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Adherence to psychopharmacological treatment in acute psychosis: observational study on the role of therapeutic drug monitoring

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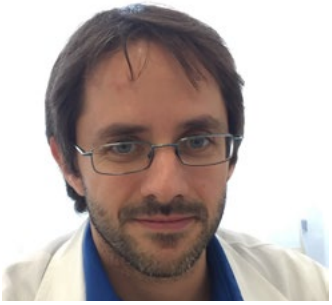

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Summary

Objectives. The aims of this study were to assess adherence to psychopharmacological treatment in a sample of patients admitted to a psychiatric emergency service for acute psychosis in a real-world setting, and to evaluate possible associations between adherence and socio-demographic and clinical variables.

Materials and methods. A monocentric observational study was conducted. All adult patients affected by acute psychosis admitted to the psychiatric emergency unit of the hospital were included. Patients were divided into adherent and non-adherent groups according to the results of the therapeutic drug monitoring on blood samples, a direct and objective measure of adherence to psychopharmacological treatment. Adherent and non-adherent patients were compared with one-way ANOVA and Chi-square tests. The association between adherence and socio-demographic and clinical variables was examined with a multivariate logistic regression.

Results. Seventy-nine patients have been included, of which 58% resulted adherent to treatment. Psychopathology characterized by anxiety and depression and a solid relationship with mental health services were associated with adherence, while more severe thought disorder and a higher duration of illness negatively affected adherence.

Conclusions. Our study highlighted a significant association between specific clinical variables and adherence to psychopharmacological treatments in a sample of inpatients admitted to a psychiatric emergency service.

Key words: adherence, therapeutic drug monitoring, acute psychosis

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Conflict of interest
The Authors declare no conflict of interest.

Introduction

Adherence to treatments is defined as "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider" [1]. In chronic diseases it is often inadequate: up to 50% of patients with chronic medical conditions have no or only partial adherence [1]. In mental health, data reported in literature are similar to what is estimated about adherence in the other major chronic diseases: up to 70% of patients living with a mental disorder have an inadequate adherence to treatments [2,3]. Non-adherence to treatments negatively affects the evolution of the mental disorder, with

greater frequency of relapses, progressive chronicity of the disorder, higher suicide risk, reduction of response to drug therapies and worsening of social functioning [4-6]. Moreover, amongst the risk factors of relapse, adherence is a modifiable factor by health care professionals, and therefore needs to be carefully addressed [7].

Adherence is a multidimensional phenomenon and is therefore influenced by several elements: patient-related factors (socio-demographics, attitude towards illness and treatment, medical and psychiatric comorbidity, alcohol or substance abuse etc.), illness-related factors (type and severity of symptoms, insight, duration of illness – DOI – etc.), treatment-related variables (side effects, complexity of the therapeutic regimen etc.), therapeutic alliance and engagement with health services, quality of mental health services, economic and social factors [8]. In psychotic disorders, adherence appears to be particularly affected by cannabis [9], alcohol and substance use, impaired insight [10], and higher levels of hostility [11,12].

Adherence can be measured by direct or indirect methods. Direct methods most widely applied are directly observed therapy and therapeutic drug monitoring (TDM). Indirect measures include subjective and objective evaluations. Subjective evaluations are represented by patients, caregivers or health care professional estimate of adherence, while objective methods are electronic drug monitoring, rate of prescriptions refill, clinical response evaluation, monitoring of biological markers of treatment effects [13,14]. Direct methods, although not extensively adopted in clinical practice, for practical and economic reasons, are generally more sensitive and specific, while indirect methods are less accurate and tend to overestimate patient's adherence [13]. Anyway, each measurement method has advantages and limitation, in terms of both accuracy and applicability, therefore, as currently recommended by the World Health Organization, a combination of both direct and indirect measures represent the best strategy to assess adherence to treatments [1].

In clinical practice, it is fundamental to identify scarcely adherent patients, in order to address non-adherence determinants and improve patient's clinical course [15]. Moreover, in case of poor clinical response, it is crucial to differentiate between resistance to treatment and pseudo-resistance, due to inadequate adherence or drug or substances interactions. However direct methods, which are most reliable, are not widely adopted in monitoring adherence in psychiatric patients, and real-world studies of adherence measurement through direct methods are relatively lacking, especially in the evaluation of acute psychosis.

The aims of the present study are: 1) evaluate treatment adherence through TDM in a sample of patients admitted in a psychiatric emergency service (PES) for acute psychosis; 2) assess which socio-demographic and clinical variables were strongly associated with non-adherence, in order to help clinicians in promoting adherence.

Materials and methods

The present work is an observational, cross-sectional, monocentric study. It was conducted in the PES "Struttura Complessa Psichiatria - Servizio Psichiatrico di Diagnosi e Cura" (SPDC) of the Department of Neuroscience and Mental Health of the university hospital "Città della Salute e della Scienza" of Turin, Piedmont, Italy, in the period between February and December 2019.

Subjects

All patients consecutively admitted who fulfilled inclusion criteria were included in the study. Inclusion criteria were the following: a) diagnosis of schizophrenia spectrum disorders or diagnosis of bipolar and related disorders, according to DSM 5 diagnostic criteria; b) age over 18; c) being in therapy, at the admission time, with a drug which can be monitored at the hospital laboratory ("Struttura Complessa Biochimica Clinica" of the university hospital "Città della Salute e della Scienza" of Turin): lithium, sodium valproate, carbamazepine, clozapine, haloperidol, olanzapine, risperidone, paliperidone, quetiapine, aripiprazole.

Exclusion criteria were the following: a) co-presence of a diagnosis of dementia, delirium or intellectual disability; b) standard informed consent to treatments and personal data collection consent not provided by patient or his legal representative.

All patients were submitted to standard care usually provided in the recruiting unit. The study was carried out in accordance with the principles of the 1983 Declaration of Helsinki and was approved by the Local Ethical Committee. Since the participation to the study did not imply any variation from standard care, in compliance with current legislation, specific informed consent for the participation to the study has not been collected. However, patients gave written standard informed consent to treatments and personal data collection, as routinely carried out in the unit.

Clinical and adherence assessment

All patients were evaluated through a semi-structured interview at the moment of inclusion in the study, assessing socio-demographic, biographic, anamnestic and clinical variables. TDM has been performed at the admission in the unit or, when not possible, before the first assumption of the monitored drug. Patients whose plasmatic drug concentration was within the dose-related reference range (DRRR) have been considered adherent to treatment, while those with drug concentration below the lower limit of DRRR have been considered non-adherent.

All subject were assessed at baseline (T0) with the following evaluation instruments: the Clinical Global Impression scale (CGI) [16]; the Brief Psychiatric Rating Scale (BPRS) [17] which encode 5 sub-scales evaluating different psychopathological dimensions: anxiety and depression (BPRS-1), negative symptoms (blunted affect, emotional

withdrawal, motor retardation) (BPRS-2), thought disorder (BPRS-3), activation (BPRS-4), hostility-suspiciousness (BPRS-5); the Services Engagement Scale (SES) [18]; the Global Assessment of Functioning scale (GAF) [19], with reference to the global functioning prior to the clinical relapse that lead to hospitalization; the Medication Adherence Rating Scale (MARS) for the psychoses [20,21] and the Udvalg for Kliniske Undersøgelser - Side Effect Rating Scale (UKU) for evaluation of psychopharmacological treatment side effects [22]. Patients were assessed at discharge (T1) with CGI and BPRS, to evaluate clinical and psychopathological course during hospitalization.

Statistical analysis

Statistical analyses were performed using the Software System Statistical Package for the Social Sciences, SPSS, version 25 for Windows (SPSS, Chicago, IL, USA). Continuous numerical variables were expressed as mean and standard deviation, while categorical variables were expressed as frequencies (absolute and percentage values). Univariate analyzes were carried out to compare the group of adherent patients with that of non-adherents. Analysis of variance (One-way ANOVA) for continuous variables and the Chi-Square test for categorical variables were used for this comparison.

A multivariate binary logistic regression was performed with the backward selection method of socio-demographic and clinical variables inserted in the model. The results of the multivariate analysis were described as Odds Ratios (OR) with their corresponding 95% confidence intervals (CI 95%). All the variables that showed Odds Ratio (OR) ≥ 1 have been considered as positive predictive factors on the adherence outcome, while those that show OR < 1 are to be considered negative predictive factors. OR with CI 95% including value 1 were not considered significant. The predictive power of the model was obtained from the percentage of patients correctly classified by multivariate analysis. The percentage of variance explained by the model was calculated with Nagelkerke's R2 index, which ranges from 0% (random predictions) to 100% (perfect predictions).

Results

Seventy-nine patients were enrolled in the present study. Socio-demographic and clinical variables of the sample are shown in Table I.

According to the results of TDM, this sample has been divided into two groups: adherent patients (n = 46; 58.2%) and non-adherent patients (n = 33; 41.8%). Adherent subjects showed significantly higher scores on BPRS anxiety and depression sub-scale (p = 0.026) and significantly lower scores on the BPRS thought disorder sub-scale (p = 0.020) and in the SES score (p = 0.019), highlighting a better relationship with mental health services. Univariate analysis results are displayed in Table II.

The regression model was statistically significant (p = 0.003) (Tab. III). The variables of the model were able to explain the 27.4% of the variance (R2 Nagelkerke). The model could correctly classify 80.4% of adherent patients, 57.6% of non-adherent patients and overall 70.9% of patients as adherents. Two variables of the model were statistically significant: the DOI and the service engagement. A higher duration of illness (OR = 0.948; p = 0.029) and a lower service engagement (i.e. a higher score on the SES scale; OR = 0.885; p = 0.002) negatively affected adherence.

Discussion and conclusions

Adherence rate (58,2%) was similar to those found in literature on schizophrenia spectrum disorders (51-70%) [23] and bipolar disorders (20-60%) [5]. This data confirms the necessity to improve adherence in patients with these two classes of major mental disorders.

The correlation between gravity of symptoms at BPRS and adherence needs to be prudently considered. BPRS anxiety and depression sub-scale scores resulted more elevated in adherent than in non-adherent subjects, while thought disorder sub-scale scores resulted lower in adherent than in non-adherent patients. A correla-

Table I. Socio-demographic and clinical variables of the sample (n = 79).

Sex, M/F (% of M)	48/31 (60,8)
Age, mean ± SD, years	48,0 ± 13,8
Education, mean ± SD, years	11,0 ± 3,5
Employment, n (%)	24 (30,4)
Married or stable relationship, n (%)	29 (36,7)
Ethnicity, Caucasian, n (%)	71 (89,9)
Duration of illness, mean ± SD, years	20,6 ± 11,9
Origin, own domicile, n (%)	67 (84,8)
Substance Use Disorder, n (%)	16 (20,3)
Smoke, n (%)	44 (55,7)
Medical comorbidity, n (%)	46 (58,2)
Prior hospitalizations for mental disorder, ≥ 5, n (%)	39 (49,4)
Diagnosis, SSD/BD (% of SSD)	35/44 (44,3)
Psychiatric comorbidity, n (%)	24 (30,4)
Compulsory hospitalization, n (%)	14 (17,7)
Monitored drug, AP/MS (% of AP)	37/42 (46,8)
Good adherence evaluated through TDM, n (%)	46 (58,2)
BPRS total, mean ± SD	44,9 ± 10,9
GAF, mean ± SD	56,6 ± 13,7

SD: standard deviation; TDM: therapeutic drug monitoring; SSD: schizophrenia spectrum disorders; BD: bipolar and related disorders; AP: antipsychotics; MS: mood stabilizers; BPRS: brief psychiatric rating scale; GAF: global assessment of functioning.

Table II. Univariate analysis results.

Socio-demographic and clinical variables	Adherent (n = 46)	Non-adherent (n = 33)	F/χ^2	P
Sex, M/F	25/21	23/10	1.899	0.168
Age, mean ± SD, years	46.5 ± 15.2	50.1 ± 11.5	1.276	0.262
Education, mean ± SD, years	10.7 ± 3.5	11.4 ± 3.5	0.700	0.405
Employment, n (%)	12 (26.1)	12 (36.4)	0.959	0.327
Married or stable relationship, n (%)	17 (21.5)	12 (15.2)	0.003	0.957
Ethnicity, Caucasian, n (%)	39 (84.8)	32 (97.0)	3.136	0.077
Duration of illness, mean ± SD, years	18.7 ± 12.8	23.2 ± 10.1	2.884	0.094
Origin, own domicile, n (%)	40 (86.9)	27 (81.8)	0.394	0.530
Substance Use Disorder, n (%)	11 (23.9)	5 (15.1)	0.913	0.339
Medical comorbidity, n (%)	24 (52.2)	22 (66.7)	1.659	0.198
Prior hospitalizations for mental disorder, ≥ 5, n (%)	24 (52.2)	15 (45.4)	0.347	0.556
Diagnosis, SSD/BD (% of SSD)	21/25 (45.6)	14/19 (42.4)	0.081	0.776
Psychiatric comorbidity, n (%)	16 (34.8)	8 (24.2)	1.009	0.315
Compulsory hospitalization, n (%)	10 (21.7)	4 (12.1)	1.219	0.270
Monitored drug, AP/MS (% of AP)	22/24	15/18	0.043	0.835
UKU adverse drug reaction severity, mean ± SD	0.2 ± 0.5	0.3 ± 0.6	0.259	0.612
BPRS anxiety and depression, mean ± SD	10.9 ± 4.4	8.6 ± 4.4	5.165	0.026*
BPRS negative symptoms, mean ± SD	9.3 ± 3.8	8.6 ± 4.7	0.427	0.515
BPRS thought disorder, mean ± SD	8.6 ± 4.0	10.9 ± 4.5	5.608	0.020*
BPRS activation, mean ± SD	7.8 ± 3.4	9.0 ± 3.2	2.188	0.143
BPRS hostility-suspiciousness, mean ± SD	7.8 ± 4.7	8.3 ± 4.1	0.250	0.619
BPRS total, mean ± SD	44.6 ± 10.5	45.2 ± 11.7	0.055	0.815
CGI severity of illness, mean ± SD	4.6 ± 0.8	4.9 ± 0.9	2.333	0.131
CGI improvement, mean ± SD	2.3 ± 0.8	2.2 ± 0.7	0.079	0.779
CGI efficacy index, mean ± SD	5.8 ± 2.7	5.9 ± 2.8	0.007	0.933
GAF, mean ± SD	57.8 ± 11.6	54.9 ± 16.3	0.851	0.359
MARS, mean ± SD	4.4 ± 2.5	5.4 ± 2.9	2.590	0.112
SES, mean ± SD	17.0 ± 8.6	21.5 ± 7.7	5.757	0.019*

** p < 0.05; SD: standard deviation; TDM: therapeutic drug monitoring; SSD: schizophrenia spectrum disorders; BD: bipolar and related disorders; AP: antipsychotics; MS: mood stabilizers; UKU: udvalg for kliniske undersøgelser; BPRS: brief psychiatric rating scale; CGI: clinical global impression; GAF: global assessment of functioning; MARS: medication adherence rating scale; SES: service engagement scale.*

tion between a greater severity of thought disorders and poor or absent adherence therefore emerges from our sample. Such result is consistent with previous findings on similar populations [24]. About services engagement, a higher engagement measured by SES was found in adherent patients, compared with the non-adherent group. Furthermore, in the regression model, a higher SES score (i.e. lower service engagement) was a variable strongly associated with non-adherence. These results agree with those reported in literature, according to which a good therapeutic alliance and a solid service engagement influence positively patients' compliance to treatments [25]. Finally, illness duration was found to be strongly associated with low adherence. This finding, likely based on a bidirectional correlation, confirms that patients affected by a chronic and severe disorder, possibly with a positive history of scarce adherence, should be particularly addressed in terms of adherence support, with an even stronger assistance from mental health care services [26].

The originality of the present study lies on the choice of the sample: acute inpatients in a real-world setting were assessed. This kind of samples are poorly represented in literature on adherence, which considers more frequently outpatients. Secondly, TDM for first- and second-generation antipsychotics, besides TDM for mood stabilizers, is poorly studied in real world settings and currently scarcely employed in clinical practice.

Table III. Regression model.

Socio-demographic and clinical variables	OR (CI 95%)	P
Education	0.883 (0.759 - 1.026)	0.104
Employment	0.305 (0.083 - 1.127)	0.075
Duration of illness	0.948 (0.904 - 0.995)	0.029*
Prior hospitalizations for mental disorder, ≥ 5	2.553 (0.829 - 7.863)	0.102
SES	0.885 (0.819 -0.957)	0.002†

** $p < 0.05$; † $p < 0.01$; OR: odds ratio; CI-95%: confidence interval at 95%; SES: service engagement scale. OR > 1 are associated with good adherence to the psychopharmacological treatment (antipsychotic or mood stabilizer), directly assessed by therapeutic drug monitoring (TDM).*

For further research, sample size has to be implemented in order to obtain results with a greater effect size, greater accuracy and higher statistical power. Moreover, the impact of possible confounding or effect-modifying variables such as cigarette smoking and drugs interaction on TDM has to be assessed.

In conclusion, according to the results obtained, within inpatients admitted for acute psychosis, valid alliance with mental health services is strongly associated with good compliance with psychopharmacological therapy assessed through TDM, whereas thought symptoms and longer duration of illness are related with poor adherence.

Implications for psychiatric care

- Non-adherence is a frequent finding in patients admitted to psychiatric units for acute psychosis and is often mistaken for resistance to treatment.
- Therapeutic drug monitoring (TDM) represents a useful, precise and objective evaluation of adherence to psychopharmacological treatments.
- Long duration of illness and severe thought disorder are often associated with non-adherence.
- Good alliance with mental health services contributes to treatment adherence.

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