

Observational Study

Testing the hypothesis of subtypes of nonadherence in schizophrenia and schizoaffective disorder: A prospective study

Dulcinea Vega, Francisco J Acosta, Pedro Saavedra

ORCID number: Dulcinea Vega 0000-0002-7360-3967; Francisco J Acosta 0000-0001-5835-2795; Pedro Saavedra 0000-0003-1681-7165.

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Dulcinea Vega, Department of Psychiatry, University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria 35016, Las Palmas, The Canary Islands, Spain

Dulcinea Vega, Francisco J Acosta, Department of Psychiatry, Insular University Hospital of Gran Canaria, Las Palmas de Gran Canaria 35016, Las Palmas, The Canary Islands, Spain

Francisco J Acosta, Department of Mental Health General Management of Healthcare Programs, Canary Islands Health Service, Las Palmas de Gran Canaria 35004, Las Palmas, The Canary Islands, Spain

Francisco J Acosta, Research Network on Health Services for Chronic Conditions (REDISSEC), Carlos III Health Institute, Madrid 28029, Spain

Pedro Saavedra, Department of Mathematics, University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria 35016, Las Palmas, The Canary Islands, Spain

Corresponding author: Francisco J Acosta, MD, PhD, Doctor, Department of Mental Health General Management of Healthcare Programs, Canary Islands Health Service, Las Palmas de Gran Canaria 35004, Las Palmas, The Canary Islands, Spain. fjacostaartiles@hotmail.com

Abstract

BACKGROUND

Nonadherence is a major problem in the treatment of psychotic disorders. It has been hypothesized that nonadherent patients with schizophrenia are not a homogeneous population and subtypes of nonadherence might exist, but this hypothesis has not been specifically tested.

AIM

To test the hypothesis of subtypes of nonadherence in schizophrenia and schizoaffective disorder.

METHODS

This prospective study included 110 consecutively admitted patients diagnosed with schizophrenia or schizoaffective disorder. Assessments were performed at baseline and at 6 mo follow-up after discharge. Sociodemographic, clinical, psychopathological and treatment-related variables were evaluated. Adherence was defined as the concurrence of adherence to antipsychotic treatment and outpatient follow-up during the six-month period. Adherence to antipsychotic

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treatment was defined as the concurrence of objective and subjective adherence. Sixty-four patients (58%) fulfilled nonadherence criteria at the end of the follow-up period and were categorized according to their subtype of nonadherence.

RESULTS

In nonadherent patients ($n = 64$), 32 (50%) fulfilled criteria of intentional nonadherence, and 32 (50%) of unintentional nonadherence (UNA). Unintentional nonadherent patients, as compared to intentional nonadherent patients, are characterized by older age, lower educational level, worse cognitive and negative symptoms, greater severity, worse knowledge of their treatment regimen, greater prevalence of supervision of the treatment, lower number of prior hospitalizations and greater use of nonpsychiatric treatment, anticholinergics and hypnotics. Low educational level (OR = 26.1; 95%CI: 2.819-241), worse treatment knowledge at six months (OR per unit = 0.904; 95%CI: 0.853-0.957) and nonpsychiatric treatment at six months (OR = 15.8; 95%CI: 1.790-139) were independently associated to UNA.

CONCLUSION

Differentiated subtypes of nonadherence according to intentionality seem to exist in patients with schizophrenia and schizoaffective disorder. Our findings suggest the need for differentiated approach, both in future research and in clinical practice.

Key Words: Adherence; Hospitalization; Psychosis; Hypothesis; Unintentional nonadherence; Intentional nonadherence

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Core Tip: Nonadherence is a major problem in the treatment of psychotic disorders. The scarcity of consistently identified variables associated with nonadherence could be due, at least in part, to real heterogeneity among nonadherent patients. Although in recent years the existence of two main subtypes according to intentionality has been hypothesized, no previous studies have specifically tested this hypothesis. This research aimed to fill this gap. We found differentiated profiles in nonadherent patients according to intentionality. Our results support the nonadherence subtypes hypothesis in psychotic disorders.

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INTRODUCTION

Despite important advances in the management of schizophrenia in recent decades, nonadherence is still a frequent phenomenon, around 40% to 50%^[1-3]. Unfortunately, there are still few predictive factors of note and the current state of the evidence may be somewhat disheartening for the practicing clinician^[4]. To date, the most consistent risk factors for nonadherence include previous nonadherence, poor insight, negative attitude towards treatment and substance abuse^[1,4-7].

The heterogeneity of findings related to several risk factors for nonadherence^[4] has been regarded as a consequence of the methodologic limitations of most available studies, especially the absence of a valid assessment method^[4,8]. Moreover, only recently has there been expert consensus providing a conceptual and operative definition of adherence^[3,8,9]. Finally, although prospective studies provide robust findings regarding cause-effect relationships, most studies are cross-sectional^[1,4].

Nevertheless, the scarcity of consistently identified correlates^[4] could also be due to real heterogeneity among nonadherent patients. Thus, in recent years the existence of two main subtypes has been hypothesized: Intentional and unintentional^[9-14].

Intentional nonadherence (INA) has been defined as a conscious patient decision to stop taking medication or to take less medication than prescribed, whereas unintentional nonadherence (UNA) occurs when practical problems or impairments related to having an illness interfere with taking medication^[7], thus involving patient-related, environment and treatment-related factors^[15], such as forgetfulness^[11], suboptimal awareness of their treatment^[16], inadequate health literacy^[17], mistakes^[18] or barriers to access mental health care^[19]. However, there are no clear limits between both subtypes, and overlaps and comorbidities exist^[12,15,20,21]. Despite its importance, few specific studies on patients with psychoses have been performed^[12,13,21]. Identification of subtypes as well as specific reasons for nonadherence would guide towards different types of interventions^[13,18,22].

In this context, we performed this prospective study in hospitalized patients diagnosed with schizophrenia or schizoaffective disorder. Hospitalizations are an important event in the course of illness. For its part, nonadherence has been found to be the main reason for admission in 58.6% of patients^[23], it is frequent in the months after discharge^[24-26] and discharge can be a good time to introduce strategies aimed at improving adherence^[27].

Therefore, this study had the following objectives: (1) To evaluate the prevalence of nonadherence at six-months post discharge; and (2) To evaluate the possible subtypes of nonadherence according to intentionality and to determine whether identified subtypes have a differential profile. We hypothesized that two different subtypes according to intentionality would be identified, and these would have a different profile.

MATERIALS AND METHODS

Patients

This naturalistic, observational and 6-mo follow-up prospective study included 110 patients diagnosed with schizophrenia or schizoaffective disorder according to ICD-10 criteria; patients were consecutively admitted to the Acute Patients' Unit of the Insular University Hospital of Gran Canaria, The Canary Islands, Spain, over an 18-mo period since recruitment commenced (February 2017), and whose follow-up was due to take place at the Community Mental Health Unit (CMHU) of Vecindario, which covers a population of 195410 people. As additional inclusion criteria, patients had to be aged over 18 years, understand the information concerning the study and agree to participate. Exclusion criteria were suffering intellectual disability or dementia. Out of 115 eligible patients, 5 (4.35%) refused to participate. This study was carried out in compliance with the latest version of the Declaration of Helsinki and approved by the Ethics Committee of Insular University Hospital of Gran Canaria. All patients were informed about the characteristics of the study and gave their written consent.

Procedure

Baseline evaluation was performed during any of the 7 d prior to discharge. Follow-up assessment was performed 6 mo from discharge. All patients were evaluated by the same psychiatrist. Baseline evaluation included sociodemographic, clinical, psychopathologic and treatment-related variables, which are shown in Tables 1 and 2. Psychopathology was evaluated by the Clinical Global Impression-Schizophrenia Scale (CGI-SCH), severity subscale, validated in Spanish^[28], at baseline and follow-up. Insight was evaluated by the first three items of the Amador Insight Scale, which assess general disorder awareness^[29], validated in Spanish^[30]. Cognitive performance was assessed by means of the SCIP-S scale (Screen for Cognitive Impairment in Psychiatry), validated in Spanish^[31].

Treatment-related variables included several objective and subjective measures. Regarding the latter, attitude towards medication was evaluated by the Drug Attitude Inventory (DAI)^[32], Spanish validated version^[33]. Beliefs about treatment were assessed through the Beliefs about Medicines Questionnaire (BMQ)^[34] in its Spanish validated version^[35]. Perceptions about shared decisions were evaluated by the 9-item Shared Decision Making Questionnaire (SDM-Q-9) in its Spanish validated version^[36].

Knowledge was evaluated by means of an ad hoc questionnaire (Supplementary Material). Treatment knowledge was restricted to that of the main antipsychotic, as considered by the psychiatrist. To avoid potential bias due to the "Hawthorne effect"^[37] patients were not informed that their knowledge of treatment, diagnosis and follow-up was to be assessed at 1 h, 2 wk and 6 mo from the time of instruction.

Table 1 Sociodemographic, clinical, and treatment-related characteristics of the sample at admission and differences between unintentional and intentional nonadherent patients

	Total non-adherence (n = 64)	Unintentional (n = 32)	Intentional (n = 32)	P value
Age (yr)	40.6 ± 9.6	44.4 ± 10.1	36.8 ± 7.4	0.001
Sex (male)	39 (60.9)	23 (71.9)	16 (50.0)	0.073
Marital status				0.522
Married or stable relationship	12 (18.8)	5 (15.6)	7 (21.9)	
Single, separated, divorced, or widowed	52 (81.2)	27 (84.4)	25 (78.1)	
Educational level				< 0.001
Primary or lower	34 (53.1)	25 (78.1)	9 (28.1)	
Secondary or higher	30 (46.9)	7 (21.9)	23 (71.9)	
Socio-economic level				0.376
Low	49 (76.6)	26 (81.2)	23 (71.9)	
Medium-High	15 (23.4)	6 (18.8)	9 (28.1)	
Employment situation				0.162
Active	5 (7.8)	1 (3.1)	4 (12.5)	
No active	59 (92.2)	31 (96.9)	28 (87.5)	
Cohabitation				0.794
Living with family	41 (64.1)	20 (62.5)	21 (65.6)	
Living alone	23 (35.9)	12 (37.5)	11 (34.4)	
Length of admission (d)	23 (14-32)	25 (14-35)	21 (14-26)	0.179
Length of the disorder (yr)	11 (5-19)	11 (5-20)	10 (6-17)	0.577
Number of previous psychiatric admissions	2.0 (1.0-5.0)	1.0 (1.0-4.0)	3.0 (1.0-5.2)	0.036
Time since last hospitalization (yr)	2.0 (1.1-5.0)	2.0 (1.0-7.3)	2.0 (1.3-3.0)	0.435
ICD diagnosis				0.079
Schizophrenia	35 (54.7)	21 (65.6)	14 (43.8)	
Schizoaffective disorder	29 (45.3)	11 (34.4)	18 (56.2)	
Current substance use or abuse	36 (56.2)	18 (56.2)	18 (56.2)	1
History of substance use or abuse	44 (68.8)	22 (68.8)	22 (68.8)	1
Daily doses (oral antipsychotic)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.243
Psychotropic pills per day	6 (4-8)	6 (4-8)	5 (3-9)	0.479
Attitude towards treatment				0.664
Negative	41 (64.1)	19 (59.4)	22 (68.8)	
Neutral	15 (23.4)	9 (28.1)	6 (18.8)	
Positive	8 (12.5)	4 (12.5)	4 (12.5)	

Data are means ± SD, frequencies (%) and medians (IQR).

Adherence

Adherence was defined as the concurrence of adherence to antipsychotic treatment and outpatient follow-up during the six-month period. Adherence to antipsychotic treatment was defined as the concurrence of objective and subjective adherence.

Objective adherence was defined as taking more than 80% of prescribed medication, as recommended by expert consensus^[3]. Medication possession ratio (MPR) was used to assess adherence to oral antipsychotics, and clinical records to assess adherence to

Table 2 Psychopathological, treatment-related, and other characteristics of nonadherent patients during hospitalization and at 6 mo post discharge, and differences between unintentional and intentional nonadherence

	Hospitalization			P value	6 mo			P value
	Total Nonadherence (n = 64)	Unintentional (n = 32)	Intentional (n = 32)		Total nonadherence (n = 64)	Unintentional (n = 32)	Intentional (n = 32)	
Amador insight scale, general disorder awareness	11 (9-15)	11 (9-15)	11 (9-15)	0.634	9 (9-11)	9 (6-11)	9 (9-13)	0.467
Mental disorder	5 (3-5)	5 (3-5)	5 (3-5)	0.750	3.0 (3.0-5.0)	3.0 (2.0-4.5)	3.0 (3.0-5.0)	0.177
Effects of the medication	3.0 (3.0-5.0)	3.0 (3.0-5.0)	3.0 (3.0-5.0)	0.638	3.0 (2.0-3.0)	3.0 (2.2-3.0)	3.0 (2.5-4.0)	0.907
Social consequences	3.0 (3.0-5.0)	3.0 (3.0-5.0)	4.0 (3.0-5.0)	0.441	3.0 (2.0-5.0)	3.0 (2.2-4.8)	3.0 (2.5-5.0)	0.861
CGI-SCH severity. Total score	11 (10-13)	11 (10-13)	10 (9-12)	0.086	10 (9-12)	12 (10-13)	9 (8-10)	0.003
Psychotic symptoms	3.0 (3.0-3.0)	3.0 (3.0-3.0)	3.0 (3.0-3.0)	0.645	2.0 (2.0-3.0)	3.0 (2.0-3.0)	2.0 (2.0-3.0)	0.118
Negative symptoms	2.0 (1.0-2.2)	2.0 (1.0-2.2)	2.0 (1.0-2.2)	0.186	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)	0.413	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.346
Cognitive symptoms	2.0 (1.0-2.0)	2.0 (2.0-2.0)	1.0 (1.0-2.0)	< 0.001	2.0 (1.0-2.0)	2.0 (2.0-2.8)	1.0 (1.0-2.0)	< 0.001
Global severity	3.0 (3.0-3.0)	3.0 (3.0-3.0)	3.0 (2.8-3.0)	0.679	3.0 (2.0-3.0)	3.0 (2.0-3.0)	2.0 (2.0-3.0)	0.210
SCIP. Total score	49 (40-55)	42 (32-52)	52 (46-59)	0.002	48 (41-59)	42 (33-49)	56 (48-62)	< 0.001
Verbal learning-immediate	13 (10-15)	12 (9-15)	13 (11-15)	0.073	15 (11-17)	13 (10-16)	15 (12-18)	0.032
Working memory	16 (13-20)	14 (11-18)	18 (16-21)	0.004	17 (14-20)	14 (12-17)	19 (17-20)	0.001
Verbal fluency	10 (8-13)	10 (7-11)	12 (9-14)	0.022	11 (8-12)	10 (7-11)	11 (8-13)	0.045
Verbal learning-delayed	4.0 (2.0-5.0)	3.0 (2.0-4.0)	4.0 (3.0-5.0)	0.003	4.0 (3.0-5.0)	3.0 (1.2-4.0)	5.0 (4.0-6.0)	< 0.001
Processing speed	4.0 (3.0-6.0)	3.0 (2.0-5.0)	5.0 (3.0-7.0)	0.004	4.0 (3.0-5.0)	3.0 (2.0-4.0)	5.0 (4.0-6.0)	< 0.001
Type of antipsychotic treatment				0.114				0.114
Oral	22 (34.4)	8 (25.0)	14 (43.8)		22 (34.4)	8 (25.0)	14 (43.8)	
Injectable or injectable + oral	42 (65.6)	24 (75)	18 (56.2)		42 (65.6)	24 (75)	18 (56.2)	
Supervision of the treatment	40 (65.6)	21 (67.7)	19 (63.3)	0.717	51 (79.7)	29 (90.6)	22 (68.8)	0.03
SDM-Q-9. total score	17 (9-23)	10 (8-19)	20 (11-30)	0.010	18 (11-21)	17 (10-21)	18 (14-22)	0.235
BMQ, beliefs about medicines, general	22 (18-27)	22 (20-27)	22 (17-25)	0.509	22 (18-26)	22 (18-26)	22 (16-25)	0.623
BMQ, beliefs about medicines, specific	6 (5-7)	6 (6-7)	6 (5-7)	0.142	31 (26-34)	31 (27-35)	30 (26-34)	0.479
DAI	3.0 (-3.0-7.0)	3.0 (-1.0-5.0)	1.0 (-3.0-7.0)	0.914	1.0 (-3.0-3.0)	1.0 (-3.0-6.5)	1.0 (-3.0-3.0)	0.374
Morisky-Green test	2.0 (2.0-3.0)	2.0 (1.8-2.2)	2.0 (2.0-3.0)	0.302	2.0 (2.0-3.0)	2.0 (2.0-3.0)	2.5 (2.0-3.0)	0.084

BARS	100 (100-100)	100 (100-100)	100 (100-100)	0.329	55 (30-74)	60 (20-78)	50 (40-70)	0.586
Knowledge of the treatment at 1 h ¹	75 (58-92)	67 (58-75)	83 (75-92)	< .001				
Knowledge of the treatment at 20 d ¹	79 (62-92)	65 (42-77)	83 (81-92)	< .001				
Knowledge of the treatment at 6 mo ¹					80 (60-90)	60 (40-70)	90 (80-100)	< 0.001

Data are means \pm SD, frequencies (%) and medians (IQR).

¹There were 3 lost cases regarding knowledge of the treatment ($n = 61$; unintentional, $n = 30$; intentional, $n = 31$). Knowledge of the treatment: Knowledge of the treatment, diagnosis, and follow-up from the time of instruction. The values represent means of percentages. BMQ: Beliefs about medicines questionnaire; CGI-SCH: Clinical Global Impression-Schizophrenia; IQR: Inter-quartile range; SCIP: Screen for Cognitive Impairment in Psychiatry; SDM-Q-9: Shared Decision Making Questionnaire; SD: Standard deviation; DAI: Drug attitude inventory; BARS: Brief adherence rating scale.

long-acting injectables (LAI). The MPR is a ratio of total days' supply to number of days of study participation per participant^[38], and were calculated by each patient by dividing the number of outpatient days' supply of medication the patient received during the study period by the number of days' supply they needed to receive if they were taking their outpatient medication continuously, as previously done^[39]. When there were two or more oral antipsychotics, the mean of the respective MPR was obtained. Regarding LAI, correct administration was considered as a dose administered within three days of the scheduled dose, as performed previously^[10].

Subjective adherence was defined as a score of 3 or 4 in the Morisky-Green test, as performed previously^[40,41] and a score higher than 80% on the BARS scale at six months. The BARS is a 4-item scale specifically developed to measure adherence to antipsychotics in schizophrenia^[42].

Adherence to outpatient follow-up was defined as the concurrence of attendance at scheduled visits greater than 80% (after excluding justified absences) and the absence of dropout, defined as nonattendance at scheduled visits for at least six months.

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

Subtypes of nonadherence

Subtypes were assigned at 6 mo follow-up, after clinical assessment, information from the CMHU therapeutic team, details of medical record, and interview of family members when needed. Based on extensive literature reviews^[14,43], we established a set of reasons for nonadherence. Patients were assigned to UNA if the main reason was any of items 2, 4, 7 or 8, and to INA for the remaining reasons. When there were two or more reasons for nonadherence, these were also recorded for descriptive purposes. The reasons included: (1) The patient does not believe in the need for treatment; (2) Forgetfulness; (3) To minimize or to avoid possible adverse effects; (4) Misunderstanding; (5) To minimize or to avoid possible risk of addiction; (6) To make the regimen more acceptable in order to fit with their daily schedule; (7) Regimen complexity; (8) Financial reasons and/or accessibility problems; (9) To see what happens without treatment; (10) Replacing medicines with non-pharmacological treatments; (11) Poor therapeutic alliance; and (12) To avoid stigma associated to antipsychotics.

Statistical analysis

Categoric and continuous variables were expressed respectively as frequencies and percentages and as mean and standard deviation (SD) when data followed a normal distribution, or as median and interquartile range (IQR = 25th-75th percentile) when distribution departed from normality. Percentages were compared, as appropriate, using Chi-square (χ^2) test or exact Fisher tests; means and medians were compared by the student *t*-test and Wilcoxon test for independent data, respectively. In order to identify factors that maintain independent association with each outcome (nonadherence; unintentional subgroup), a multivariate logistic regression analysis was performed. Variables that revealed statistically significant association with the corresponding outcome in univariate analysis were entered into the multivariate analysis. Variables based on the best subset regression and Akaike information

criterion were then selected. Models were summarized as coefficients (SE), *P* values (likelihood ratio test) and odds-ratio, which were estimated by means of 95% confidence intervals. Statistical significance was set at $P < 0.05$. Data were analyzed using the R package, version 3.3.1.^[44]. The statistical review of the study was performed by a biomedical statistician.

RESULTS

Nonadherence and characteristics of the sample

We recruited 110 patients, of whom 64 (58%) fulfilled nonadherence criteria; 56.4% nonadherence to antipsychotic treatment, and 20.9% nonadherence to outpatient follow-up. Since this study is focused on evaluation of possible subtypes of nonadherence, the total sample was comprised of nonadherent patients ($n = 64$). The percentage of men (60.9%) was higher than that of women, and mean age was 37.4 years. The most common diagnosis was schizophrenia (54.7%), the length of the psychiatric disorder showed a median of 11 years, the length of admission was 23 d, and prevalence of current substance use or abuse was high (56.2%). Sociodemographic, clinical, psychopathologic and treatment-related variables are shown in Tables 1 and 2.

Subtypes and subgroups of nonadherence

In nonadherent patients ($n = 64$), 32 (50%) fulfilled criteria of INA, and 32 (50%) of UNA. The prevalence of the main reasons identified in INA patients was: The patient does not believe in the need for treatment (75%), to minimize or to avoid possible adverse effects (18.8%), to make the regimen more acceptable in order to fit with their daily schedule (3.1%), to see what happens without treatment (3.1%). The prevalence of the main reasons identified in UNA patients was: Forgetfulness (65.6%), financial reasons and/or accessibility problems (15.6%), misunderstanding (12.5%), regimen complexity (6.3%). Mixed reasons (*i.e.*, concurrence of two or more reasons, belonging to both INA and UNA) were found in 42.2% of the patients.

Variables associated with nonadherence subgroups

UNA patients, as compared to INA patients, showed older age (44.4 *vs* 36.8 respectively, $P < 0.001$), higher prevalence of low educational level (78.1% *vs* 28.1%, $P < 0.001$), lower number of prior hospitalizations (1.0 *vs* 3.0, $P = 0.036$), greater severity at six months (12 *vs* 9, $P = 0.003$), worse negative symptoms at 6 mo (2 *vs* 2, $P < 0.001$), worse cognitive symptoms at admission and at 6 mo, as assessed both by the CGI (2 *vs* 1 respectively, $P < 0.001$) and the SCIP (42 *vs* 56, $P < 0.001$), worse knowledge of the treatment regimen at 1 h (67 *vs* 83, $P < 0.001$), at 20 d (65 *vs* 83, $P < 0.001$), and at 6 mo (60 *vs* 90, $P < 0.001$), greater prevalence of supervision of the treatment (90.6% *vs* 68.8%, $P = 0.03$), greater use of anticholinergics at admission (35.5% *vs* 12.5%, $P = 0.032$) and at six-month follow-up (35.5% *vs* 12.5%, $P = 0.032$), hypnotics at admission (90% *vs* 71.9%, $P = 0.055$), and nonpsychiatric treatment at admission (60% *vs* 25%, $P = 0.005$) and at 6 mo (60% *vs* 25%, $P = 0.005$).

Tables 1 and 2 summarize the sociodemographic, clinical, psychopathologic and treatment-related differences between unintentional and intentional nonadherent patients. The multivariate logistic regression model for nonadherence according to subgroups is shown in Table 3. Factors that revealed an independent association with UNA were nonpsychiatric treatment at six months (OR = 15.8; 95%CI: 1.790-139), low educational level (OR = 26.1; 95%CI: 2.819-241), and treatment knowledge at six months (average) (OR per unit = 0.904; 95%CI: 0.853-0.957).

DISCUSSION

Nonadherence in the post discharge period was high. Up to 58% of patients did not fulfil adherence criteria at six-month follow-up. This high rate is consistent with that found in other prospective studies using electronic monitoring devices. Thus, nonadherence rates were 48% at 3 mo^[45] and 62.7% at six months from discharge^[26]. In addition to the alarming high rate of nonadherence, identification of distinguishable profiles of nonadherent patients according to their intentionality was the main finding of this study. Our findings are consistent with the hypothesis regarding the existence of nonadherence subtypes according to intentionality^[9-14] and, therefore, support this hypothesis.

Table 3 Variables associated with nonadherence according to intentionality after multivariate logistic regression (reference: Unintentional nonadherence)

	<i>P</i> value ¹	AIC ²	Odds ratio (95%CI)
Low educational level	< 0.001	52.1	26.1 (2.819; 241)
Non-psychiatric treatment at 6 mo	0.003	47.7	15.8 (1.790; 139)
Treatment knowledge at 6 mo, mean	< 0.001	64.9	0.904 (0.853; 0.957)

¹Likelihood ratio test.

²If the variable is removed. AIC for the full model = 41.1; AIC is a measure of lack of fit. The removal of any variable leads to a model with more lack of fit. AIC: Akaike information criterion.

Worse negative symptoms and cognitive deficits were associated with UNA patients. Persistent negative symptoms^[3,46] and cognitive symptoms^[7,47] can affect the ability to manage medications. Cognitive deficits may hinder understanding the treatment regimen, its awareness as well as the organizational capacity needed for adherence, particularly with complex regimens^[7,48]. In this regard, nonpsychiatric treatment at six months was strongly and independently associated with UNA patients in this study. However, the relationship between cognition and nonadherence is still inconclusive^[4]. This heterogeneity of findings may have been influenced by methodologic difficulties and by the fact that the impact of cognitive deficits likely depends on other conditions and circumstances, such as whether or not there is good family support involved in planning and monitoring medication intake^[7]. Nevertheless, an additional factor may be the hypothesized heterogeneity of nonadherent patients. According to this hypothesis, cognitive deficits could be relevant only or especially for UNA. To the best of our knowledge, this is the first study that specifically assesses the association between cognitive features and different nonadherence subtypes.

For its part, knowledge of treatment, diagnosis and follow-up was lower in UNA at the three time points assessed. In addition, worse knowledge of the treatment regimen at six months was independently associated with this subtype. This area remains little studied. Most studies have found suboptimal knowledge of the treatment^[16,49,50]. Moreover, physicians have been found to overestimate understanding the treatment by their patients^[51]. Some authors have found an association between knowledge of the purpose for taking medication and adherence, but not with other aspects^[49], while others have not found such an association^[50]. This disparity of findings may have been influenced by methodologic issues, such as the absence of a uniform description of what adequate knowledge of treatment is and absence of operational definitions; or again, by a real heterogeneity within nonadherent patients, as we hypothesize. To the best of our knowledge, this is the first study that specifically assesses the association between knowledge of the treatment and different nonadherence subtypes.

Lower educational level and older age were found to be associated with UNA patients. In addition, educational level was independently associated with this subtype. Most studies have not found an association between educational level and adherence^[1,3,4]. Nevertheless, when considering the possible subtypes of nonadherence, it seems plausible that a lower educational level may contribute to inadequate understanding of treatment regimen, and this in turn may lead to UNA. In this context, in a study on community-dwelling seniors admitted to acute medicine services, inadequate and marginal health literacy patients were likely to have UNA, whereas those with adequate health literacy were more likely to have INA^[17]. Future studies that assess the possible association between educational level and UNA in schizophrenia would shed light on this issue. With regard to age, this variable has also yielded contradictory results. Whereas some studies have found younger age associated with adherence problems^[3,52], others have failed to find such an association^[1,10].

Finally, neither insight nor any of its three basic components were associated with different subtypes of nonadherence. This finding contrasts with the notion that poor insight is an important reason for INA^[7], or specifically a risk factor likely to affect willingness to take medication^[3,53]. It is likely that this absence of differences has been influenced by the fact that the global sample of nonadherent patients showed poor insight. This finding was to be expected, since our sample consisted of admitted patients evaluated both during hospitalization and at follow-up. Another factor may

be that we found mixed reasons in 42.2% of the patients, which is consistent with the notion that overlapping between both subgroups seems to exist^[11,12,20,21]. In any case, although poor insight is an unquestionable risk factor for nonadherence^[1,3,5,10,54], the role of insight in intentional *vs* unintentional adherence has not been sufficiently studied.

This study has certain limitations and strengths. The assessment method of adherence was not the reference standard, *i.e.*, electronic monitoring^[55-57]. However, this method is an indirect measure of treatment adherence and also has drawbacks^[7,58], and we have combined objective and subjective methods from multiple sources to assess adherence, as recommended^[3,4,7,59]. Moreover, we worked in accordance with the operational criteria for nonadherence recommended in the expert consensus^[3]. Furthermore, one of the scales used to assess adherence has revealed similar estimates of adherence to those produced by electronic monitoring^[42]. Unfortunately, intentional and unintentional dimensions of patient medication taking are poorly categorized within adherence literature^[60]. Thus, there is neither consensus regarding the differentiation of these subtypes nor standardized instruments to assess them. Finally, the modest sample size and the nature of the sample may affect both the statistical power and the generalizability of our findings. The main strengths of this study are its prospective design - which confers strength in the establishment of cause-effect relationships - and a wide evaluation of variables including subjective aspects, treatment-related variables and knowledge of the treatment, usually neglected in the literature.

CONCLUSION

In conclusion, we have found differentiated profiles among nonadherent patients according to intentionality. UNA patients, as compared to INA patients, are characterized by lower educational level, worse knowledge of their treatment regimen, worse cognitive and negative symptoms, older age, greater use of nonpsychiatric treatment, and fewer prior hospitalizations, as most prominent features. These findings support the hypothesis that there are nonadherence subtypes in patients with psychotic disorders, and suggest the need for a differentiated approach, both in future research and clinical practice.

ARTICLE HIGHLIGHTS

Research background

Despite important advances in the management of schizophrenia in recent decades, nonadherence remains a common phenomenon, with prevalence rates of approximately 40%-50%. The heterogeneity of findings regarding several risk factors for nonadherence could also be due to real heterogeneity among nonadherent patients.

Research motivation

The existence of two main subtypes according to intentionality has been hypothesized: Intentional and unintentional. Identification of subtypes as well as specific reasons for nonadherence would provide guidance in terms of different types of interventions.

Research objectives

To evaluate possible subtypes of nonadherence according to intentionality and to determine whether identified subtypes show a differential profile.

Research methods

This naturalistic, observational, and 6-mo follow-up prospective study included 110 admitted patients diagnosed with schizophrenia or schizoaffective disorder. Baseline evaluation included sociodemographic, clinical, psychopathologic and treatment-related variables. Adherence was defined as the concurrence of adherence to antipsychotic treatment and outpatient follow-up during the six-month period. Adherence to antipsychotic treatment was defined as the concurrence of objective and subjective adherence. Subtypes were assigned at 6 mo follow-up based on a set of reasons for nonadherence.

Research results

Sixty-four patients (58%; $n = 64$) fulfilled nonadherence criteria at the end of the follow-up period and were categorized according to subtype of nonadherence: 32 (50%) fulfilled criteria of intentional nonadherence, and 32 (50%) unintentional nonadherence (UNA). Several variables were independently associated with UNA: Low educational level (OR = 26.1; 95%CI: 2.819-241), worse treatment knowledge at six months (OR per unit = 0.904; 95%CI: 0.853-0.957) and nonpsychiatric treatment at six months (OR = 15.8; 95%CI: 1.790-139).

Research conclusions

This study specifically tests the subtypes hypothesis in psychotic disorders. We found two subtypes of nonadherence according to intentionality, as well as differentiated profiles. Our results support the nonadherence subtypes hypothesis in psychotic disorders.

Research perspectives

We propose some directions for future research: (1) Replication studies to confirm the existence of differentiated subtypes of nonadherence in psychotic disorders; and (2) If confirmed, adoption of a differentiated approach, both in future research and clinical practice.

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