

Post-discharge medication adherence in schizophrenia

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Summary

Aim: To assess medication adherence and risk factors for non-adherence in outpatients with schizophrenia after hospital discharge.

Method: Patients with schizophrenia (n=40) were recruited one month after hospital discharge after an acute episode and followed up for 5 months. Medication adherence, relevant clinical variables and socio-demographic factors were assessed at baseline and at the end of follow-up.

Results: One month after hospital discharge 32.5% of the patients showed high treatment adherence, but six months after discharge adherence rates dropped to 16.7%. While antipsychotic side-effects differentiated adherent from non-adherent patients at baseline, both groups were differentiated at follow-up by the level of insight. Non-adherence in the first month after hospital discharge and hospitalization in the previous year predicted further non-adherence.

Discussion: Medication adherence in schizophrenia decreases substantially after hospital discharge with partial adherence being common in clinical practice. Risk factors for non-adherence have been identified. The post-discharge period seems important for establishing high treatment adherence in schizophrenia.

Conclusions: Vigorous interventions should be applied in the post-discharge period in community-based settings in order to improve medication adherence and outcome in outpatients with schizophrenia.

adherence/post-discharge/risk factors/antipsychotics/schizophrenia

INTRODUCTION

Medication adherence is essential in schizophrenia as pharmacotherapy is the mainstay in managing this chronic and often disabling disease. Nevertheless, non-adherence to antipsychotic medication is common in clinical practice and affects approximately 50% of outpatients with schizophrenia [1]. Although treat-

ment discontinuation is rare, partial adherence, i.e. dose omissions, dose reduction, additional doses or “drug holidays”, is an even more pervasive problem, partly because it often remains undetected [1-3]. Suboptimal medication adherence in schizophrenia may have serious negative consequences for patients and society, including higher rates of relapse and rehospitalizations [1, 4], violence and self-harm [4, 5], poorer outcome [3, 5] and increased healthcare costs [6].

A number of disease-related, patient-related, treatment-related and environmental factors may influence adherence in schizophrenia [1, 4, 7]. Among the variables most consistently found

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to predict antipsychotic medication adherence are illness insight [4, 7], the severity of psychopathology [7], cognitive impairments [8], attitudes toward medication [4, 9], substance abuse [2], antipsychotic side-effects [10] and the quality of the therapeutic relationship [11]. No single factor or a set of risk factors have been identified to reliably predict medication-taking behaviour in all patients with schizophrenia, suggesting that interventions for improving medication adherence should focus on individual patient needs.

In addition, adherence rates vary over time, even in the same individual [1]. Despite the view that medication adherence in schizophrenia is high after hospital discharge, the transition to home-based treatment may be complicated, especially for those individuals who lack family or social support [12]. Weiden et al. [13], in a large observational study of patients with schizophrenia, found that almost half of the prescription gaps occurred in the first 50 days after starting a second-generation antipsychotic. Furthermore, 15-25% of patients with schizophrenia failed to adequately adhere to treatment in the first 7 to 10 days after hospital discharge [14]. The post-discharge period seems important for establishing and maintaining high treatment adherence in schizophrenia. Better knowledge of fluctuations in medication adherence could have practical implications in focusing more precisely the interventions for enhancement of treatment adherence to specific periods in the course of the illness related to higher risk of non-adherence.

The aim of this study was to explore the stability of treatment adherence and the risk factors for non-adherence in outpatients with schizophrenia discharged from hospital after an admission for an acute psychotic exacerbation.

METHOD

Participants

Medical records of all patients discharged from active treatment in a psychiatric clinic in Sofia, Bulgaria, one month before the study were examined. Patients with a diagnosis of schizophrenia according to the criteria of the *International*

Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) were contacted. Inclusion criteria were a diagnosis of schizophrenia, treatment with an oral antipsychotic, age above 18 years and signed informed consent. Exclusion criteria were: a first psychotic episode, drug or alcohol dependence, organic brain disorders and re-admission to a psychiatric ward in the first month after hospital discharge.

Assessment and measures

Patients were interviewed within a month after discharge from acute hospitalization (T_0) and five months later, i.e. six months after hospital discharge (T_1). Assessments of medication adherence, drug attitudes, psychopathology, level of insight, quality of therapeutic alliance and subjective side-effects of treatment were performed at T_0 and T_1 via a set of semi-structured clinical interviews and self-rating scales. Sociodemographic characteristics of the sample were obtained.

A Bulgarian translation and back-translation of the instruments prepared for the purpose of a previous study on medication adherence in schizophrenia [15] was used. All of the self-rating scales applied were validated prior to the study in a sample of 30 Bulgarian outpatients with schizophrenia.

Adherence

The Medication Adherence Questionnaire (MAQ) was used to assess adherence levels in the sample [16]. MAQ is a four-item self-report questionnaire assessing medication-taking behaviour. The items produce a total score ranging from 0 to 4, with higher scores indicating higher adherence.

Drug attitudes

The Drug Attitude Inventory 10 (DAI-10) is an abbreviated form of DAI-30 and consists of 10 yes/no statements reflecting patients' experiences of and attitudes towards medication [17]. The correlation between the scales in a sample

of patients with schizophrenia was shown to be high (0.94) [18]. A positive total score of the scale predicts high treatment adherence.

Insight

The Schedule for the Assessment of Insight (SAI) is a semi-structured clinical interview providing an assessment of the three main components of insight – recognition of illness, treatment adherence and symptom re-labelling [19]. Higher total scores indicate better insight. The scale revealed significant correlations with other instruments for assessment of insight [20].

Psychopathology

The Brief Psychiatric Rating Scale-Expanded (BPRS-E) is a widely used observer-rated scale consisting of 24 items [21]. It is a sensitive and effective measure of psychopathology and treatment-related symptom change [22].

Side-effects

The Liverpool University Neuroleptic Side Effect Rating Scale (LUNTERS) [23] is a 51-item, four-point Likert type scale measuring the subjectively perceived side-effects of antipsychotic medication, focusing on the previous month of treatment. A low total score indicates fewer reported side-effects.

Therapeutic relationship

The Helping Alliance Scale (HAS) [24] is a self-rating scale exploring the patient's view of the therapeutic relationship with the healthcare professional. It consists of six items regarding basic aspects of the therapeutic relationship, with a higher total score indicative of higher quality of the therapeutic alliance.

Statistical analysis

Descriptive statistics, statistical variation and correlation analysis were performed to analyse

the relationship between adherence levels and the studied variables. After dichotomizing the sample according to the adherence levels, Student's *t*-test, Fisher's exact test and Mann-Whitney *U*-test analyses were performed to explore the differences of the studied clinical variables and socio-demographic factors between the adherence groups at baseline and at T_1 . A logistic regression analysis was carried out, using the dichotomized global score of the MAQ at T_1 as a dependent variable and the studied clinical and socio-demographic characteristics as predictor variables. The SPSS (version 16.0 for Windows) was used in all cases for statistical analysis.

RESULTS

A total of 45 patients with schizophrenia, consecutively discharged from acute psychiatric hospitalization were contacted within a month after hospital discharge (mean time to first contact 29.2 days, $SD=2.99$). Informed consent for participation in the study was given by 40 patients (88.8%). The mean duration of the psychiatric admission was 21.7 days ($SD=6.81$). At T_1 three of the patients reported a psychiatric admission during the study period and one patient could not be contacted. These four patients were excluded from the statistical analysis at T_1 . Significant differences were found regarding the severity of positive symptoms at T_0 between the patients with a psychiatric admission during the follow-up period and the rest of the sample ($p=0.023$), but no differences were found regarding adherence levels, socio-demographic and illness-related factors and other clinical variables assessed in the study.

Adherence levels in the sample at T_0 , i.e. one month after discharge from acute hospitalization, were in the range of partial adherence – the mean MAQ score was 2.40 ($SD=1.41$). One-third of the patients (32.5%) were fully adherent to the prescribed treatment regimen (score of 4 on MAQ), 40% showed partial adherence (score of 3 or 2 on MAQ, 15% and 25.0% respectively) and 27.5% were non-adherent (score of 1 or 0 on MAQ, 15.0% and 12.5% respectively). For the main analysis the MAQ scores were dichotomized by classifying the 13 patients with

a score of 4 as adherent (32.5%) and the 27 patients with a score of 3 to 0 as non-adherent/partially adherent (67.5%).

The socio-demographic characteristics of the total sample at T_0 were quite typical for individ-

uals with chronic schizophrenia (Table 1). No significant differences were found between the adherence groups regarding the patients' socio-demographic characteristics.

Table 1. Socio-demographic characteristics of the sample and differences between adherent and non-adherent patients at T_0 .

Variable	Total sample n=40	Adherent patients n=13	Non-adherent patients n=27	Test (two-tailed)	P
Age, years: mean (SD)	42.65 (10.54)	44.38 (9.81)	41.81(10.95)	t-test	0.478
Female, n (%)	22 (55.0)	5 (38.5)	17 (63.0)	F*	0.185
University education, n (%)	12 (30.0)	5 (38.5)	7 (25.9)	F*	0.209
Occupational status, n (%)					
– employed	4 (10.0)	1 (7.7)	3 (11.1)	U-test	0.826
– receiving disability benefits	26 (65.0)	8 (61.5)	18 (66.7)	U-test	0.734
Married/cohabiting, n (%)	6 (15.0)	1 (7.7)	5 (18.5)	U-test	0.884
Living alone, n (%)	26 (65.0)	9 (69.2)	17 (63.0)	F*	0.413

*F: Fisher's exact test.

The mean illness duration was 15.77 years (SD=8.53). Most of the patients received a monotherapy with an atypical antipsychotic (87.5%) and had one or more hospitalizations in the year prior to the study (65.0%). Only 30% of the sample participated in a psychosocial rehabilitation programme after the hospital discharge and during the follow-up period. The adherent patients were found to have significantly lower number of hospitalizations in the previous year compared with the patients with treatment non-adherence ($p=0.020$).

A significant decrease in the adherence rates in the sample was observed from T_0 to T_1 ($t=3,250$;

$df=35$, $p=0.003$), with a mean T_1 MAQ score of 1.83 (SD=1.36). At T_1 there were 6 individuals (16.7%) adherent to treatment and 30 (83.3%) non-adherent.

At the end of the follow-up period (T_1) there was a significant reduction in the severity of the psychopathology ($p<0.000$) and the perceived side-effects ($p=0.017$). Based on the total scores on HAS, patients reported an improved quality of the therapeutic relationship at T_1 compared with T_0 ($p=0.046$). Attitudes toward medication and the level of insight in the sample remained relatively stable during the study period (Table 2).

Table 2. Mean values of the studied variables and differences at T_0 and T_1 in the total sample.

Variable	Scale (total score)	Total sample		P*
		T_0 (n=40)	T_1 (n=36)	
Adherence, mean (SD)	MAQ	2.40 (1.41)	1.83 (1.36)	0.003
Attitudes, mean (SD)	DAI-10	6.00 (1.87)	5.99 (1.70)	0.466
Psychopathology, mean (SD)	BPRS-E	39.56 (8.40)	31.50 (7.07)	0.000
Insight, mean (SD):	SAI	7.35 (3.69)	9.15 (2.88)	0.165
- illness awareness		3.52 (2.33)	4.84 (1.46)	0.205
- need of treatment		2.88 (1.28)	3.15 (0.89)	0.367
- symptom re-labelling		0.91 (1.46)	1.15 (1.34)	0.461
Side-effects, mean (SD)	LUNSERS	30.94 (21.31)	19.44 (10.38)	0.017
Therapeutic alliance, mean (SD)	HAS	37,83 (9,26)	38.00 (5.93)	0.046

*t-test (two-tailed). Bold denotes significance.

The level of insight (total score on the SAI) was the only variable differentiating the adherent from non-adherent patients at T₁ (p=0.037). The difference between the adherence groups regarding the subjective experienced side-

effects at T₀ approached significance (p=0.051). The severity of the psychopathology, attitudes toward medication and the quality of the therapeutic alliance did not differentiate the patients in the adherence groups at T₀ and T₁ (Table 3).

Table 3. Mean values of the studied variables and differences between the adherence groups at T₀ and T₁.

Variable	Scale	T ₀		T ₁	
		Adherence n=13	Non-adherence n=27	Adherence n=6	Non-adherence n=30
Attitudes toward treatment, mean (SD)	DAI-10	5.66 (1.81)	6.28 (1.92)	5.98 (1.68)	6.00 (1.71)
Psychopathology, mean (SD)	BPRS-E	38.42 (8.24)	40.65 (8.67)	28.33 (5.85)	32.36 (7.37)
Insight, mean (SD):	SAI	7.21 (4.45)	7.47 (2.94)	11.66 (1.52)*	8.40 (2.79)*
-illness awareness		4.42 (1.92)	4.42 (1.59)	6.00 (0.41)	4.50 (1.50)
-need of treatment		1.63 (1.80)	2.52 (1.60)	4.00 (0.52)*	2.90 (0.87)*
-symptom re-labeling		1.15 (1.70)	0.52 (1.03)	1.66 (1.52)	1.00 (1.33)
Side-effects, mean (SD)	LUNSERS	22.85 (14.04)*	36.60 (23.92)*	10.00 (9.09)	9.37 (11.09)
Therapeutic alliance, mean (SD)	HAS	39.10 (8.83)	36.50 (9.77)	43.00 (7.88)	37.54 (6.00)

* Differences significant at p<0.05 level; t-test (two-tailed).

The logistic regression analysis revealed two variables that were independently associated with medication non-adherence: medication non-adherence in the first month after hospital discharge and one or more hospitalizations in the previous year. The odds ratio, which represents the increased relative risk of medication non-adherence, was 4.8 (CI=1.9 to 11.9) for medication non-adherence after hospital discharge and 4.2 (CI=1.6 to 10.8) for hospitalizations in the year prior to the study. The severity of the psychopathology, attitudes toward medication, antipsychotic treatment side-effects and quality of the therapeutic alliance were not significantly related to medication non-adherence in the sample.

DISCUSSION

The present study explores the adherence rates, stability of medication adherence and predictors of treatment non-adherence in outpatients with schizophrenia after a hospital discharge for acute exacerbation.

One month after hospital discharge medication adherence rates in the sample were in the

range of *partial* adherence. Partial medication adherence is common in outpatients with schizophrenia and can have a profound impact on the prescribing behaviour, patient outcomes and healthcare costs in schizophrenia [1]. Nevertheless, it often remains undetected in clinical practice until psychotic symptoms emerge or are exacerbated [25]. An additional effort should be put into timely recognition of partial adherence in primary care and psychiatric settings.

During hospitalization in a psychiatric ward, medication-taking behaviour is closely supervised by the medical personnel and medication adherence approaches 100%. In this regard, the present study revealed a substantial decrease in medication adherence one month after hospital discharge (32.5% of the sample were adherent at T₀). The adherence rates in the sample six months after discharge from an acute psychiatric ward were even lower at 16.7%. However, when classifying the patients as adherent or non-adherent, it is of note that treatment discontinuation is rare in clinical practice, and partially adherent patients could still benefit from the treatment depending on medication dosage, half-life, therapeutic range etc. This could explain the relatively low levels of psychopathology in the sample despite inadequate adherence rates.

Medication adherence is assumed to be a dynamic variable. It is usually good after hospital discharge and tends to decrease with time. Nevertheless, Berger et al. [26] found that during the six-month period following hospitalization, patients with schizophrenia ($n=43$) received an average of 101 therapy-days and the mean medication possession ratio at six months was 55.1%.

The present study found even higher non-adherence rates in the first six months after a hospital discharge. A possible explanation of the rapid decrease in medication adherence we observed could be the lack of supervision of medication-taking behaviour in community-based settings and the type of healthcare system in Bulgaria, where public outpatient services provide psychiatric assessment and medication but no psychosocial rehabilitation (public psychosocial rehabilitation programmes are few and lack regular funding).

Family caregivers could help patients with schizophrenia to maintain high medication adherence, but 65% of the sample reported they are living alone. Lack of social or family support may adversely affect adherence, necessitating the assistance of healthcare professionals, such as social workers [12].

Only 30% of the sample participated in a psychosocial rehabilitation programme on a regular basis after hospital discharge, but these programmes varied significantly in their approach (cognitive-behavioural and psychoanalytical therapies, psychoeducation, art therapy, group or individual setting) and were not primarily focused on improving medication adherence among the participants. This, along with the relatively small sample size, may explain the lack of correlations between adherence rates in the sample and participation in a psychosocial rehabilitation programme. Despite the fact that the literature provides evidence for the effectiveness of psychosocial interventions in improving medication adherence in schizophrenia [27], this opportunity is underused in Bulgaria as a way of improving treatment adherence and outcomes in patients with schizophrenia.

Despite the significant decrease in adherence rates in the sample from T_0 to T_1 , the psychopathology, mild to moderate at baseline, decreased further during the follow-up period. A possible contributing factor may be the relatively short

period of inpatient care (21.7 days) that is often insufficient for achieving full treatment efficacy of the antipsychotics. It could be seen within weeks and months after initiating treatment, which overlaps with the follow-up period in the present study. In addition to this, total non-adherence, meaning treatment discontinuation, was low in the sample. Partial adherence was the main pattern of non-adherence, and partially adherent patients could still have suboptimal but positive effects of treatment resulting in a decrease of the psychopathology. What is more, there is a subgroup of patients with schizophrenia who continue to function well for a number of years without treatment [28].

At the end of the follow-up period the only variable differentiating adherent from non-adherent patients was the level of insight (total score on the SAI). Lack of illness insight is one of the most consistently found predictors of medication non-adherence in schizophrenia [1, 4, 9]. Nevertheless, one month after hospital discharge there was no significant difference between the adherence groups in the sample regarding the level of insight. To the contrary, Yen et al. [29], in a prospective study of 74 patients with schizophrenia and 65 patients with bipolar disorder, found in the schizophrenia group a significant association between adherence levels and insight into treatment (one of the components of insight) at index interview, but not one year later. The authors referred to the study of Tait et al. [30], in which the recovery style from a psychotic episode, rather than insight or symptoms, predicted further service engagement.

Attitudes toward medication were relatively stable during the study period, despite the substantial decrease in the adherence levels from baseline to the end of the follow-up. Although used for assessment of medication adherence in some studies, these results demonstrate that attitudes toward medication are not equivalent to medication-taking behaviour, which is in line with the Expert Consensus Guidelines [1]. Other factors, such as financial difficulties, cognitive impairments etc., may negatively affect patients' adherence, despite their positive attitudes toward medication.

The present study found two factors predictive of medication non-adherence in the sample – medication non-adherence one month af-

ter hospital discharge and a history of psychiatric hospitalization in the previous year.

Medication adherence at index interview was shown to predict further medication adherence in outpatients with schizophrenia [1, 2, 29, 31]. In a large, three-year, prospective observational study with outpatients with schizophrenia ($n=6731$) starting or changing an antipsychotic, Novick et al. [2] found that the strongest predictor of adherence was medication adherence in the month before the baseline assessment. Similar results were reported by Ascher-Svanum et al. [5] in a three-year prospective study of 1579 patients with schizophrenia where the best single predictor of future non-adherence was non-adherence during the six months prior to enrolment in the study. Non-adherence to therapy at baseline and newly starting antipsychotics were both found to increase the likelihood of non-adherence up to 12-fold in the studied patients with schizophrenia (a total of 28,238) [31]. Although a dynamic variable, 'medication non-adherence, once established, seems to have a discrete persistence, at least in the absence of dedicated interventions' [32]. It is proposed that individual proneness to poor medication-taking behaviour is a relatively stable trait [32].

The link between medication non-adherence and subsequent hospitalizations in schizophrenia is consistently reported in the literature [33-35]. In a retrospective study of 12,032 patients with schizophrenia, one of the predictors of hospitalization risk during one-year period was non-adherence to the antipsychotic therapy [33]. Gilmer et al. [35] reported that rates of psychiatric hospitalization were substantially lower among adherent (14%) than partially adherent (24%) or non-adherent (35%) patients. Non-adherence to treatment is an important predictor of hospitalization risk. However, the present study found a converse relationship – non-adherence in patients with schizophrenia could be predicted by the presence of one or more hospitalizations in the previous year. Similar results were reported by Novick et al. [2], who found hospitalization in the previous six months, alcohol dependence, substance abuse and independent living to be predictive of non-adherence in patients with schizophrenia.

A practical implication of the findings in the present study could be increased attention to pa-

tients with a history of non-adherence and one or more hospitalizations in the previous year, and a timely application of interventions focusing on the enhancement of medication adherence even without the evidence of present non-adherence.

LIMITATIONS

Several limitations of this study should be acknowledged. First, measurement of adherence was patient-rated and self-rating scales tend to overestimate the actual adherence, though they were shown to correlate significantly with the serum concentration of medication [36]. Second, the sample consisted of patients recently admitted for an acute psychotic exacerbation. One of the main predictors of relapse and hospitalization in patients with schizophrenia is antipsychotic medication non-adherence. Thus, adherence rates in the sample may differ significantly from those of stabilized outpatients with schizophrenia, which limits the generalizability of our findings. Third, the study was not powered to detect differences between adherent and non-adherent patients. This could explain the lack of significant differences between the groups regarding the socio-demographic and illness-related characteristics. And fourth, despite the relatively wide range of potentially important factors assessed in the study, relevant variables with possible impact on treatment adherence in schizophrenia (such as cognitive impairments, financial difficulties, dosage), which could add to the predictors of non-adherence found in the sample, were not included.

In conclusion, medication adherence in outpatients with schizophrenia decreases substantially after a hospital discharge for an acute exacerbation, with only 16.7% of the patients maintaining high adherence rates six months later. Non-adherence in the first month after hospital discharge and psychiatric hospitalization in the previous year predict further non-adherence. Patients at risk of non-adherence are suitable for vigorous post-discharge interventions for enhancing treatment adherence and outcomes in schizophrenia.

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