistical tests for comparison are applied.
[1] Mean normative values: Positive Symptom Total, 25.32 (SD: 14.3); Global Severity Index, 0.51 (0.36); Positive Symptom Distress Index, 1.75 (0.48).
[2] Patients on clozapine from the total 35 on atypical antipsychotics.
[3] At evaluation, 5 months after discharge.
DSM-IV-Diagnostic and Statistical Manual Disorders, Fourth Edition;
SCL-90-R-Symptom Checlist-90-Revised; PANSS=Positive and Negative Syndrome Scale.

Table 1. Sociodemographic and clinical characteristics of study cohort

Figure 1a and 1b display relations between antipsychotic drugs and performance of first-order ToM tasks at discharge and follow-up respectively: 78.6% of patients performed correctly at discharge, with a slight non-significant advantage for atypical drugs, whereas 83% performed right, with a moderate advantage for clozapine at follow-up. Figure 2a and 2b display antipsychotic drugs and performance of second-order ToM tasks at discharge and follow-up: 63.9% of patients performed correctly at discharge, with a slight non-significant advantage for atypical drugs, whereas 79.2% performed right, with moderate advantage for clozapine at follow-up study. Tables 5a and 5b show the variables included in the ordinal regression models for first- and second-order ToM tasks, respectively. The negative sign of the regression coefficients corresponding to premorbid adjustment (PAS social isolation) in both models indicates a negative relationship between that variable and the outcome. That is, ordinal regression analysis revealed a main association between deficits in first-order and second-order ToM tasks both with poor social premorbid adjustment (social isolation). In first-order ToM tasks, deficits were also related to poor performance on Trail Making Test B. The test showed the highest significant association between second-order ToM tasks with block design, males and clozapine treatment. R-square values amounted to 0,300 and 0.657, respectively. No association was found between first-order ToM tasks with variables of treatment resistance, whereas second-order ToM tasks deficits were linked to factors of unfavourable response to treatment.

	Schizophrenia group (N=58)	**Control group (N=48)**	**p-value**
Neuropsychological measures			
General cognition abilities			
Intelligence Quotient	96.8 (19.2)	104.1(19.5)	t=-1.918: p=0.060
Speed of processing			
Trail Making Test A	43.1 (16.8)	30.9(10.1)	**t=4.333; p=0.000**
Working Memory			
Digit span backward	5.5 (1.1.9)	5.3(1.7)	t=0.708 p=0.481
Executive function			
Stroop word color	36.1 (11.2)	42.3 (10.7)	**t=-2833; p=0.006**
Trail Making Test B	106.9 (51.9)	84.8 (27.3)	**t= 2.829; p=0.01**
Block design	40.6 (11.9)	44.1 (11.6)	t=-1504; p=0.136
Social cognition measures			
ToM category			
First order			
0	11.8%	0%	**χ^2=12602; p=0.002**
1	11.8%	0%	
2	76.5%	100%	
Second order			
0	11.5%	4.%	**χ^2=6917; p=0.031**
1	26.9%	10.6%	
2	61.5%	85.1%	

Results are presented as mean (standard deviation) in case of continuous variables and as frequency (%) in case of categorical variables

Table 2. Neuropsychology and social cognition measures of study cohort

PANSS	Conventional	Atypical	Clozapine
POSITIVE **Main measures**			
Hospitalization starts	20.9(4.9)	15.2(7.2)	22.8 (6.6)
Hospitalization ends	13.8(3.9)	10.5(4.7)	13.1 (4.1)
5 month after discharge	12.0(3.9)	10.2(3.7)	13.7 (4.3)
Follow-up	12.8(3.9)	10.6(3.1)	10.6(4.9)
NEGATIVE **Main measures**			
Hospitalization starts	21.9(9.5)	28.7(10.4)	27.4 (13.5)
Hospitalization ends	13.8(4.0)	10.5(4.7)	13.1 (4.1)
5 month after discharge	18.5(7.4)	18.8(10.8)	14.1 (10.5)
Follow-up	19.0(12.3)	11.7(6.9)	13.4(6.1)
GENERAL **Main measures**			
Hospitalization starts	43.2(9.5)	46.5(10.5)	48.9(8.3)
Hospitalization ends	33.7 (5.7)	34.6(12.8)	31.8(8.9)
5 month after discharge	34.1 (8.0)	31.6(9.7)	30.4(10.1)
Follow-up	27.2(9.5)	26.0(12.0)	25.9(8.3)
TOTAL **Main measures**			
Hospitalization starts	88.0(19.2)	90.4(19.3)	97.7(23.9)
Hospitalization ends	66.9 (11.9)	62.9(22.2)	66.5(13.2)
5 month after discharge	65.1 (15.1)	61.1(18.8)	58.1(22.7)
Follow-up	59.0(24.5)	48.3(18.5)	49.9(13.3)
DOSE HALOPERIDOL equivalents (mg/day)			
Main measures	13.2 (8.4)	4.3 (2.4)	10.3 (6.6)
Long term Follow-up	17.6 (5.4)	8.3 (7.3)	13.2 (7.5)

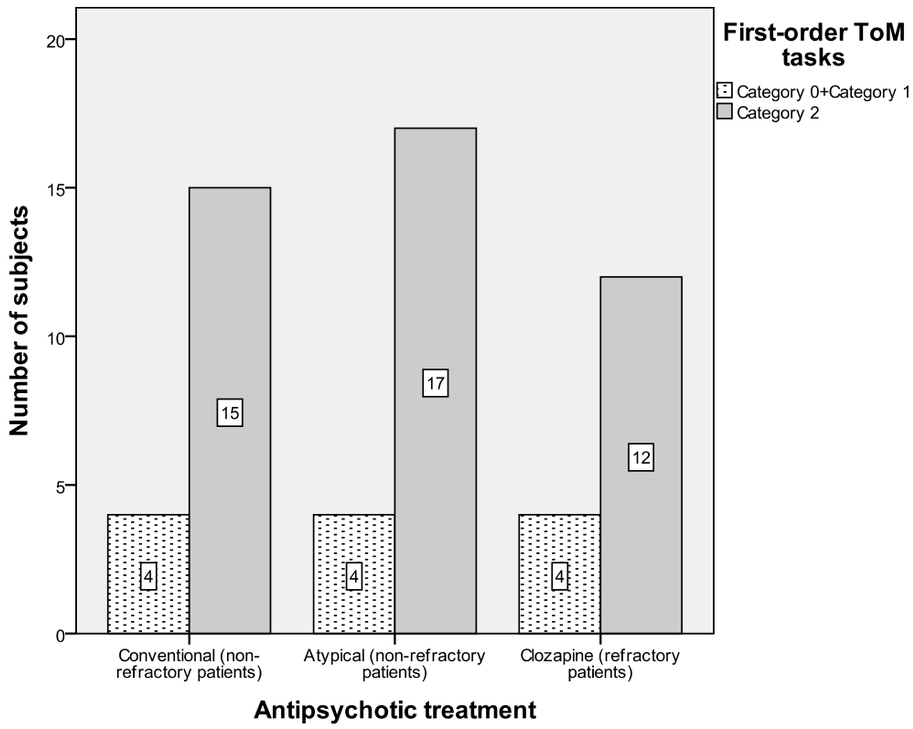
Results presented as mean (standard deviation). For Main measures N=58: Conventional N=19; Atypical N=21; Clozapine N=16; A Follow-up N= 24: Conventional N=5; Atypical N=7; Clozapine N=12

Table 3. PANSS changes over time in relation to antipsychotic medication and dose of haloperidol equivalents (mg/day) in schizophrenics patients

ToM Tasks	Discharge N=58	Follow-up N=24
First-Order ToM Tasks		
Category 0 + Category 1	(N=12) 11.9 (8.0)	(N=4) 14.3 (8.3)
Category 2	(N=46) 7.3 (6.7)	(N=20) 13.2 (8.1)
p value	**U=190.500 p=0.009***	
Second-order ToM Tasks		
Category 0+ Category 1	(N=20) 10.4 (7.1)	(N=5) 17.8 (5.1)
Category 2	(N=38) 7.5 (7.4)	(N=19) 13.3 (8.4)
p value	**U=276.000 p=0.052**	

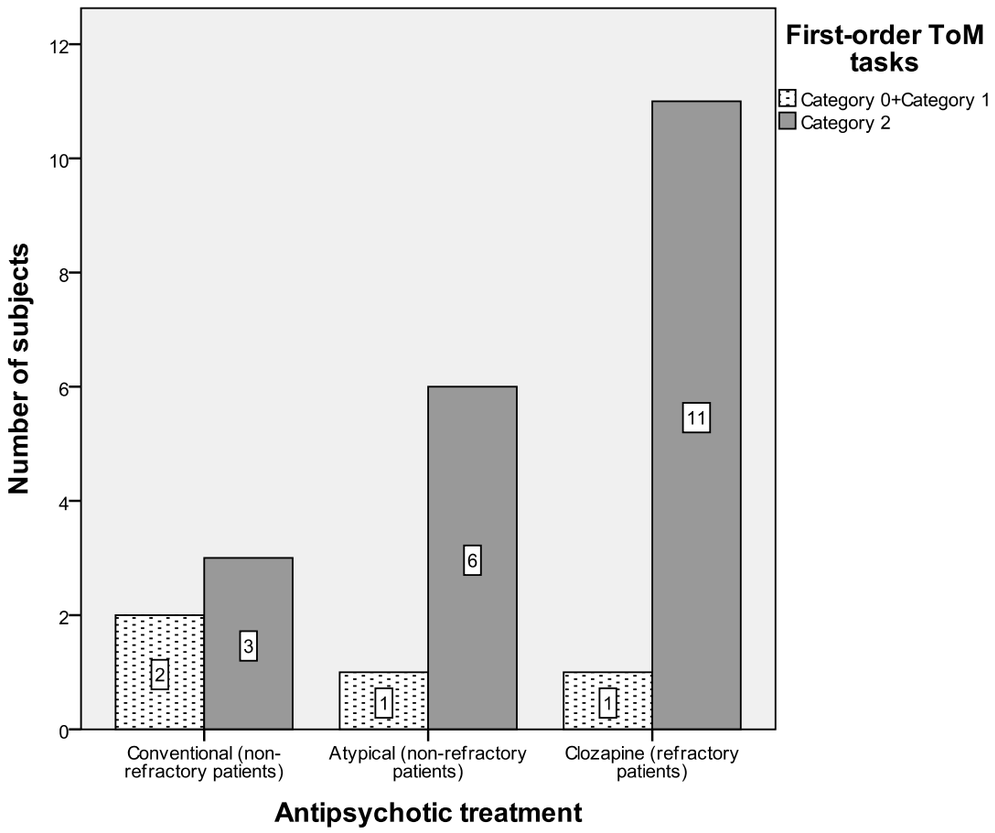
Results are presented as mean (standard deviation) of mean dosage of haloperidol equivalents. Analysis of distribution between ToM tasks categories with mean dosage of haloperidol at discharge were carried out with the Mann-Whitney test; *p<0.05 level of significance

Table 4. Relations between first- and second-order ToM tasks performance and mean dosage of haloperidol equivalents at discharge and follow-up of the schizophrenia group



*Conventional (non-refractory patients): mixed antipsychotic group is included within this group. Percentage of good performance at ToM tasks were: conventional 26.8%, atypical 30.4% and clozapine 21.4%; (X^2=0.194; p=0.908).

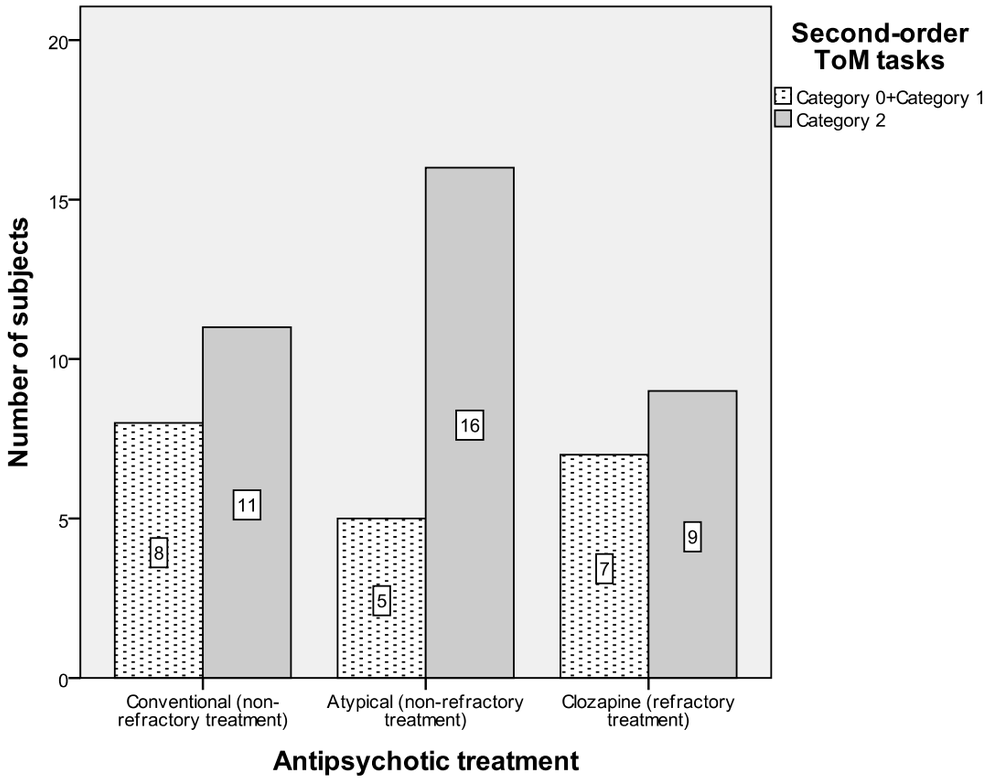
(a)



*Conventional (non-refractory patients): mixed antipsychotic group is included within this group. Percentage of good performance at ToM tasks were: conventional 12.5%, atypical 25.0% and clozapine 45.8%.

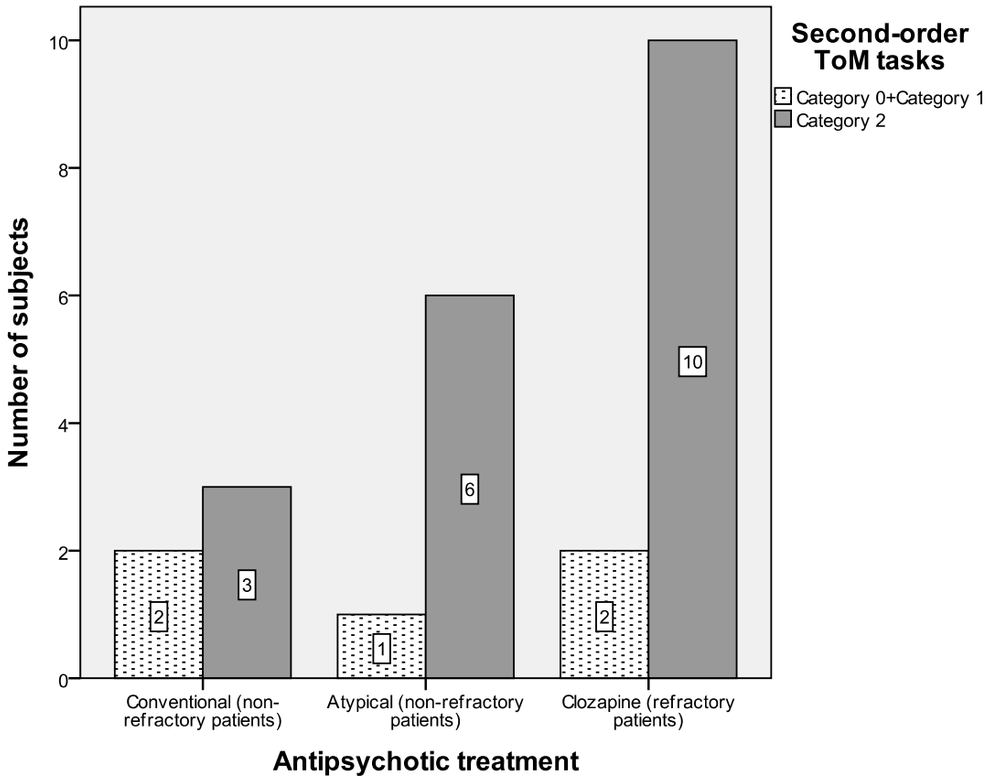
(b)

Fig. 1. (a) Antipsychotic treatment type and first-order ToM tasks at discharge study
(b) Antipsychotic treatment type and first-order ToM tasks at the long term follow-up in a subsample of the schizophrenia patients



*Conventional (non-refractory patients): mixed antipsychotic group is included within this group. Percentage of good performance ToM tasks were: conventional 19.1%, atypical 28.6% and clozapine 16.1% ; (X^2=2.084; p=0.353)

(a)



*Conventional (non-refractory patients): mixed antipsychotic group is included within this group. Percentage of good performance ToM tasks were: conventional 12.5%, atypical 25.0% and clozapine 41.7%.

(b)

Fig. 2. (a) Antipsychotic treatment type and second-order ToM tasks at discharge study
(b) Antipsychotic treatment type and second-order ToM tasks at the long term follow-up in a subsample of the schizophrenia patients

	Regression coefficient	95% Confidence interval	p-value
Threshold [ToM1 = 0]	-3.225	(-4.700; -1.750)	<0.001
Threshold [ToM1 = 0]	-2.667	(-4.057; -1.278)	<0.001
PAS: Social isolation	-1.990	(-3.754; -0.227)	0.027
Trail B	-0.009	(-0.016; -0.001)	0.026
Males	-0.385	(-1.357; 0.586)	0.586

The link function applied was the probit link. Pseudos R-square values amounted to: 0.224 (Cox and Snell); 0.300 (Nagelkerke); and 0.184 (McFadden).

Table 5a. Regression coefficients of an ordinal model to explore the relative weight of first order ToM tasks at predicting treatment resistance factors including premorbid adjustment (social isolation), trail B and gender as explanatory variables

	Regression coefficient	95% Confidence interval	p-value
Threshold [ToM2 = 0]	-5.975	(-12.251; 0.300)	0.062
Threshold [ToM2 = 0]	-0.317	(-4.673; 4.040)	0.887
PAS: Social isolation	-14.003	(-26.340; -1.666)	0.026
Blocks design	0.291	(0.033; 0.549)	0.027
Clozapine	-3.379	(-6.734; -0.025)	0.048
Males	-5.580	(-10.775; -0.385)	0.035

The link function applied was the Cauchy link. Pseudos R-square values amounted to: 0.551 (Cox and Snell); 0.657 (Nagelkerke); and 0.440 (McFadden).

Table 5b. Regression coefficients of an ordinal model to explore the relative weight of second-order ToM tasks at predicting treatment resistance factors including premorbid adjustment (social isolation), blocks design, clozapine and gender as explanatory variables

4. Discussion

This study identified distinctive responses on ToM performance with different antipsychotic medications in stable schizophrenics: initially patients responded relatively better with atypical antipsychotics in contrast to clozapine and conventional agents. Nevertheless, over time clozapine provided some hints of better restoration of mentalizing abilities than other antipsychotics agents. Also, the findings confirmed predictors of unfavourable response to antipsychotic treatment in patients with poor mentalizing deficits. These predictors include male gender, social isolation (poor premorbid adjustment), low performance in block design and receiving clozapine treatment at start higher severity. That constellation of factors characterized a well-studied subgroup of patients having a poor prognosis. Cohering with previous findings, the present sample of stabilized schizophrenia outpatients showed difficulties across diverse interpersonal functions in contrast to healthy controls: they were mainly less independent, with no children, and either unemployed or disabled. Decreased premorbid adjustment across age epochs in which full-blown schizophrenia symptoms appear has also been found in other studies (Strous et al., 2004; Vourdas et al., 2003). Schizophrenic patients performed worse than control group on both first and second order

ToM tasks, without differences in intelligence quotient measures. Regarding the links between ToM performance and antipsychotic medication, the results showed drug's positive effects on mentalizing abilities with a tendency to increase over the years in the restricted subsample re-examined at follow-up meaning perhaps that the deficits in social cognitive abilities were relatively restored over the long-term. After discharge the patients who had been prescribed atypical antipsychotic drugs displayed a modest superiority on mentalizing skills in contrast with those receiving conventional antipsychotic or clozapine. Almost a decade later, in the follow-up, clozapine showed a modest trend of better efficacy, despìte that at least a fraction of those patients were highly resistant to treatment and showed deep second-order mentalizing handicaps when first studied at the start of the study.This trend may cohered with Savina and Berninger (2007) findings, showing that clozapine (and olanzapine) improves ToM abilities due to the enhancement of mPFC function, although they measured that over the short-term. Dosage of antipsychotic was lower in patients with good performance on mentalizing skills, indicating less illness severity.

The accumulating evidence suggests that improvement in cognitive function might be expected to follow reduction of psychotic symptoms, with differences between antipsychotics at improving cognitive performance, being rather modest and never normalizing cognitive function (Barnes, 2011; Lieberman et al., 2005). Also, the literature suggests a parallel path for both atypical antipsychotics in non-resistant patients and clozapine in resistant ones at improving psychosis and cognition deficits (O'Carroll, 2000; Keefe and Fenton, 2007). It is worth noting that clozapine treatment remains as one of the most effective for schizophrenia and consensus treatment guidelines from a wide range of prominent expert panels specify that (APA, 2004; Goodwin et al., 2009; NICE, 2010), recommending its use after the failure of 2 adequate trials with other antipsychotics, including an atypical one, to get adequate response or in patients with persistent suicidal gestures or ideation. So it would be desirable to introduce clozapine in appropriate time and dosages (Joober and Boksa, 2010), to improve social cognitive abilities as well as to enhance pro-social function (Toua et al., 2010; Möller et al., 2011).

Concerning disease state at baseline, before treatment commencement, it is important to highlight that second-order ToM tasks deficits disclosed well-characterized factors related with poor prognosis: male gender, (Caspi et al., 2007), poor premorbid functioning (Duñó et al., 2008; Strous et al., 2004) and executive functioning deficits, specifically planning and coordination dysfunction (Béchard-Evans et al., 2010; Koelkebeck et al., 2010; Rabinowitz et al., 2000), together with particular drug regimes (clozapine) required to achieve a quick clinical stabilization (Barnes, 2011). Severe deficits in social cognition have been repeatedly shown along these factors (Duñó et al., 2008; Montreuil et al., 2010; Schenkel et al., 2005; Uhlhaas and Silverstein 2005). It is interesting to note that mentalizing deficits had not been previously described as a predictor factor of poor response to treatment. Therefore it is important to note that refractory responses to drug treatment ought to be expected in patients with poor mentalizing skills especially if they are accompanied with these factors of poor outcome.

This study had obvious limitations. The ToM tasks employed, although widely used in the literature, have not been fully validated. The study characterized a substantial homogeneous sample, but at the long term follow-up study half of the sample did not accept to collaborate

again thus restricting the weight of those results. In conclusion, our findings reflect beneficial effects of antipsychotic agents at restoring ToM ability, especially clozapine, in a sample of stabilized schizophrenics. Also we found second-order ToM tasks deficits as a predictor factor of poor response to antipsychotic treatment together with others well described in the literature: male gender, poor premorbid adjustment, executive dysfunctions (coordination-planning) and clozapine at baseline (higher clinical severity).

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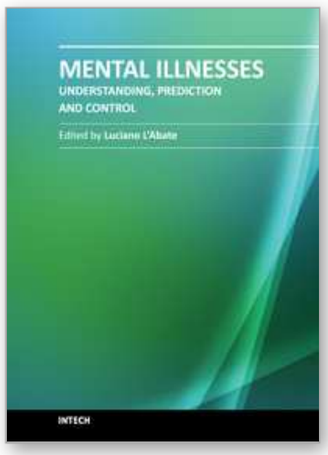

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In the book "Mental Illnesses - Understanding, Prediction and Control" attention is devoted to the many background factors that are present in understanding public attitudes, immigration, stigma, and competencies surrounding mental illness. Various etiological and pathogenic factors, starting with adhesion molecules at one level and ending with abuse and maltreatment in childhood and youth at another level that are related to mental illness, include personality disorders that sit between mental health and illness. If we really understand the nature of mental illness then we should be able to not only predict but perhaps even to control it irrespective of the type of mental illness in question but also the degree of severity of the illness in order to allow us to predict their long-term outcome and begin to reduce its influence and costs to society. How can we integrate theory, research evidence, and specific ways to deal with mental illness? An attempt will be made in the last conclusive chapter of this volume.

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