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Antipsychotic response in delusional disorder and schizophrenia: a prospective cohort study

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Introduction. Scientific evidence focused on the treatment response in delusional disorder (DD) patients is scarce, and the findings are controversial. Our goal was to compare the antipsychotic response at the 12-week follow-up between patients diagnosed with DD and patients diagnosed with schizophrenia and to identify potential response dimensions.

Methods. A prospective, observational, cohort study with 12-week follow-up was conducted with DD and schizophrenia patients matched for sex, age and cumulative years of disease. The following scales were assessed: Positive and Negative Syndrome Scale (PANSS; 5-factors), Personal and Social Performance Scale (PSP), Clinical Global Impression Scale (CGI), and Columbia-Suicide Severity Rating Scale (C-SSRS). Treatment response was defined as a $\geq 30\%$ reduction in the total PANSS score. Linear and logistic regression models were used to investigate the potential predictive value of psychopathological variables for the antipsychotic response.

Results. Response percentages in DD and schizophrenia were 61.5% and 69.2%, respectively. The duration of untreated psychosis, antipsychotic dosage, and diagnosis did not predict antipsychotic response. In the whole sample, improvement in positive symptoms was significantly associated with the clinical global improvement ($p=0.006$), explaining almost 20% of the variance in the model. Within the DD group, improvement in cognitive symptoms explained 30% of the variance in clinical global improvement.

Conclusions. Both response percentages and required antipsychotic doses were similar between DD and schizophrenia. Changes in positive symptoms were associated with clinical global improvement in the entire sample, and improvement in cognitive symptoms was correlated with global improvement exclusively in DD.

Keywords: Antipsychotics, Antipsychotic response, Delusional disorder, Schizophrenia, Plasma levels

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Respuesta antipsicótica en trastorno delirante y esquizofrenia: estudio prospectivo de cohortes

Introducción. La evidencia científica centrada en la respuesta terapéutica en pacientes con trastorno delirante (TD) es escasa, y los hallazgos contradictorios. Nuestro objetivo fue comparar la respuesta antipsicótica a las 12 semanas en pacientes con TD y esquizofrenia, e identificar potenciales dimensiones de respuesta.

Metodología. Se llevó a cabo un estudio prospectivo, observacional, de cohortes de 12 semanas de seguimiento en pacientes con TD y esquizofrenia, apareados por sexo, edad y años de evolución. Se administraron las siguientes escalas: Escala de los Síndromes Positivo y Negativo (PANSS; 5-factores), Funcionamiento Social y Personal (PSP), Impresión Clínica Global (CGI) y Escala Columbia de Severidad Suicida (C-SSRS). La respuesta al tratamiento fue definida como una reducción en puntuación total de PANSS $\geq 30\%$. Se realizaron análisis de Regresión Lineal y Regresión Logística para investigar el valor predictivo de los dominios psicopatológicos sobre la respuesta antipsicótica.

Resultados. Los porcentajes de respuesta en TD y esquizofrenia fueron 61,5% y 69,2% respectivamente. La duración de la psicosis no tratada, la dosis antipsicótica y el diagnóstico no predijeron la respuesta antipsicótica. En la muestra total, la reducción de síntomas positivos se asoció de forma significativa a una mejoría clínica global ($p=0.006$).

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dando cuenta de hasta un 20% de la varianza del modelo. En la submuestra de pacientes con TD, la mejoría en síntomas cognitivos se asoció a la mejoría en impresión clínica global llegando a explicar un 30% de su varianza ($p=0.030$).

Conclusiones. Tanto los porcentajes de respuesta como las dosis antipsicóticas fueron similares en el TD y en la esquizofrenia. El cambio en síntomas positivos se asoció a mejoría clínica global en la muestra total, y el cambio en síntomas cognitivos se correlacionó con la impresión clínica global exclusivamente en el TD.

Palabras clave: Antipsicóticos, Respuesta antipsicótica, Trastorno delirante, Esquizofrenia, Niveles plasmáticos

INTRODUCTION

For many decades, delusional disorder (DD) has been considered a difficult disorder to treat, showing high rates of treatment resistance. Specifically, the lack of adherence to drug therapy is considered a core feature of the disorder.^{1,2}

Scientific evidence focused on the treatment response in patients with DD is scarce, and the reported findings are contradictory. Munro and Mok³ were the first authors who reviewed the available literature published between 1961 and 1994. The authors analyzed 209 cases of DD and reported detailed findings regarding relationships with some aspects of treatment, and they concluded that DD is a disease with an acceptable and good prognosis when treated adequately.

Subsequently, Manschreck and Khan² reviewed the available evidence on the therapeutic response published between 1994 and 2004 and identified 134 new cases. The authors highlighted that depressive disorders were the comorbid psychiatric disorders most frequently found, medication adherence was uncommonly reported, and response to drug therapies was shown in at least 50% of the cases.

Lepping et al.⁴ carried out a systematic review focused on antipsychotic treatment of delusional parasitosis, selecting those cases with primary delusional parasitosis (DD, somatic type) and excluding cases of delusional parasitosis related to other causes. The authors concluded that despite the lack of controlled clinical trials, antipsychotics are useful and effective drugs for the treatment of delusional parasitosis; however, second-generation antipsychotics would be more effective for secondary delusional parasitosis patients compared with patients diagnosed with primary delusional parasitosis. The antipsychotic response to risperidone and olanzapine was reported in close to 70% of the cases.^{5,6}

Mews and Quante⁷ conducted a retrospective case series of DD and a review of the literature focused on the effectiveness and acceptability of psychoactive drugs in these patients. Consistent with the aforementioned reviews, the authors found that DD has a moderate prognosis, and the lack of adherence to medication was one of the most common reasons associated with a poor response to medication. For this reason, recent studies show that DD patients treated with long-acting injectable antipsychotics show higher attendance rates for outpatient appointments and a lower rate of prescriptions for other psychotropic drugs; hence, these drugs might be useful in the treatment of DD.⁸

Given the inconsistency of the reported results and the psychopathological complexity of the disorder, recent reviews⁹⁻¹¹ emphasize that antipsychotic drugs are the first line treatment in DD. For the lack of a clinical response to antipsychotics, it was recommended to identify the existence of other medical conditions, comorbid substance abuse disorders or the presence of other comorbid psychiatric disorders, while also considering treatment with other therapies to enhance the therapeutic efficacy.

In an attempt to investigate the psychopathological structure in patients with DD, Serretti et al.¹² identified four factors or domains: depressive symptoms, non-prominent hallucinations, delusions and irritability. These findings are in line with de Portugal et al.¹³, who identified four psychopathological dimensions using a factor analysis of the PANSS, including paranoid, cognitive, schizoid and affective dimensions, with each of the dimensions associated with different clinical features. Additionally, when focusing on the study of psychopathological dimensions in psychotic spectrum disorders, a recent study published by the same team^{14,15} reported that a dimensional model was useful to explain the differences and similarities among DD, schizophrenia and schizoaffective disorder.

With regard to the treatment of DD with non-prominent hallucinations, a recent study showed that these patients show a better response to long-acting injectable treatments compared to patients without non-prominent hallucinatory phenomena consistent with the content of delusions.¹⁶

Following these investigations, González-Rodríguez et al.¹⁷ recently proposed a decision-making model focused on different psychopathological dimensions that may be present in DD. This model is based on the aforementioned studies¹²⁻¹⁵, integrates the different dimensions of the disorder (e.g., pure or paranoid, affective, cognitive, aggressive and suicidal behaviours) and suggests the association of different therapies with antipsychotic treatments based on the prominent and identified psychopathological dimensions.

When searching for comparative studies including patients with schizophrenia and DD¹⁸⁻²⁰, most of the studies

were focused on neurocognitive performance. A recent study showed that patients with DD have lower scores for cognitive functions compared to healthy controls^{21,22} and these patients also showed deficits in cognitive functioning when compared to patients with schizophrenia.

Another clinically significant dimension described in patients with DD is the affective domain^{23,24}. Recent studies report a high frequency of comorbid affective disorders in this population^{23,24}, as well as low rates of antidepressant prescriptions, which have shown a moderate efficacy in DD, especially when combined with antipsychotics.

Another premise reported in the literature is that patients with DD show a poor compliance to treatment and poor adherence to psychiatric appointments, a fact that would contribute to the difficulty in elucidating response percentages in these patients. The available studies so far have tried to assess adherence to medication indirectly, using medical records, letters and questionnaires to patients²⁵. To our knowledge, however, no study has obtained plasma levels of antipsychotics in DD with the aim of monitoring treatment compliance in these patients.

Despite the increasing interest in the effectiveness of treatment strategies for this disorder, no study to date has compared the medium-term antipsychotic response in patients with DD and schizophrenia, and no study has compared the impact of these treatments in different psychopathological dimensions in both disorders.

Thus, our main objective was to compare the antipsychotic response after 12 weeks of treatment in patients with DD and schizophrenia and to identify the potential response dimensions. As our second objective, we aimed to compare the response percentages between both disorders and to investigate the impact of antipsychotic treatment on functionality in these patients by monitoring compliance to treatment by means of antipsychotic plasma levels.

METHODS

Participants and study design

A prospective, observational, cohort study with 12-week follow-up was conducted. Two different cohorts of patients were defined. The first group included patients with delusional disorder (DD) who initiated an antipsychotic treatment for the first time or after discontinuation of a previous treatment. The second group included schizophrenia patients who were consecutively selected during the same period of time in our Schizophrenia Unit and initiated an antipsychotic treatment. Schizophrenia patients were

matched on sex, age and cumulative years of disease with DD patients. Diagnoses were established according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)²⁶. Inclusion criteria for the study were as follows: aged 18 years or older and a diagnosis of DD or schizophrenia. Patients with a previous diagnosis of mental retardation or organic psychosis were excluded.

Adequate medication compliance was recorded by monitoring plasma levels of antipsychotics at 4 weeks follow-up. The determinations were performed in the laboratory of Pharmacology and Toxicology at the Service of Biochemistry and Molecular Genetics at our center using high-resolution liquid chromatography (HPLC/DAD).

Plasma concentrations of the following antipsychotics were analyzed: risperidone, paliperidone (9-OH risperidone), olanzapine and desmethyl olanzapine, quetiapine, risperidone long-acting injection, paliperidone palmitate (9-OH risperidone), aripiprazole and dehydroaripiprazole, ziprasidone, clozapine and norclozapine, and haloperidol. Measurement of antipsychotic plasma levels allowed us to confirm the compliance or non-compliance of patients to antipsychotic medications, which was a variable of interest as it lets to the discussion of more reliable findings focusing on the antipsychotic response.

The study was approved by the Ethics Committee of our hospital and all patients provided written informed consent to participate.

Variables and assessment instruments

Sociodemographic and clinical variables were registered at the time of study inclusion. The sociodemographic data included the following: age, sex, marital status, educational level, employment status. The clinical variables included the following: diagnosis, age at onset of disorder, cumulated years of disease, duration of untreated psychosis (DUP), number of previous episodes, number of previous admissions, and other clinical variables.

Doses of prescribed antipsychotics were expressed in equivalent doses of olanzapine²⁷. The present study has an observational design; therefore, patients received the treatment prescribed by the clinician in charge of their case.

The following psychometric instruments were assessed at baseline and after 12 weeks of follow-up: the Positive and Negative Syndrome Scale (PANSS)²⁸ for the assessment of psychotic symptoms, Personal and Social Performance Scale (PSP)^{29,30} to evaluate functionality, Clinical Global Impression Scale (CGI)³¹, and Columbia Suicide Severity Rating Scale (C-SSRS)³².

The PANSS scale is one of the most commonly used psychometric instruments for the assessment of psychotic symptoms in patients with schizophrenia. It is an observer-rated scale composed of 30 items that are grouped into three factors: positive syndrome (7 items), negative syndrome (7 items) and general psychopathology (16 items). The PANSS has been considered a useful instrument for the assessment of changes in psychotic symptoms in studies focused on antipsychotic response. Particularly, in this study, we applied the 5 factors of the PANSS derived from the van der Gaag model³³ with the main aim of investigating five psychopathological dimensions in both cohorts of patients (i.e., DD, schizophrenia). This model consists of the following factors: positive, negative, excitement, depressive/anxiety and cognitive.

The PSP scale is a valid and reliable instrument used to evaluate personal and social functioning in patients with schizophrenia. It consists of four sub-dimensions or domains: patient self-care, usual social activities including work and study, personal and social relationships, and disturbing and aggressive behaviours. In a second step, the scores of the four domains are added to obtain a total score ranging from zero to one hundred. A higher score in the PSP scale indicates a better overall performance.

The CGI scale for Schizophrenia (CGI-SCH) is used for evaluating the severity of a patients' psychopathology and the degree of change related to treatment during the progression of the disease. It is a useful and reliable observer-rated instrument formed by two components: I. Scale of Severity of Illness and II. Improvement Scale. Both components are composed of five subscales: positive, negative, depressive, cognitive and global. Both scales include a coded system of responses based on a 7-point Likert scale; in the first component, (I) 1 means normal and 7 extremely ill, and in the second component (II), 1 means very much improved and 7, very much worse.

The C-SSRS is an assessment observer-rated scale designed to evaluate suicidal ideation, the severity of suicidal ideation and the assessment of the presence of suicidal behaviour. In the first section, 5 items of suicidal ideation are measured: wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods (not plan) without intent to act, active suicidal ideation with some intent to act, without specific plan, and active suicidal ideation with specific plan and intent. In a further step, the frequency of suicidal ideation, duration, controllability, deterrents and reasons for ideations are assessed, and an overall score of severity is given. The higher the score, the greater is the severity of suicidal ideation. Finally, the presence of actual attempts, interrupted attempts, and aborted attempts are assessed, at baseline and at endpoint.

Outcome variables

Outcome variables included changes in scores of the assessment scales and the original subscales of the PANSS, CGI, PSP and severity of suicidal ideation using the C-SSRS scale. Changes in the PANSS scale were defined as the mean differences from baseline scores and scores at the 12-week follow-up. Changes in the PSP scale were defined as the mean difference from baseline scores and scores at the 12-week follow-up, whereas changes in the CGI scale was measured using the improvement/degree of change component of this scale. Treatment response was defined as a reduction in PANSS score $\geq 30\%$.³⁴

Statistical analysis

Statistical analysis was performed by using IBM SPSS Statistics, version 19 (SPSS, Chicago, IL). The mean differences from baseline scores and endpoint scores were calculated for all scales and subscales. Due to the non-normal distribution found for the continuous variables, comparisons of the mean differences between both cohorts were conducted by means of the Mann-Whitney U test. In a second step, comparisons among the responders' proportions were performed using the chi-squared test.

With the aim of investigating the relationship between clinical global improvement and different psychopathological dimensions (i.e., positive, negative, excitement, depressive and cognitive), and controlling for potential confounding factors, multiple linear regression was used to examine the entire sample and the DD and schizophrenia subgroups. In these three analyses, the scores for the CGI global subscale served as dependent variables, and DUP, olanzapine equivalent doses and mean changes in the 5 subscales of PANSS were covariates/potential predictive factors.

To investigate the effect of potential confounding variables and the diagnosis on the percentage of responses (Yes/No responses), binary logistic regression models were calculated with the percentage of response as the dependent variable, DUP and olanzapine equivalent doses as continuous variables, and diagnosis (i.e., TD vs. schizophrenia) as a categorical covariate.

RESULTS

Baseline sociodemographic and clinical characteristics between diagnostic groups

Fifty-four patients were included in the study. Twenty-seven had a delusional disorder (DD) and 27 were diagnosed

with schizophrenia. After 12 weeks, 2 patients were lost at follow-up due to non-adherence to the protocol, including 1 patient with DD and one patient with schizophrenia.

Baseline sociodemographic, clinical and psychopathological variables in the whole sample according to diagnosis are shown in table 1.

In the univariate analyses, no statistically significant differences were found at baseline between the groups with regard to marital status, employment status or educational level. Regarding clinical variables, at the time of the study inclusion, no statistically significant variables were found in terms of the age at onset of the disorder and duration of untreated psychosis (DUP). Neither group included the cumulative years of disease; therefore, the cumulative years of disease were controlled by matching both cohorts.

Further, the number of previous admissions, number of previous psychotic episodes, the presence of lifetime suicide attempts, and number of suicide attempts at follow-up did not differ between DD and schizophrenia patients.

At baseline, schizophrenia patients compared to DD patients had higher scores for the negative symptoms as measured by the negative subscale of the PANSS ($p < 0.001$) and the subscale CGI-negative symptoms ($p < 0.001$), even after controlling for the cumulative years of disorder. DD patients had a higher severity for the clinical global impression (CGI-global) ($p = 0.006$) and lower scores in cognitive symptoms (CGI) ($p = 0.003$) than the schizophrenia group.

Comparisons of the assessment scale scores between diagnostic groups after 12 weeks

The percentage of antipsychotic responses at 12 weeks and changes in the assessment instrument scores for the whole sample and diagnostic groups are presented in Table 2.

One patient with DD (1.9%) and one patient with schizophrenia (1.9%) were lost at follow-up. The 12-week assessment was completed for 52 patients ($n = 26$ DD, $n = 26$ schizophrenia).

Twenty-four patients with DD (88.9%) and 21 patients with schizophrenia (80.8) received antipsychotic treatment in monotherapy. No statistically significant differences were found between the diagnostic groups regarding the number of prescribed antipsychotics ($p = 0.467$). Schizophrenia patients had higher changes in the PANSS-negative symptoms ($p = 0.041$) than DD patients. However, no statistically significant differences were found between groups in terms of the mean changes in scores for the PANSS total scale, CGI global subscale, PSP, and subscales of the PANSS, CGI and PANSS.

Many DD patients (61.5%) were responders (reduction PANSS $\geq 30\%$), as well as 69.2% of the schizophrenia patients. No statistically significant differences were found between the diagnostic groups with regard to the percentage of responses and the required antipsychotic doses expressed as olanzapine equivalent doses.

Antipsychotic plasma levels

In the whole sample, most of the antipsychotic plasma concentrations were obtained, except for pimozide and trifluoperazine. The DD patient who was lost at follow-up had quetiapine concentrations below the detection limit (quetiapine < 11 ng/mL); other DD patients also had risperidone and 9-OH risperidone concentrations below the detection limit (Risperidone < 0.5 ng/mL; Hydroxy-risperidone < 0.5 ng/mL).

As the present study had an observational/naturalistic design, patients received antipsychotic treatments that were prescribed by the clinician in charge of their case. Therefore, given the different detection limits of the various atypical antipsychotics, antipsychotic plasma levels could not be compared between diagnostic groups (i.e., DD, schizophrenia).

Linear Regression Model. Correlations between Clinical Global Impression and Scores for PANSS Subscales

Linear regression analysis was conducted to investigate the predictive value of the mean changes in the PANSS subscales (i.e., positive, negative, excitement, depressive and cognitive) on the clinical global impression. Moreover, the moderating effect of DUP and antipsychotic doses expressed in olanzapine equivalent doses were tested (Table 3).

In the whole sample ($N = 52$), improvement in the psychotic symptoms (PANSS positive) was significantly associated with global clinical improvement ($p = 0.006$), explaining almost 20% of the variance in the model. Further, a weak correlation between changes in the scores for the PANSS cognitive subscale and the clinical global impression was found ($p = 0.035$), which explained 13% of the variance in the entire model.

Within the subgroup of patients with DD ($n = 26$), the improvement in scores for the PANSS cognitive subscale was significantly associated ($p = 0.030$) with improvement in the clinical global impression, explaining 30% of the variance in the model.

Within the subgroup of schizophrenia patients ($n = 26$), improvement in scores for the PANSS positive subscale ($p = 0.043$) was correlated with an improvement in the clinical

Table 1 Sociodemographic, clinical characteristics and scores of the assessment scales at baseline (N=54)

Variables	Whole sample N=54	Delusional disorder N=27	Schizophrenia N=27	Statistics
<i>Sociodemographics</i>				
Age, mean (SD)	60.1 (10.08)	60.96 (10.78)	59.22 (9.45)	U=331.5, Z=-0.572, p=0.567
Women, n (%)	40 (74.1)	20 (74.1)	20 (74.1)	P=1, FET
Marital status, n (%)				$\chi^2=0.869$, df=4, p=0.929
Married/Partner	15 (27.78)	8 (29.6)	7 (25.93)	
Separated	3 (5.56)	1 (3.7)	2 (7.41)	
Widowed	6 (11.11)	3 (11.1)	3 (11.1)	
Divorced	3 (5.56)	1 (3.7)	2 (7.41)	
Single	27 (50)	14 (51.9)	12 (44.4)	
Employment status, n (%)				$\chi^2=5.765$, df=5, p=0.330
Employed	9 (16.67)	5 (18.5)	4 (14.81)	
Unemployed	3 (5.56)	1 (3.7)	2 (7.41)	
Retired	17 (31.48)	11 (40.7)	6 (11.11)	
Disabled	23 (42.59)	9 (33.3)	14 (51.86)	
Family caregiver	1 (1.9)	1 (3.7)	0 (0)	
Trainer	1 (1.9)	0 (0)	1 (3.7)	
Educational level, n (%)				$\chi^2=11.928$, df=4, p=0.563
Illiterate	0 (0)	0 (0)	0 (0)	
No studies	1 (1.9)	1 (3.7)	0 (0)	
Primary	16 (29.63)	5 (18.5)	11 (40.74)	
Secondary	17 (31.48)	6 (22.2)	11 (40.74)	
Trained	13 (24.1)	8 (29.6)	5 (18.5)	
Graduate	7 (12.96)	7 (25.9)	0 (0)	
Doctoral degree	0 (0)	0 (0)	0 (0)	
<i>Clinical</i>				
Age at onset, mean (SD)	44.34 (13.65)	47.59 (14.17)	40.96 (12.48)	U=258.5, Z=-1.647, p=0.100
Duration of untreated psychosis (DUP), mean(SD)	3.91 (6.83)	4.7 (8.53)	3.02 (4.23)	U=299.5, Z=-0.466, p=0.641
Cumulated years disorder, mean (SD)	15.47 (12.27)	13.36 (11.3)	17.65 (13.06)	U=278.5, Z=-1.291, p=0.197
Time without treatment, months (SD)	0.85 (0.88)	0.93 (0.96)	0.78 (0.96)	U=340.5, Z=-0.443, p=0.658
N. admissions, mean (SD)	1.79 (2.51)	1.30 (1.54)	2.32 (3.21)	U=272.5, Z=-0.460, p=0.219
N. previous episodes, mean (SD)	3.06 (2.59)	2.37 (1.74)	3.80 (3.14)	U=233.5, Z=-1.947, p=0.052
Previous suicide attempt, n (%)	15 (27.78)	8 (29.6)	7 (35)	P=1, FET
N. suicide attempts, mean (SD)	0.36 (0.98)	0.22 (0.69)	0.50 (1.21)	U=331.5, Z=-0.572, p=0.567
<i>Scores in assessment scales (SD)</i>				
PANSS positive	29.64 (4.89)	30.19 (4.82)	29.14 (4.99)	U=336.5, Z=-0.478, p=0.633
PANSS negative	36 (7.96)	31.96 (5.41)	39.75 (8.19)	U=160.5, Z=-3.528, p=0.000*
PANSS excitement	27.8 (5.06)	26.69 (3.72)	28.82 (5.93)	U=334.5, Z=-0.277, p=0.782
PANSS depressive	19.07 (3.71)	19.42 (3.32)	18.75 (4.07)	U=310.5, Z=-0.932, p=0.351
PANSS cognitive	16.74 (3.07)	16.38 (2.86)	17.07 (3.27)	U=330.5, Z=-0.584, p=0.559
PANSS total	90.68 (12.6)	88.11 (9.62)	93.35 (14.81)	U=269, Z=-1.460, p=0.144
PSP total	49.23 (13.53)	49.52 (12.05)	48.92 (15.16)	U=327.5, Z=-0.419, p=0.676
CGI positive	5.40 (1.23)	5.89 (1.086)	4.88 (1.18)	U=191, Z=-2.944, p=0.003*
CGI negative	3.34 (1.4)	2.59 (1.15)	4.12 (1.21)	U=135, Z=-3.938, p<0.001*
CGI depressive	3.32 (1.43)	3.26 (1.32)	3.38 (1.55)	U=346, Z=-0.091, p=0.927
CGI cognitive	3.09 (1.08)	2.78 (1.09)	3.42 (0.99)	U=233, Z=-2.176, p=0.030*
CGI global severity	5.09 (1.1)	5.52 (0.94)	4.65 (1.09)	U=202.5, Z=-2.77, p=0.006*
C-SSRS, intensity of suicidal ideation	5.47 (8.05)	6.11 (8.3)	4.81 (7.88)	U=328.5, Z=-0.460, p=0.646
SD: Standard Deviation; N: Number; PANSS: Positive and Negative Syndrome Scale; PSP: Personal and Social Performance Scale; CGI: Clinical Global Impression Scale; C-SSRS: Columbia Suicide Severity Rating Scale. *p<0.05				

Table 2	Comparison of percentages of response at 12 weeks (PANSS ≥ 30) and differences in scores of the assessment scales by diagnostic groups			
Variables	Whole sample N=52	Delusional disorder N=26	Schizophrenia N=26	Statistics
Olanzapine equivalent doses AP, mean (SD)	11.70 (9.7)	9.26 (7.09)	14.24 (11.39)	U=259, Z=-1.645, p=0.100
Responders, n (%)	34 (65.4)	16 (61.5)	18 (69.2)	P=0.771; FET
<i>Differences in scores of the assessment scales, mean (SD)</i>				
PANSS positive	11.09 (3.8)	10.84 (3.6)	11.32 (4.04)	U=316.5, Z=-0.600, p=0.549
PANSS negative	10.51 (5.85)	8.36 (4.76)	12.43 (6.14)	U=235.5, Z=-2.047, p=0.041*
PANSS excitement	10.19 (5.57)	9.24 (4.37)	11.04 (6.41)	U=300.5, Z=-0.884, p=0.377
PANSS depressive	4.36 (4.38)	4.64 (3.55)	4.10 (5.07)	U=322, Z=-0.500, p=0.617
PANSS cognitive	1.87 (3.39)	2.2 (3.11)	1.57 (3.66)	U=328.5, Z=-0.385, p=0.700
PANSS total	30.50 (11.79)	27.77 (7.88)	33.23 (14.35)	U=255, Z=-1.520, p=0.129
PSP total	23.06 (11.83)	22.46 (12.25)	23.65 (11.61)	U=320, Z=-0.330, p=0.742
CGI positive	1.81 (0.56)	1.81 (0.49)	1.81 (0.63)	U=333, Z=-0.109, p=0.913
CGI negative	2.67 (0.90)	2.50 (0.81)	2.50 (0.81)	U=261, Z=-1.496, p=0.135
CGI depressive	2.29 (1.07)	2.38 (1.02)	2.19 (1.13)	U=298, Z=-0.763, p=0.445
CGI cognitive	2.87 (0.84)	3 (0.94)	2.73 (0.72)	U=269.5, Z=-1.341, p=0.180
CGI global severity	2.10 (0.66)	1.96 (0.6)	2.87 (0.84)	U=264, Z=-1.512, p=0.131
AP: Antipsychotic; SD: Standard Deviation; FET: Fisher's Exact Test; N: Number; PANSS: Positive and Negative Syndrome Scale; PSP: Personal and Social Performance Scale; CGI: Clinical Global Impression Scale; C-SSRS: Columbia Suicide Severity Rating Scale; U: U Mann-Whitney test.				

Table 3	Multiple Linear Regression Model between Clinical Global Impression (CGI) and of the PANSS Subscale Scores					
Whole sample (N=52)			Delusional disorder (n=26)		Schizophrenia (n=26)	
			Percentage of response		Percentage of response	
Change scores	Standardized coefficient	p	Standardized coefficient	p	Standardized coefficient	p
PANSS positive	-0.398	0.006*	-0.339	0.092	0.034	0.043*
PANSS negative	0.065	0.659	0.095	0.649	-0.016	0.941
PANSS excitement	-0.215	0.138	-0.269	0.194	-0.234	0.281
PANSS depressive	-0.120	0.419	-0.164	0.450	-0.097	0.662
PANSS cognitive	-0.299	0.035*	-0.435	0.030*	-0.225	0.304
The model was corrected by duration of untreated psychosis (DUP) and olanzapine equivalent doses. * p<0.05						

global impression, which explained 20% of the variance in the model.

Binary Logistic Regression Model. Variables Associated with Percentage of Antipsychotic Response between Cohorts

As the main goal was to investigate whether the two cohorts differed in their percentages of antipsychotic responses, a binary logistic regression model was used by

including the response percentage as the dependent variable (Response/Non-response), DUP and olanzapine equivalent doses as the continuous covariates, and diagnosis as the potential categorical predictor.

The model did not identify any variable as a predictor of the percentage of the antipsychotic response. Thus, DUP and olanzapine equivalent doses and diagnosis were not found to be predictors of treatment response.

The variables used in the equation for the logistic regression model are shown in Table 4.

Table 4

Logistic Regression Analyses. Variables in the equation associated with Percentage of Antipsychotic response

	B	S.E.	Wald	df	Sig.	Exp (B)
DUP	-0.010	0.043	0.058	1	0.810	0.990
Olanzapine equivalent	-0.003	0.034	0.009	1	0.924	0.997
Diagnosis (DD vs. Schizophrenia)	-0.628	0.649	0.938	1	0.333	0.534
Constant	1.178	0.719	2.685	1	0.101	3.249

* p<0.05

DISCUSSION

The main goal of this study was to compare antipsychotic response after 12 weeks of treatment between delusional disorder (DD) and schizophrenia patients and to compare the response percentages between cohorts. Further, we aimed to investigate the relationship between clinical global impression and improvement in different psychopathological dimensions because no study has compared antipsychotic response in the medium term between these patients.

The percentages of antipsychotic response in DD and schizophrenia were similar at the 12-week follow-up. Sixty-nine percent of patients with schizophrenia were responders (reduction PANSS $\geq 30\%$), whereas 61.5% of patients diagnosed with DD had a clinical response according to the aforementioned criteria. In a second step, a binary logistic regression analysis was conducted to identify whether DUP, antipsychotic doses or diagnosis were predictors for the percentage of antipsychotic response. This analysis showed that no aforementioned variables (even diagnosis) predicted the percentage of response, and therefore, it was confirmed that antipsychotic response did not differ between cohorts. These findings are in contrast with previous reviews that reported an antipsychotic response in 50% of patients with DD², but they are consistent with a systematic review published by Freudenmann and Lepping⁵, who focused on delusional parasitosis and reported an antipsychotic response ranging from 60 to 100%.

In our study, no statistically significant differences were found between DD and schizophrenia patients with regard to required antipsychotic doses expressed in terms of olanzapine equivalent doses, which are findings that contrast with the review conducted by Freudenmann and Lepping⁵. The authors reported that patients with DD, somatic type, required lower doses of antipsychotics compared to schizophrenia patients who presented a delusional parasitosis. However, findings of the aforementioned study are not representative of our sample, and it was not possible to reliably compare the reported findings.

The percentages of antipsychotic response in DD and required antipsychotic doses in our study support the hypothesis that DD is a disorder with a reasonably good response to antipsychotics³ when treated adequately. In our sample pimozide was not the antipsychotic most commonly prescribed, hence it was not the antipsychotic which showed the best antipsychotic response.

A recent review⁷ highlighted that one of the factors most frequently associated with a poor prognosis in DD is the lack of adherence and compliance to antipsychotic medications. For this reason, in our study, antipsychotic plasma levels were determined at the 4-week follow-up to obtain an objective monitoring of treatment compliance. In two cases (2/27) of DD patients, antipsychotic plasma levels were lower than the lower limit of detection. One of the patients was lost at follow-up, and the second was assessed at the endpoint despite that non-compliance to treatment was suspected. Thus, the degree of compliance with medication was higher than expected.

These findings are in line with a recent observational study focused on adherence to medication in patients diagnosed with DD somatic type²⁵. The authors reported that two out of 51 patients included in the study showed non-adherence to medication; therefore, most of the patients were compliant. However, few studies regarding DD, excluding DD somatic type, have reported compliance with medication based on monitoring antipsychotic plasma levels.

In the present study, we compared the mean differences in scores for the assessment scales between cohorts, which were matched by sex, age and cumulative years of disorder. Consistent with this matching of variables, DD and schizophrenia patients did not differ in terms of age at onset of the disorder and cumulative years of disease, which would be in contrast with the available literature reporting that DD patients had a later onset^{1,2}.

Schizophrenia patients showed a greater improvement in negative symptoms when compared to DD patients, which

is in agreement with the dimensional model of schizophrenia¹⁴ and the findings reported by Marneros et al.¹⁸, who found that relevant negative symptoms may appear in schizophrenia but are seldom in DD patients. While the existence of the negative domain in schizophrenia is a well-established fact, few studies investigating the efficacy of antipsychotics in the treatment of the primary negative symptoms are available. The consensus of the World Federation of Societies of Biological Psychiatry (WFSBP)³⁵ emphasizes that the vast majority of studies include patients with prominent positive symptoms and few patients suffering from prominent negative symptoms. Our study supports the notion that the negative dimension would be a potential domain for treatment response in schizophrenia patients.

In a second step, we investigated the potential predictive value of improvement in different symptomatic domains on changes in clinical global impression at the end of the study, while controlling for DUP and olanzapine equivalent doses. The relationship between improvements in different psychopathological domains (i.e., PANSS positive, negative, excitement, depressive and cognitive) and clinical global impression was analyzed in the whole sample and separately in both cohorts.

Particularly, in the whole sample, improvement in positive symptoms was significantly associated with global clinical improvement, explaining almost 20% of the variance in the model. These findings are in line with a recent study that identified positive symptoms as psychopathological dimensions explaining differences and similarities between the diagnostic groups, which may be included in the psychosis spectrum¹⁴.

Within the DD group, improvement in cognitive symptoms was significantly associated with clinical global improvement by means of the CGI scale. These findings support the hypothesis that cognitive symptoms may be a specific psychopathological domain present in DD. Particularly, Muñoz-Negro et al.¹⁴ identified the cognitive domain as one of the potential dimensions of the psychosis continuum, and de Portugal et al.¹³ clinically validated the cognitive domain as a present psychopathological dimension in a more accurate conceptualization of DD. Our results, on the other hand, not only support the presence of the cognitive domain in DD, they also show a relationship between global clinical improvement and improvement in cognitive symptoms. Overall, we consider of special interest that other therapies for the treatment of DD should associate the main aim of improving the cognitive dimension³⁶.

Further, our findings are in agreement with previous studies^{37,38} that reported a correlation between scores for the CGI and PANSS scales, which indicates an overlap between these two psychometric instruments in detecting

changes in psychotic symptoms. Thus, these results seem to be replicated in our sample formed by DD and schizophrenia patients.

Limitations and strengths

Several limitations in our study should be mentioned. For instance, the small sample size in our sample could have limited the statistical power of the statistical comparisons. We carried out a prospective, longitudinal, cohort study by including DD and schizophrenia patients, which were matched by age, sex and cumulated years of disorder. The small sample size is also a result of the sample homogeneity determined by the inclusion criteria, and the fact that DD patients often initiate the disorder in the fourth decade of life, which is in contrast with schizophrenia patients who show a later onset of the disorder. Our study has an observational, naturalistic design in which patients received antipsychotic medication because of purely clinical criteria, and correlations between antipsychotic response and specific treatment could not be established.

However, our study has strengths that should be mentioned. First, this is a prospective, observational, cohort study reflecting clinical practice that allows the comparison of antipsychotic response between two groups of psychotic patients who was controlled for age, sex and cumulative years of the disorder. To ensure adequate compliance with treatment, antipsychotic plasma levels were obtained in both groups. These findings were discussed in depth with members from the Biochemistry and Molecular Genetics Service at our center, and comparisons of antipsychotic doses were expressed in olanzapine bioequivalent doses, which were determined by procedures encountered in recent studies. Another strength was that the psychometric assessment instruments we used are validated and adapted to our population and show a good correlation with measurements of change in the antipsychotic response.

CONCLUSIONS

The percentages of antipsychotic response in the medium term (12 weeks) in DD and schizophrenia were similar in our sample, and no significant differences between groups were found regarding the required antipsychotic doses. These findings support the hypothesis that DD is a disorder that shows a good response when adequately treated and with compliance of medication; DD is not associated with a lack of response or the clinical course of the disorder. In the whole sample, global clinical improvement (CGI) was associated with higher changes in positive symptoms as measured by the PANSS scale, which has shown sensitivity in detecting changes in schizophrenia and DD patients. Within the DD

group, improvements in clinical impression were explained in part by an improvement in cognitive symptoms measured by the PANSS-cognitive factor. Thus, when treating these groups of patients (i.e., DD and schizophrenia), the observer-rated therapeutic response should be considered in each of the different psychopathological domains.

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CONFLICTS OF INTEREST

Miquel Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, Boehringer, Eli Lilly, Ferrer, Forum Pharmaceuticals, Janssen-Cilag, Lundbeck, Otsuka, Pfizer. Alexandre González-Rodríguez has received honoraria or has been paid for travels from Pfizer, Janssen, and Ferrer. Rosa Catalán has received honoraria or has been paid for travels from Lilly, Lundbeck, Janssen, Ferrer, Pfizer, and Bristol. Rafael Penadés has received honoraria or been paid for travels from Otsuka-Lundbeck. The remaining authors report no other conflicts of interest in this work.

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