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Knowledge of the treatment in schizophrenia and schizoaffective disorder and its relationship with nonadherence

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ABSTRACT

Background and objectives. Despite its potential importance for adherence, knowledge of the treatment has been little studied in patients with psychosis. We performed this study to assess the possible association between knowledge of the treatment and nonadherence, unintentional nonadherence (UNA) and intentional nonadherence (INA).

Methods. We assessed 106 consecutively admitted patients diagnosed with schizophrenia or schizoaffective disorder. Evaluations were carried out during hospitalization and after six-months of follow-up. This included sociodemographic, clinical, psychopathologic variables and those related to treatment. Adherence was interpreted as the concurrence of adherence to antipsychotic treatment and adherence to outpatient follow-up over the course of the six-month period. We established two subtypes according to the main reason for nonadherence: unintentional and intentional nonadherence.

Results. Inadequate knowledge of the treatment was detected in 45.3% of patients. Adherent patients, as compared to nonadherent patients, showed no difference regarding knowledge of the treatment (median 77 vs. 77, respectively; $p = 0.232$). Nevertheless, UNA patients showed worse knowledge of the treatment as compared to adherent patients (median 62 vs. 77 respectively; $p < 0.001$), whereas INA patients showed better knowledge of the treatment as compared to adherent patients (median 86 vs. 77, respectively; $p = 0.026$).

Conclusions. A large number of patients with schizophrenia or schizoaffective disorder did not have an appropriate knowledge of their treatment. More importantly, our results suggest that inadequate knowledge of the treatment may contribute to nonadherence in patients with unintentional nonadherence.

Keywords. Knowledge; Adherence; Schizophrenia; Intentional nonadherence; Unintentional nonadherence

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CONOCIMIENTO DEL TRATAMIENTO EN ESQUIZOFRENIA Y TRASTORNO ESQUIZOAFECTIVO Y SU RELACIÓN CON LA NO ADHERENCIA

RESUMEN

Introducción. El conocimiento del tratamiento ha sido escasamente estudiado en pacientes con psicosis, a pesar de su potencial importancia para la adherencia. Evaluamos la posible asociación entre el conocimiento del tratamiento y la no adherencia, no adherencia no intencional (NANI) y no adherencia intencional (NAI).

Metodología. Se incluyeron 106 pacientes con diagnóstico de esquizofrenia o trastorno esquizoafectivo que ingresaron consecutivamente. Las evaluaciones se realizaron durante la hospitalización y a los seis meses de seguimiento. Se incluyeron variables sociodemográficas, clínicas, psicopatológicas y relacionadas con el tratamiento. La adherencia se definió como la concurrencia de adherencia al tratamiento antipsicótico y adherencia al seguimiento ambulatorio durante ese periodo de seis meses. Establecimos dos subtipos de no adherencia dependiendo del motivo principal de no adherencia: NANI y NAI.

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Resultados. El 45,3% de los pacientes mostraron un inadecuado conocimiento del tratamiento. Los pacientes adherentes, comparados con los no adherentes, no mostraron diferencias en el conocimiento del tratamiento (mediana 77 vs. 77, respectivamente; p = 0,232). Sin embargo, los pacientes NANI presentaron peor conocimiento del tratamiento comparados con los pacientes adherentes (mediana 62 vs. 77 respectivamente; p < 0,001), mientras que los pacientes NAI presentaron mejor conocimiento del tratamiento comparados con los pacientes adherentes (mediana 86 vs. 77, respectivamente; p = 0,026).

Conclusión. Un alto porcentaje de los pacientes con esquizofrenia y trastorno esquizoafectivo no tienen un adecuado conocimiento del tratamiento. Además, nuestros resultados sugieren que un inadecuado conocimiento del tratamiento puede contribuir a la no adherencia en pacientes con no adherencia no intencional.

Palabras clave. Conocimiento; Adherencia; Esquizofrenia; No adherencia intencional; No adherencia no intencional

INTRODUCTION

Nonadherence in schizophrenia is still a common phenomenon, approximately 40% to 50%.[1,2] Unfortunately, there are still not many predictive factors of note.[3] Thus far, the most consistent risk factors for nonadherence include previous nonadherence, poor awareness, negative attitude towards treatment and substance abuse.[1,3-6]

The heterogeneity of findings related to several risk factors for nonadherence[3] may be attributable to some major factors. First, most available studies have methodologic limitations, such as the absence of a valid assessment method[3,7] or a cross-sectional design.[1,3] Moreover, only recently has there been expert consensus providing a conceptual and operative definition of adherence.[2] Second, the scarcity of consistently identified correlates[3] could also be due to real heterogeneity among nonadherent patients. Thus, the existence of two main subtypes according to intentionality has been hypothesized,[7-11] and we recently supported this hypothesis in a study specifically designed to test it.[12] Third, some variables remain understudied.[3]

Knowledge of the treatment has been studied little in psychosis patients. Some studies are descriptive.[13-15] One study explored the demographic correlates of knowledge about prescribed antipsychotics,[16] another study explored the demographic correlates of knowledge regarding diagnosis and treatment,[17] and two further studies explored both the characteristics and the relationship with nonadherence.[18-19] Although such studies failed to find an association between knowledge of the treatment and adherence, Lau *et al.*[18] found adherence to medication to be positively associated with knowledge of the purpose for taking medication. Unfortunately, there is no uniform description for the precise constituents of patient drug knowledge, and operational definitions of this concept vary significantly in the literature.[18] Furthermore, this absence of association could be influenced by heterogeneity in the nature of nonadherent patients with psychosis.

Against this backdrop, we conducted this prospective study on patients admitted to hospital diagnosed with schizophrenia or schizoaffective disorder. Nonadherence has been revealed as the most important reason for entering hospital in 58.6% of patients[20] and it is common in the months after discharge.[21] Since differentiated subtypes of nonadherence according to intentionality seem to exist in patients with schizophrenia and schizoaffective disorder[12], it would be advisable to study not only the possible relationship between knowledge of the treatment and nonadherence, but also between knowledge of the treatment and both unintentional and intentional nonadherence.

The objectives of this study were:

1. To assess the prevalence of inadequate knowledge of the treatment

2. To assess the variables associated with inadequate knowledge of the treatment.

3. To evaluate the possible relationship between knowledge of the treatment and nonadherence.

4. To assess the possible relationship between knowing about the treatment and subtypes of nonadherence according to intentionality.

We hypothesized that inadequate knowledge of treatment would be associated with nonadherence or otherwise that it would be associated with unintentional nonadherence.

MATERIAL AND METHODS

Patients

This naturalistic, observational and six-month follow-up prospective study included a total of 110 patients diagnosed with schizophrenia or schizoaffective disorder according to ICD-10 criteria, consecutively admitted to the Acute Patients Unit of the Insular University Hospital of Gran Canaria, The Canary Islands, Spain. This was over an 18-month period since recruitment began (February 2017), and whose

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follow-up was set to take place at the Community Mental Health Unit (CMHU) of Vecindario, which covered a total population of 195,410 people. Additional inclusion criteria included patients being aged over 18, understanding the information pertaining to the study and agreeing to take part. Exclusion criteria were suffering from intellectual disability or dementia. Although a total of 115 patients complied with the inclusion criteria, five patients refused to take part. Since there were four lost cases at six months assessment, our final sample included 106 patients. This study was approved by the Insular University Hospital of Gran Canaria Ethics Committee. All patients were notified about the study's features and provided their consent in writing.

Procedure

Baseline evaluation was conducted on any of the seven days before discharge, preferably on the day before discharge. Follow-up assessment was conducted six months after discharge. All patients were assessed by the same psychiatrist (D.V.). The evaluating psychiatrist obtained further information in regard to adherence from the CMHU therapeutic team. This evaluation was performed in addition to those carried out by the CMHU therapeutic team, which is made up of a psychiatrist, mental health nurse, and social worker if necessary.

Baseline evaluation included sociodemographic, clinical, psychopathologic and variables related to treatment, which are shown in Tables 1 and 2. The different scales used to assess psychopathologic variables have been reported elsewhere. [12,22]

Knowledge of treatment

Knowing about the treatment was assessed by means of an ad hoc questionnaire, whose items are displayed in Table 3. These included knowing about the treatment, diagnosis and follow-up. Knowing about the treatment was restricted to the main antipsychotic, as deemed by the psychiatrist. Each item was worded as a question. Each response was given a score of 1 if correct or 0 if incorrect. To avoid potential bias due to the "Hawthorne effect"[23] patients were not notified that their knowledge of treatment, diagnosis and follow-up was to be evaluated at one hour, two weeks and six months after the instruction.

We studied knowledge of treatment as a continuous and dichotomous variable. We used it as a continuous variable when analyzing differences between groups according to adherence and subtypes of nonadherence, and as a dichotomous variable when analyzing the relationship between inadequate knowledge of the treatment and the variables studied. We defined inadequate knowledge of the treatment as a total mean score below 75%, and appropriate or sufficient knowledge when the score was 75% or over. This cut-off point was arbitrary, due to the absence of any consensus regarding operational definitions in the literature. Total average was calculated at six-months evaluation and shows the average of the values at the three time-points.

Knowledge of the treatment was evaluated from a comprehensive perspective, which included pharmacologic treatment and also outpatient follow-up.[24] We also included an item related to diagnosis, since we considered it essential and related to the need for treatment.

Adherence

Adherence was understood as adherence to antipsychotic treatment and outpatient follow-up over the six-month period. Adherence to antipsychotic treatment was understood as the simultaneity of objective and subjective adherence.

Objective adherence was understood as taking more than 80% of prescribed medication, as recommended by expert consensus.[2] Medication Possession Ratio (MPR) was used to evaluate adherence to oral antipsychotics. Medical records were used to evaluate adherence to long-acting injectables (LAI). The MPR is a ratio of number of days' supply to total days' study participation per participant.[25] They were calculated per patient by dividing the number of outpatient days' supply of medication the patient received over the study period by the number of days' supply they required if they were taking their outpatient medication continuously, as done before.[26] In the event of two or more oral antipsychotics, the mean of the respective MPR was obtained. In regard to LAI, the right administration was deemed a dose administered within three days of the planned dose, as previously.[9]

Subjective adherence was understood as a score of three to four on the Morisky-Green test,[27] and a score above 80% on the Brief Adherence Rating Scale (BARS) after six months. The BARS is a four-item scale specifically devised to measure adherence to antipsychotics in schizophrenia.[28]

Adherence to outpatient follow-up was understood as attendance at planned visits over 80% (after removing justified absences) and the absence of dropout, defined as not attending planned visits for at least six months.

Therefore, nonadherence was defined as nonadherence to antipsychotic treatment, nonadherence to outpatient follow-up, or both. For its part, nonadherence to antipsychotic treatment was understood as the occurrence of objective nonadherence, subjective nonadherence or both.

Table 1 Sociodemographic and clinical characteristics of the sample during hospitalization and six-month follow-up and differences between patients with or without appropriate knowledge of treatment

	Hospitalization				6-months follow-up			
	Total N=106	IK N=48	AK N=58	*P*-value	Total N=106	IK N=48	AK N=58	*P*-value
Age (years)	40.6 ± 11.0	45.3 ± 11.3	36.7 ± 9.2	**< .001**				
Sex (male)[a]	65 (61.3)	33 (68.8)	32 (55.2)	0.153				
Marital status (married)[b]	25 (23.6)	12 (25.0)	13 (22.4)	0.755				
Educational level (secondary or higher)[c]	55 (51.9)	15 (31.2)	40 (69.0)	**< 0.001**				
Socio-economic level (low)[d]	64 (60.4)	30 (62.5)	34 (58.6)	0.684				
Employment situation (active)[e]	12 (11.3)	3 (6.2)	9 (15.5)	0.134				
Social situation (living alone)[f]	31 (29.2)	15 (31.2)	16 (27.6)	0.680				
Reason for admission				0.841				
Change in treatment regimen	13 (12.3)	4 (8.3)	9 (15.5)					
Nonadherence	11 (10.4)	6 (12.5)	5 (8.6)					
Outpatient dropout	52 (49.1)	25 (52.1)	27 (46.6)					
Substance use or abuse	13 (12.3)	6 (12.5)	7 (12.1)					
Stressful life events	11 (10.4)	4 (8.3)	7 (12.1)					
Length of admission (days)	23 (14 - 34)	26 (15 - 35)	19 (13 - 26)	**0.010**				
Length of the disorder (y)	9.0 (4.0 - 18.0)	10.0 (5.0 - 20.0)	8.0 (3.0 - 13.0)	0.109				
Number of prior psychiatric admissions	1.0 (0.0 - 4.0)	1.0 (0.0 - 3.0)	2.0 (0.0 - 4.0)	0.218				
Time since last hospitalization (y)	3.0 (1.5 - 6.0)	3.0 (1.9 - 7.1)	3.0 (1.5 - 5.0)	0.419				
ICD Diagnosis				0.182				
Schizophrenia	61 (57.5)	31 (64.6)	30 (51.7)					
Schizoaffective disorder	45 (42.5)	17 (35.4)	28 (48.3)					
Current substance use or abuse	49 (46.2)	22 (45.8)	27 (46.5)	0.941				
History of substance use or abuse	61 (57.5)	26 (54.2)	35 (60.3)	0.522				
Number of daily doses (oral anti-psychotic)	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)	0.111				
Number of psychotropic tablets per day	5.0 (4.0 – 8.0)	6.0 (4.8 – 9.0)	5.0 (3.0 – 8.0)	0.084				
SUMD, general awareness	11 (9 - 15)	11 (9 - 15)	11 (9 - 15)	0.854	9.0 (6.0 - 11.0)	9.0 (6.0 - 13.5)	9.0 (5.0 - 10.5)	0.242
CGI-S-SCH								
Psychotic symptoms	3.0 (3.0 – 3.0)	3.0 (3.0 – 4.0)	3.0 (2.2 – 3.0)	**0.024**	2.0 (1.2 – 3.0)	2.5 (2.0 – 3.0)	2.0 (1.0 – 2.0)	**0.002**
Negative symptoms	2.0 (1.0 – 2.0)	2.0 (2.0 – 3.0)	2.0 (1.0 – 2.0)	**0.028**	2.0 (1.0 – 2.0)	2.0 (2.0 – 3.0)	2.0 (1.0 – 2.0)	**< 0.001**
Depressive symptoms	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)	0.870	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)	2.0 (1.0 – 2.0)	0.131
Cognitive symptoms	2.0 (1.0 – 2.0)	2.0 (2.0 – 2.2)	1.0 (1.0 – 2.0)	**< 0.001**	2.0 (1.0 – 2.0)	2.0 (2.0 – 2.0)	1.0 (1.0 – 2.0)	**< 0.001**
Overall severity	3.0 (3.0 – 3.0)	3.0 (3.0 – 3.0)	3.0 (2.0 – 3.0)	**0.045**	2.0 (2.0 – 3.0)	3.0 (2.0 – 3.0)	2.0 (2.0 – 3.0)	**0.002**
SCIP. Total score	49 (39 - 57)	40 (31 - 52)	52 (44 - 61)	**< 0.001**	50 (42 - 58)	44 (33 - 51)	56 (47 - 61)	**< 0.001**
Verbal Learning-Immediate	13 (9 - 15)	10 (8 - 15)	13 (11 - 16)	**0.003**	14 (11 - 17)	12 (10 - 15)	15 (12 - 18)	**< 0.001**
Working Memory	17 (13 - 21)	14 (11 - 18)	19 (16 - 21)	**< 0.001**	17 (14 - 20)	14 (12 - 18)	18 (16 - 20)	**< 0.001**
Verbal Fluency	10 (8 - 13)	9 (6 - 10)	12 (9 - 14)	**< 0.001**	11 (8 - 13)	9 (7 - 11)	11 (9 - 13)	**< 0.001**
Verbal Learning-Delayed	4.0 (2.0 – 5.0)	3.0 (2.0 – 4.0)	4.0 (3.0 – 5.0)	**0.002**	4.0 (3.0 – 5.0)	3.0 (2.0 – 4.0)	5.0 (4.0 – 6.0)	**< 0.001**
Processing Speed	4.0 (3.0 – 5.0)	3.0 (2.0 – 4.2)	5.0 (3.0 – 6.8)	**< 0.001**	4.0 (3.0 – 6.0)	3.0 (2.8 – 5.0)	5.0 (4.0 – 6.0)	**< 0.001**
SDM-Q-9. Total score	17 (9 - 27)	13 (9 - 20)	20 (11 - 30)	**0.002**	21 (14 - 36)	18 (11 - 36)	24 (17 - 36)	0.068
BMQ Overuse	3.0 (2.2 – 3.5)	3.2 (2.4 – 3.5)	3.0 (2.2 – 3.7)	0.740	3.0 (2.5 – 3.5)	3.0 (2.5 – 3.3)	3.0 (2.5 – 3.5)	0.740
BMQ Harm	2.5 (2.0 – 3.0)	2.5 (2.0 – 2.8)	2.5 (2.1 – 3.2)	0.519	2.2 (2.0 – 3.0)	2.5 (2.0 – 3.0)	2.2 (1.8 – 2.8)	**0.009**
BMQ Necessity	3.0 (2.4 – 3.8)	3.2 (2.4 – 4.0)	2.8 (2.2 – 3.6)	0.516	3.2 (2.6 – 3.7)	3.2 (2.4 – 3.6)	3.2 (2.6 – 4.0)	0.356
BMQ Concern	2.8 (2.4 – 3.4)	2.8 (2.4 – 3.0)	2.8 (2.4 – 3.6)	0.570	2.8 (2.4 – 3.4)	3.0 (2.4 – 3.4)	2.8 (2.2 – 3.4)	0.717
Drug Attitude Inventory (DAI)	2.0 (-3.0 - 7.0)	3.0 (-1.0 - 7.0)	1.0 (-3.0 - 7.0)	0.690	3.0 (-3.0 – 7.0)	3.0 (-3.0 – 5.5)	3.0 (-1.0 – 7.0)	0.818
10. Sustituirlo por tratamiento no médico	4 (3.8)	2 (4.2)	2 (3.5)	1	6 (5.7)	1 (2.1)	5 (8.6)	0,218
11. Deciente alianza terapéutica	2 (1.9)	0	2 (3.5)	0.5	10 (9.4)	2 (4.2)	8 (13.8)	0,108
12. Evitar el estigma asociado al tratamiento antipsicótico	26 (24.8)	11 (22.9)	15 (26.3)	0.837	31 (29.2)	9 (18.8)	22 (37.9)	**0,031**
13. Otros	3 (2.8)	3 (6.2)	0	0,090	6 (5,7)	2 (4,2)	4 (6,9)	0,687

AK: Appropriate knowledge of treatment, diagnosis and follow-up (≥75%). IK: Inadequate Knowledge of treatment, diagnosis and follow-up (<75%). Data are shown as means ± SD, frequencies (%) and medians (IQR). a: Man vs. woman; b: Married or stable relationship vs. single, separated, divorced or widowed; c: Primary or lower vs. higher secondary education or higher education; d: Medium-high vs. low; e: Active vs. inactive. f: Living alone vs. living with others. BMQ: Beliefs about Medicines Questionnaire: CGI-S-SCH: Clinical Global Impression–Schizophrenia, severity subscale; SCIP: Screen for Cognitive Impairment in Psychiatry; SDM-Q-9: Shared Decision-Making Questionnaire; SUMD: Scale to Assess Unawareness of Mental Disorders; y: years.

AC: Adecuado conocimiento del tratamiento, diagnóstico y seguimiento (≥75%). IC: Inadecuado conocimiento del tratamiento, diagnóstico y seguimiento (≥75%). Los datos se muestran como medias ± DE (desviación estándar), frecuencias (%) y medianas (IQR: Interquartile range, rango intercuartil).

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Table 2 Characteristics of the sample related to the treatment during hospitalization and six-month follow-up and differences between patients with or without appropriate knowledge of treatment

	Hospitalization				***6-months follow-up***			
	Total N=106	**IK N=48**	**AK N=58**	**p-value**	**Total N=106**	**IK N=48**	**AK N=58**	***P*-value**
Supervision of the treatment				0.815				**0.027**
No	36 (37.1)	18 (38.3)	18 (36.0)		21 (19.8)	5 (10.4)	16 (27.6)	
Yes	61 (62.9)	29 (61.7)	32 (64.0)		85 (80.2)	43 (89.6)	42 (72.4)	
Route of administration of antipsychotic				0.744				0.976
Injectable/Injectable plus Oral	60 (56.6)	28 (58.3)	32 (55.2)		62 (58.5)	28 (58.3)	34 (58.6)	
Oral	46 (43.4)	20 (41.7)	26 (44.8)		44 (41.5)	20 (41.7)	24 (41.4)	
Pharmacologic treatment								
Antipsychotic	104 (98.1)	48 (100.0)	56 (96.5)	1	106 (100)	48 (100)	58 (100)	1
Mood stabilizer	33 (31.4)	15 (31.2)	18 (31.6)	0.971	34 (32.4)	14 (29.8)	20 (34.5)	0.609
Antidepressant	20 (18.9)	10 (20.8)	10 (17.2)	0.638	26 (25.0)	10 (21.3)	16 (28.1)	0.426
Anxiolytic	96 (90.6)	44 (91.7)	52 (89.7)	1	79 (75.2)	39 (81.2)	40 (70.2)	0.190
Anticholinergic	24 (22.6)	13 (27.1)	11 (19.0)	0.32	29 (27.6)	16 (34.0)	13 (22.4)	0.185
Hypnotic	100 (94.3)	46 (95.8)	54 (93.1)	0.687	79 (74.5)	41 (85.4)	38 (65.5)	**0.019**
Nonpsychiatric treatment	33 (31.1)	18 (37.5)	15 (25.9)	0.198	40 (38.5)	23 (50.0)	17 (29.3)	**0.031**
Reasons for nonadherence								
1. The patient does not believe in the need for treatment	75 (70.8)	36 (75.0)	39 (67.2)	0.382	74 (69.8)	33 (68.8)	41 (70.7)	0.829
2. Forgetfulness	24 (22.6)	15 (31.2)	9 (15.5)	**0.054**	52 (49.1)	46 (95.8)	6 (10.3)	**< 0.001**
3. To minimize or obviate possible adverse effects	53 (50.0)	23 (47.9)	30 (51.7)	0.834	64 (60.4)	21 (43.8)	43 (74.1)	**< 0.001**
4. Misunderstanding	6 (5.7)	2 (4.2)	4 (6.9)	0.687	18 (17.0)	12 (25.0)	6 (10.3)	**0.045**
5. To minimize or obviate possible risk of addiction	3 (2.8)	1 (2.1)	2 (3.5)	1	3 (2.8)	2 (4.2)	1 (1.7)	0.589
6. To make the regimen more acceptable to fit with their daily schedule	13 (12.3)	4 (8.3)	9 (15.5)	0.262	23 (21.7)	3 (6.2)	20 (34.5)	**< 0.001**
7. Regimen complexity	4 (3.8)	3 (6.2)	1 (1.7)	0.327	9 (8.5)	7 (14.6)	2 (3.5)	**0.075**
8. Financial reasons and/or accessibility problems	7 (6.6)	3 (6.2)	4 (6.9)	1	14 (13.2)	7 (14.6)	7 (12.1)	0.704
9. To see what happens without treatment	13 (12.3)	4 (8.3)	9 (15.5)	0.262	32 (30.2)	6 (12.5)	26 (44.8)	**< 0.001**
10. Replacing medicines with non-pharmacologic treatments	4 (3.8)	2 (4.2)	2 (3.5)	1	6 (5.7)	1 (2.1)	5 (8.6)	0.218
11. Poor therapeutic alliance	2 (1.9)	0	2 (3.5)	0.5	10 (9.4)	2 (4.2)	8 (13.8)	0.108
12. To avoid stigma associated with antipsychotics	28 (26.4)	11 (22.9)	17 (29.3)	0.457	31 (29.2)	9 (18.8)	22 (37.9)	**0.031**
13. Others	3 (2.8)	3 (6.2)	0	0.090	6 (5.7)	2 (4.2)	4 (6.9)	0.687

AK: Appropriate knowledge of treatment, diagnosis and follow-up (≥75%). IK: Inadequate Knowledge of treatment, diagnosis and follow-up (<75%). Data are shown as means ± SD, frequencies (%) and medians (IQR).

Nonadherence subtypes

Subtypes were assigned at six months follow-up, after medical evaluation, information from the CMHU therapeutic team, clinical record details, and interview of family members when required. Two subtypes were established according to the main reason for nonadherence: unintentional nonadherence (UNA) and intentional nonadherence (INA).[12] When patients claimed several reasons these were recorded, in order to identify patients with mixed reasons (i.e. related to both UNA and INA). The full set of reasons for nonadherence used was based on extensive literature reviews[29,30] as shown in Table 2.

Statistical analysis

Categoric and continuous variables were expressed respectively as frequencies and percentages and as mean and standard deviation (SD) when data were in accordance with a normal distribution, or as median and interquartile range (IQR=25th-75th percentile) when distribution moved away from normality. Percentages were compared, as appropriate, using Chi-square ($\chi 2$) test or exact Fisher tests; means and medians were compared by the student *t*-test and Wilcoxon test for independent data, respectively. Statistical significance was fixed at $P<0.05$. Tendency to significance was considered for p-values between 0.05 and 0.1. Data were analyzed using the software R package, version 3.3.1.[31] The study's statistical review was performed by a biomedical statistician.

Table 3 Characteristics of knowledge of the treatment, diagnosis and follow-up at the three time-point assessments

	1 hour			20 days			6 months		
Knowledge of the treatment, diagnosis and follow-up	TOTAL (N=106)	IK (N=48)	AK (N=58)	TOTAL (N=106)	IK (N=48)	AK (N=58)	TOTAL (N=106)	IK (N=48)	AK (N=58)
1. Diagnosis	64 (60.4)	22 (45.8)	42 (72.4)	62 (58.5)	22 (45.8)	40 (69.0)	63 (59.4)	21 (43.8)	42 (72.4)
2. Name of antipsychotic	60 (**56.6**)	16 (33.3)	44 (75.9)	49 (46.2)	7 (14.6)	42 (72.4)	70 (**66**)	15 (31.2)	55 (94.8)
3. Route of administration	101 (95.3)	43 (89.6)	58 (100)	101 (95.3)	43 (89.6)	58 (100)	99 (93.4)	42 (87.5)	57 (9.3)
4. Number of daily doses	77 (72.6)	23 (47.9)	54 (93.1)	81 (76.4)	26 (54.2)	55 (94.8)	88 (83)	32 (66.7)	56 (96.6)
5. Scheduled hours of medication intake	69 (65.1)	21 (43.8)	48 (82.8)	73 (68.9)	21 (43.8)	52 (89.7)	77 (72.6)	25 (52.1)	52 (89.7)
6. Dosage	40 (**37.7**)	7 (14.6)	33 (56.9)	31 (29.2)	4 (8.3)	27 (46.6)	41 (**38.7**)	5 (10.4)	36 (62.1)
7. Objective of the treatment	85 (80.2)	32 (66.7)	53 (91.4)	84 (79.2)	31 (64.6)	53 (91.4)	81 (76.4)	29 (60.4)	52 (89.7)
8. Possible adverse effects	86 (81.1)	37 (77.1)	49 (84.5)	84 (79.2)	31 (64.6)	53 (91.4)	93 (87.7)	38 (79.2)	55 (94.8)
9. Estimated treatment duration	88 (83)	33 (68.8)	55 (94.8)	83 (78.3)	31 (64.6)	52 (89.7)	81 (76.4)	28 (58.3)	53 (91.4)
10. Outpatient follow-up, place	105 (99.1)	47 (97.9)	58 (100)	103 (97.2)	45 (93.8)	58 (100)	85 (80.2)	31 (64.6)	54 (93.1)
11. Outpatient follow-up, visit date	86 (81.1)	36 (75.0)	50 (86.2)	88 (83)	34 (70.8)	54 (93.1)	--	--	--
12. Outpatient follow-up, estimated duration	91 (85.8)	38 (79.2)	53 (91.4)	97 (91.5)	40 (83.3)	57 (98.3)	--	--	--

AK: Appropriate knowledge of treatment, diagnosis and follow-up (≥75%). IK: Inadequate knowledge of treatment, diagnosis and follow-up (<75%). Data are shown as frequencies (%).

RESULTS

Sample features and knowledge of the treatment

In our sample, the number of men (61.3%) was greater than the number of women, and average age was 40.7 years. The most frequent diagnosis was schizophrenia (57.5%), the duration of the psychiatric condition revealed a median of nine years, and prevalence of current drug use or dependency was high (46.2%). The full set of sociodemographic, clinical, psychopathologic and treatment-related variables is shown in Tables 1 and 2. The description of knowing about the therapy, clinical-diagnosis and follow-up, including its items and prevalence at one hour, 20 days and six months, is shown in Table 3. Up to 45.3% of patients showed inadequate knowledge of the treatment (mean scores below 75% comprising the three time-point assessments).

Associated variables to inadequate knowledge of the treatment

Patients with inadequate knowledge of the treatment, as compared to those with appropriate knowledge of the treatment, revealed older age (45.3 vs. 36.7; $P<0.001$), lower educational level (secondary or higher: 31.2% vs. 69%; $P<0.001$), longer hospital stay (26 vs. 19; $P=0.010$), greater prevalence of treatment supervision at six months (89.6% vs. 72.4%; $P=0.027$), greater prevalence of hypnotic use at six months (85.4 % vs. 65.5 %; $P=0.019$), and nonpsychiatric therapy at six months (50% vs. 29.3%; $P=0.031$), greater overall severity of symptoms, psychotic, negative and cognitive symptoms, as measured by the Clinical Global Impression–Schizophrenia, severity subscale (CGI-S-SCH), both at admission and at six months, worse cognitive impairment, as measured by the Screen for Cognitive Impairment in Psychiatry scale (SCIP), worse perception of the degree of shared decision-making, and several differences regarding reasons for nonadherence. In this regard, forgetfulness was the only reason for nonadherence associated with inadequate knowledge of the treatment both at admission (tendency to significance) and at six months. The detailed description of the variables associated with inadequate knowledge of the treatment is shown in Tables 1 and 2.

Nonadherence and subtypes of nonadherence

In the sample, a total of 64 patients (58.2%) fulfilled nonadherence criteria after the follow-up period had ended. In regard to some specific nonadherence components, nonadherence to antipsychotic therapy was detected in a total of 62 patients (56.4%); objective and subjective nonadherence were 33.6% (n=37) and 48.2% (n=53) respectively; and nonadherence to follow-up was detected in 20.9% (n=23) of patients. Among nonadherent patients (N=64), 32 (50%) complied with criteria of intentional nonadherence (INA), and 32 (50%) unintentional nonadherence (UNA). Mixed reasons (i.e., simultaneity of two or more reasons, which have a bearing on both INA and UNA) were detected in a total of 42.2% of patients. A detailed description of these subtypes has been published elsewhere.[12]

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Knowledge of the treatment and nonadherence, UNA and INA

Adherent patients, as opposed to nonadherent patients did not show any difference regarding knowledge of the treatment (median 77 vs. 77, respectively; *P*=0.232). Even so, when taking into consideration nonadherence subtypes, UNA patients showed worse knowledge of the treatment as compared to adherent patients (median 62 vs. 77 respectively; *P*<0.001), whereas INA patients showed better knowledge of the treatment as compared to adherent patients (median 86 vs. 77, respectively; *P*=0.026) (Table 4).

DISCUSSION

To our knowledge, this is the first study to assess a possible relationship between knowing about the treatment and both unintentional and intentional nonadherence. The first remarkable finding of this study was the high prevalence (45.3%) of inadequate knowledge of the treatment, despite the fact that patients were evaluated in the subsequent and crucial months after discharge. When analyzing the specific components of this knowledge at six months from discharge, we found that essential aspects, such as name of the antipsychotic, its dosage, and diagnosis are only known by 66%, 38.7% and 59.4% of patients, respectively. Our results are consistent with the findings of other studies. In a sample of 109 inpatients with schizophrenia, it was found that only 60.6% were aware of their diagnosis and 67.0% knew details of their treatment plan.[17] In another study a considerable prevalence of unawareness of the name of the antipsychotic (51.4%) and its dosage (28.6%) was found.[18] In contrast, in a sample of outpatients with schizophrenia, 93% of patients knew the correct names of the drugs prescribed for them.[13]

Interestingly, we found a characteristic profile associated with inadequate knowledge of the treatment compared to those with appropriate knowledge, consisting mainly of older age, less education, worse cognitive impairment, more serious symptoms, more frequent hypnotic use and non-psychiatric treatment at six months, and greater prevalence of forgetfulness at six-months assessment as a reason for nonadherence. It seems plausible that forgetfulness is more common in patients with cognitive deficits, and that this deficit leads to worse understanding and memory of the treatment.[32,33] Prospective memory may play a key role in medication management skills.[34] Other authors have also found an association between inadequate knowledge of the treatment and older age and lower educational level.[16,18] More complex treatment has been found to be associated with nonadherence,[35,36] and hypnotics may affect cognitive function.[37] In clinical practice, the identification of this profile might point to the convenience of being especially careful when explaining treatment adjusted to cognitive abilities, as well as assessing knowledge of the treatment, both on a periodic basis.

The main finding of this study was the relationship between inadequate knowledge of the treatment and unintentional adherence. Although inadequate knowledge of the treatment was not associated with nonadherence, when considering subtypes of nonadherence, it was associated with unintentional nonadherence. This finding points to two important aspects. First and from a general perspective, the fact that there are few regularly detected correlates for nonadherence in schizophrenia[3] could also be because of actual diverseness among nonadherent patients.[12] This heterogeneity could lead, as in this case, to the assumption that a certain variable is not relevant

Table 4 Relationship between knowing about the treatment and nonadherence, including subtypes

	Total sample (N=106)	Adherent (N=45)	vs. Nonadherent (N=61)	P	vs. UNA (N=30)	P	vs. INA (N=31)	P
Knowledge* (continuous)								
At 1 hour	75 (67 - 92)	75 (67 - 92)	75 (58 - 92)	0.329	67 (58 - 74)	**0.001**	83 (75 - 92)	0.125
At 20 days	75 (64 - 91)	75 (67 - 91)	83 (64 - 92)	0.640	65 (42 - 73)	**0.002**	83 (83 - 92)	**0.022**
At 6 months	80 (60 - 90)	80 (62 - 100)	80 (60 - 90)	0.233	60 (40 - 70)	**< 0.001**	90 (80 - 100)	0.059
Average of time-points	77 (63 - 88)	77 (66 - 88)	77 (62 - 86)	0.232	62 (50 - 71)	**< 0.001**	86 (81 - 92)	**0.026**
Knowledge* (dichotomous)				0.882		**< 0.001**		**< 0.001**
Inadequate (<75%)	48 (45.3)	20 (44.4)	28 (45.9)		27 (90.0)		1 (3.2)	
Appropriate (≥75%)	58 (54.7)	25 (55.6)	33 (54.1)		3 (10.0)		30 (96.8)	

Data are scorings of knowing about the treatment, diagnosis and follow-up: medians (25th - 75th percentile) and n (%)

*Knowledge about the treatment, diagnosis and follow-up

to nonadherence when in fact, it may be relevant for a specific subtype of nonadherent patients. Based on this assumption, this heterogeneity could be the underlying reason why the only two available studies that have explored the relationship between knowing about the treatment and nonadherence[18,19] did not reveal such a relationship. Second and more importantly, it indicates the importance of knowledge of the treatment to achieve adherence in schizophrenia patients who may have the will to adhere to the treatment, but may lack the abilities for this. Although this reasoning may seem obvious, to date it has been a neglected area both in research and in clinical practice. We have previously pointed out the scarcity of studies in this specific area. In clinical practice, it is common to assume that once the treatment has been explained, the patient has assimilated such information; disregarding an adjustment to the patient's capacities, or checking to what extent this information has been correctly understood. Physicians tend to overestimate patients' understanding of their treatment,[38] and need to be cautious that their patients may have insufficient knowledge about the prescribed medications.[39] Finally, our results seem logical and plausible within the subtypes framework. Thus, whereas inadequate knowledge of the treatment seems relevant to achieve adherence in patients who want to follow the treatment plan, it may be less important in patients unwilling to take any medication.

This study has some advantages and disadvantages. As in any emerging area of research, operational definitions of knowledge of the treatment vary significantly in the literature, there is no uniform description for its precise constituents,[18] and there is no validated scale to specifically assess this. The way to evaluate adherence was not the reference standard, i.e., electronic monitoring.[36,40] However, this approach is an indirect measure of treatment adherence and also has some limitations.[6,41] We have integrated objective and subjective approaches from various sources to evaluate adherence, as suggested.[2,3,6,42] Moreover, we worked in accordance with the operational criteria for nonadherence recommended in the expert consensus.[2] One scale used to evaluate adherence has also detected adherence estimates approximate to those produced by electronic monitoring.[28] As for subtypes, there is no consensus in terms of the differentiation of these subtypes or standardized instruments to evaluate them, and a variety of reasons (i.e., simultaneity of two or more reasons, relating to both INA and UNA) were detected in 42.2% of patients; albeit this is compatible with the idea that there appears to be an intersection between both subdivisions.[8,10,43,44] Finally, the type of sample may have a bearing on whether our findings can be generalized. Advantages include a strict methodologic approach to evaluate adherence. In comparison to the routine cross-sectional evaluation with a subjective approach, our study included objective and subjective assessment approaches, a six-month prospective period, and an operational understanding of adherence comprising not only pharmacologic treatment but also follow-up adherence.[24] Another advantage was a broad evaluation of variables including subjective points, variables related to treatment and others usually overlooked in the literature. Finally, all patients were evaluated by the same psychiatrist, which takes away the possibility of poor inter-observer reliability.

CONCLUSIONS

We detected that a considerable number of schizophrenia or schizoaffective disorder patients did not have an appropriate knowledge of their treatment, despite being in a process of hospitalization and follow-up after leaving hospital. Their profile identified might be useful to clinicians, since it may characterize a subgroup of patients in whom special efforts should be made, in terms of information about the treatment, adjustment to their cognitive deficits and checking the patients' understanding. Finally and more importantly, our results suggest that inadequate knowledge of the treatment may contribute to nonadherence in patients with unintentional nonadherence, whereas in those with intentional nonadherence, their knowledge of the treatment may be less relevant.

ETHICAL CONSIDERATIONS

This study was approved by the Institutional Review Board of the Ethics Committee. All patients were notified about the study's features and provided their consent in writing, and all the ethical procedures were performed.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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