Patient perception of medication benefit and early treatment discontinuation in a 1-year study of patients with schizophrenia

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Objective: The objective of this study was to examine the relationship between patient beliefs about medication use and their likelihood of discontinuing treatment prematurely. Associations of patient beliefs about medication with clinical psychopathology and their life satisfaction were also assessed.

Methods: This post-hoc analysis used data from a randomized, open label, 1-year trial of antipsychotics in the treatment of patients with schizophrenia or schizoaffective disorders (N = 664). Medication management including dosage adjustment and medication switching was at doctors' discretion, reflecting naturalistic treatment in usual clinical care settings. Early treatment discontinuation was defined as all-cause study drop out. Patient-reported beliefs about medication were assessed by Rating of Medication Influences (ROMI), degree of clinical psychopathology was measured by Positive and Negative Syndrome Scale (PANSS), and patient quality of life was measured by Lehman Quality of Life Interview (LQLI).

Results: Patient perception of medication benefit was the only strong predictor of treatment duration among the 5 underlying dimensions of medication influence. Higher level of perceived beneficial effect of medication was associated with reduced risk of early treatment discontinuation (Hazard ratio = 0.56, 95% Confidence Interval [0.40, 0.79], p = 0.001). Patients with greater beliefs in the beneficial effect of treatment also had better clinical psychopathology outcome and were more satisfied with their quality of life and well-being.

Conclusion: Understanding the predictors of early treatment discontinuation in the care of schizophrenia patients is important for the development of interventions to improve treatment outcome. Current findings suggest that patient perception of beneficial effect of medication may be a critical factor in achieving treatment persistence and a satisfactory treatment outcome.

Keywords: adherence, compliance, antipsychotic, schizophrenia, patient attitude

Background

The duration of maintenance treatment of schizophrenia-related disorders is a critical determinant of a patient's successful recovery. The consequences of sub-optimal antipsychotic treatment duration or poor treatment adherence include risk of relapse (Ayuso-Gutierrez and del Rio Vega 1997; Perkins 2002) and increased hospitalization (Ayuso-Gutierrez and del Rio Vega 1997; Perkins 2002) which may derail functional recovery. Despite the important role of persistence with medication, most patients do not stay in treatment with the initially prescribed medication and switch to other medication or discontinue treatment (Lieberman et al 2005; McEvoy et al 2006; Stroup et al 2006). In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study of 1493 patients with schizophrenia, patients randomized to 5 different antipsychotic drugs had all-cause discontinuation rates from 64% to 82% over an 18-month period (Lieberman et al 2005). Of these patients who discontinued their initial study medication, approximately 43% dropped out of the study opposed to approximately

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57% who switched treatments and entered Phase 1b or Phase 2 of the study (Lieberman et al 2005; McEvoy et al 2006; Stroup et al 2006, 2007).

There are many factors associated with poor treatment persistence. The Health Belief Model (HBM) suggests that patient likelihood to continue with medication intake is a product of an implicit and subjective assessment of the relative costs and benefits of the medicine in relation to personal goals and constraints (Becker and Maiman 1975; Fenton et al 1997; Perkins 1999). In this model, patients are more likely to stay in treatment of medication regimen when they believe that their need for treatment and the benefits of treatment outweigh the negative aspects.

Previous studies have found association between poor treatment persistence and negative aspects of treatment, including exacerbation of symptoms (Liu-Seifert et al 2005) and a 2-fold increase in the risk of psychiatric hospitalization (Valenstein et al 2002). The impact of patient perception of medication benefits on treatment persistence has not been well characterized. It has been reported that perceived benefits of medication have a greater influence on persistence levels than treatment adverse events (Perkins et al 2006). Psychotic patients who recognized positive effects of medication that were secondary to symptom relief were more likely to adhere to their treatment regimens.

The aim of the present study was to identify the specific aspects of patient perception of medication intake that are most influential for dropping out prior to completion of treatment in a large, 1-year randomized, open-label clinical trial of antipsychotics in the treatment of patients with schizophrenia-related disorders, in which medication management reflected usual clinical practice. Patients could switch medications and dosage during the trial based on the decision of the treating clinician. Thus, study drop-out would primarily be due to patient decision to discontinue treatment. This study also examined the relationship between patient beliefs about medication taking and psychopathology and their functional outcome. A better understanding of the factors that promote patient acceptance and persistence with treatment may lead to interventions to improve the management of schizophrenia patients.

Methods

This was a post-hoc analysis of a randomized, open-label, 1-year, multi-site effectiveness trial of antipsychotics in the treatment of patients with schizophrenia or schizoaffective disorder (HGGD). The study was conducted between May 1998 and September 2002 at 21 sites across 15 US states.

A brief description of the patient population and study design is provided here. Additional details can be found in the primary report of the trial (Tunis et al 2006).

Patient population

Male and female patients at least 18 years old who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder were screened for inclusion in this study. Eligible patients had a score of at least 18 on the Brief Psychiatric Rating Scale (BPRS$_{1-7}$, extracted from the PANSS). A total of 664 individuals were entered into the study (olanzapine [229], conventionals [214], and risperidone [221]). All treatment groups were collapsed and analyzed as a pooled sample. Table 1 lists the patient demographics, diagnosis, baseline illness characteristics and symptom severity. Institutional review board approval was secured, and written informed consent was obtained from all participants.

Study design

This effectiveness study enrolled a heterogeneous group of patients with a variety of psychiatric and medical comorbidities, including substance abuse. The study was designed to reflect usual clinical care of schizophrenia patients by leaving

Table 1 Baseline patient characteristics

Variable[a]	Overall[b]
Age, years, mean (SD)	42.8 (12.0)
Sex	
Female	244 (37%)
Male	420 (63%)
Race/Ethnicity	
Caucasian	361 (54%)
African American	224 (34%)
Other	79 (12%)
Primary psychiatric diagnosis	
Schizophrenia	431 (65%)
Schizoaffective disorder	228 (34%)
Schizophreniform disorder	5 (~1%)
Currently employed	128 (19%)
Age at 1st psychiatric hospitalization, yrs, mean (SD)	26.2 (9.5)
# of Previous episodes of schizophrenia, mean (SD)	6.8 (9.6)
Time in hospital (past yr) for mental/emotional problems Days, mean (SD)	9.1 (34.1)
Inpatient setting at trial entry	31 (5%)
PANSS total score, mean (SD)	86.9 (19.8)
LQLI satisfaction with social relations subscale, mean (SD)	13.9 (3.7)

Notes: [a]variables are presented as n (%) unless otherwise noted; [b]n = 664 for Age, sex, race/ethnicity, primary psychiatric diagnosis, currently employed, inpatient care setting, and PANSS; n = 584 for age at first psychiatric hospitalization; n = 644 for previous episodes of schizophrenia; n = 650 for time spent in hospital; n = 592 for LQLI satisfaction.

all medication management decisions to the physicians, who could adjust dosages and switch medications according to their clinical discretion. Participants were randomly assigned to begin treatment with one of three open-label antipsychotic regimens: 1) olanzapine as first-line treatment; 2) first-line treatment with a maximum of two (consecutive) conventional agents before a possible switch to olanzapine; and 3) risperidone as first-line treatment. Choice of a particular conventional agent was made by the treating physician and was based on an individual's clinical and treatment history. Initial dosing, titration, and dosing adjustments were determined by treating physicians, with instructions to consider clinical indications, as well as most current product labeling and package insert recommendations. Switching antipsychotic agents was also at the discretion of treating physicians. The simultaneous use of two antipsychotics was restricted to the interval needed for any switch. Most other psychotropic and nonpsychotropic medications could be used concomitantly.

Outcome measures

Patients' perception about their medication intake was measured with the modified version of ROMI scale (Weiden et al 1994). The ROMI scale is used to assess subjective reasons for medication compliance and noncompliance. The modified version used in the trial consisted of 19 items, each scored on a scale from 1 to 3. Patients were shown 9 statements that might reflect reasons for compliance and 10 statements with reasons for noncompliance, and were required to indicate the level of agreement between each statement and their own attitude toward medication on a 3-point scale: strong (3), mild (2), none (1). The ROMI was assessed at all post baseline visits, Visits 3 (2 weeks), Visit 4 (2 months), Visit 5 (5 months), Visit 6 (8 months) and Visit 7 (1 year), but was not available at baseline.

The PANSS (Kay et al 1987) was used to assess psychopathology. Five distinct symptom domains were assessed using PANSS factor scales (Davis and Chen 2001): positive symptoms, negative symptoms, disorganized thought, impulsivity/hostility, and anxiety/depression. PANSS was assessed at baseline and all post baseline visits.

The Lehman Quality of Life Interview (LQLI) was used at baseline and visits 4 (2 months), 5 (5 months), and 7 (1 year) to assess the life circumstances of patients in terms of what they actually do and experience (objective quality of life) and their feelings about these experiences (subjective quality of life or life satisfaction) (Lehman 1988).

Medication persistence was defined as remaining in the study for the full 1 year regardless of the specific medication. Conversely, early treatment discontinuation was defined as dropping out of study prior to completion of the trial for any cause. It is important to note that patients could switch medications based on the decision of the treating clinician and remain in the study. Thus, in this study treatment/study drop-out would primarily be a patient decision.

Statistical methods

All analyses in the current study were performed by pooling the 3 randomized treatment groups together. A two-sided alpha level of 0.05 was used for test of significance.

In order to identify the underlying dimensions of patient beliefs about medication intake, we conducted Principal Component Analysis (PCA) on ROMI. The factors were derived based on the first assessment time point for ROMI-visit 3 (2 weeks). Further factors analyses were also conducted at visit 4 (2 months), as well as for each of the randomized treatment groups individually to test the robustness of the constructed factors. The number of factors extracted was determined based on the criteria of an eigenvalue of 1 or greater. The VARIMAX rotational method was applied to obtain orthogonal rotation of the factors. Cronbach's coefficient alpha was used to measure internal consistency of the factors. Titles were assigned to each of the derived factors based on the clinical interpretation of the factors. The factor scores were created by averaging the items within each factor and were used to represent the factors.

To test the predictive value of the underlying dimensions of patient beliefs about medication intake on early treatment discontinuation, a Cox Regression model on time to early discontinuation was constructed with the derived ROMI factors as time-dependent covariates. Hazard Ratio (HR) and 95% Confidence Interval (CI) of HR, as well as the p-value based on the model, were obtained and reported.

The visit-wise mean scores of ROMI factors were given at visits 3 through 7 and the changes from visit 3 to visit 7 were tested for significance using Wilcoxon signed-rank test. Visit-wise mean scores in changes from baseline were given for the PANSS factors at visits 3 through 7 and for the LQLI subscales at visits 4, 5 and 7. Wilcoxon signed-rank tests were used for assessing the significance of these changes. The correlation of ROMI factors with PANSS factors were measured by Pearson's correlation coefficients at visits 3 through 7. The correlation of ROMI factors with LQLI subscales were measured by Pearson's correlation coefficients at visits 4, 5 and 7. We also examined relationship between ROMI factors

and changes in PANSS factors at visits 3 through 7 using Pearson's correlation coefficients.

Results

Patient beliefs about medication

Five factors were extracted as the underlying dimensions of patient beliefs about medication intake based on the modi-fied, 19-item version of ROMI scale using PCA: F1-Negative Aspects of Medication, F2-Denial of Illness, F3-Positive External Influence, F4-Perceived Medication Benefit and F5-Stigma. Table 2 lists the ROMI items that loaded onto each of the 5 factors and their loadings. For each factor, the correlation between each of its items and the total of all items for that factor is given. Cronbach's alphas based on all the items included in each factor are also provided in Table 2 to measure the internal consistency of each factor. To test the robustness of the derived factors, additional factor analyses were conducted for each of the randomized treatment groups as well as at different time points during the study and the resulting factors remained largely consistent.

Predictors of treatment discontinuation

Of the 5 underlying dimensions of patient beliefs about medi-cation taking, perceived medication benefit (composed of the perceived daily benefit, fear of relapse, side effect relief, and fulfillment of life goals items) was the only significant predictor of early treatment discontinuation (Table 3). A

higher level of perceived beneficial effect of medication was associated with reduced likelihood of early treatment discon-tinuation (HR = 0.56, 95% CI [0.40, 0.79], p = 0.001). This result indicated that, at any given visit where patient beliefs were assessed, a higher level of perceived medication benefit by one point, such as strong versus mild or mild versus none, was associated with 44% less risk of discontinuing from the study during the following visit.

Association with clinical outcome

There was a significant negative correlation between per-ceived medication benefit and all of the 5 PANSS factors at 2 weeks, indicating a greater belief in medication benefit was associated with a better state of clinical psychopathology (Table 4). This relationship persisted throughout the course of the 1-year study. No other ROMI factors were associ-ated with all 5 psychopathology domains. Greater level of perceived medication benefit was also found to be similarly and significantly associated with greater improvement in symptoms as measured by changes in all of the 5 PANSS factors at 2 weeks, 2 months and 1 year.

Perceived medication benefit was the only ROMI fac-tor that showed significant improvement during the study from 2 weeks to 1 year (p < 0.001) (Figure 1). Since ROMI was only collected after baseline, it was not possible to assess changes in patient beliefs from baseline over the first 2 weeks. All of the 5 PANSS factors had significant

Table 2 ROMI collapsed factors

ROMI factors	Loading of item on factor	Corr w/ total of collapsed factor items	Cronbach's alpha including all items
Factor 1- Negative aspects of medication			0.74
NC10. No daily benefit	0.73	0.52	
NC13. Interferes with life goals	0.68	0.58	
NC14. Distressed by side effects	0.74	0.60	
Factor 2-Denial of illness			0.72
NC11. Medications currently unnecessary	0.86	0.56	
NC12. Never was ill	0.77	0.56	
Factor 3-Positive external influence			0.72
C6. Positive relation with clinical staff	0.74	0.47	
C7. Outside positive opinion about taking medications	0.78	0.61	
C8. Outside opinion that current medication is better	0.75	0.56	
Factor 4-Perceived medication benefit			0.70
C1. Perceived daily benefit	0.78	0.54	
C2. Fear of relapse	0.72	0.50	
C3. Side effect relief	0.58	0.41	
C4. Fulfillment of life goals	0.72	0.52	
Factor 5-Stigma			0.64
NC15. Embarrassment/Stigma over med	0.83	0.47	
NC16. Change in appearance	0.73	0.47	

Abbreviation: ROMI, Rating of Medication Influences.

Table 3 Predictors of early treatment discontinuation based on ROMI factors

	Hazard Ratio	95% Confidence Interval	p value
ROMI factor 1	1.27	(0.91, 1.78)	0.16
Negative aspects of medication			
ROMI factor 2	1.10	(0.77, 1.59)	0.60
Denial of illness			
ROMI factor 3	0.87	(0.65, 1.18)	0.37
Positive external influence			
ROMI factor 4	0.56	(0.40, 0.79)	0.001
Perceived medication benefit			
ROMI factor 5	1.30	(0.89, 1.89)	0.17
Stigma			

Abbreviation: ROMI, Rating of Medication Influences.
Notes: Analysis based on Cox Regression model on time to early treatment discontinuation with ROMI factors as time-dependent covariates. Early treatment discontinuation was defined as all-cause study discontinuation.

improvement from baseline at all time points throughout the study ($p < 0.001$).

Association with quality of life

Patient beliefs about medication benefit were significantly correlated to most aspects of patients' subjective feelings about their quality of life as measured by LQLI subscales at 2 months, the first available visit for LQLI after baseline (Table 5). Similar patterns were observed at 5 months and 1 year. The data suggested subjective domains of LQLI had greater association with perceived medication benefit than objective domains as indicated by the magnitude of correlation coefficients.

Most LQLI subscales had significant improvement from baseline at all post baseline visits. Living situation was not significantly improved until 1 year post treatment, and amount of money spent on self was not improved until

5 months post treatment. Job, objective family contact, and social contact did not achieve significant improvement from baseline at any time point.

Discussion

Patient perception of medication benefits was the only strong predictor of medication persistence among the 5 underlying dimensions of medication influences. Poor perception of medication benefits significantly increased the likelihood of stopping treatment prematurely in the current 1-year study of medication management in usual clinical practice. Patients with greater beliefs in the beneficial effect of treatment also had better clinical symptoms, experienced greater symptom improvement, and were more satisfied with their quality of life and well-being.

Research on the impact of positive effect of medication as perceived by patients on treatment persistence has been

Table 4 Pearson's correlation coefficient between ROMI factors and PANSS factors at 2 weeks

Correlation coefficients (p value)	PANSS positive	PANSS negative	PANSS disorganized thought	PANSS hostility	PANSS depression
ROMI factor 1	−0.0986	−0.0685	−0.0776	0.0434	0.0457
Negative aspects of medication	(0.018)	(0.102)	(0.064)	(0.300)	(0.275)
ROMI factor 2	0.0191	0.0095	−0.0122	0.0284	−0.0594
Denial of illness	(0.649)	(0.822)	(0.772)	(0.499)	(0.157)
ROMI factor 3	0.0248	0.0764	0.0574	−0.0147	−0.0044
Positive external influence	(0.549)	(0.065)	(0.165)	(0.723)	(0.915)
ROMI factor 4	−0.2496	−0.2695	−0.2202	−0.1884	−0.1878
Perceived medication benefit	(<0.001)	(<0.001)	(<0.001)	(<0.001)	(<0.001)
ROMI factor 5	0.1113	0.0445	0.0639	0.2300	0.1584
Stigma	(0.007)	(0.281)	(0.121)	(<0.001)	(<0.001)

Notes: Greater level of perceived medication benefit was also found to be significantly associated with greater improvement in symptoms as measured by changes in all of the 5 PANSS factors at 2 weeks, 2 months, and 1 year.
Abbreviations: ROMI, Rating of Medication Influences; Factor 1, 2, and 5: greater score indicates poorer compliance attitude; Factor 3 and 4: greater score indicates greater compliance attitude; PANSS, Positive and Negative Syndrome Scale; greater score indicates more severe symptom for all 5 factors.
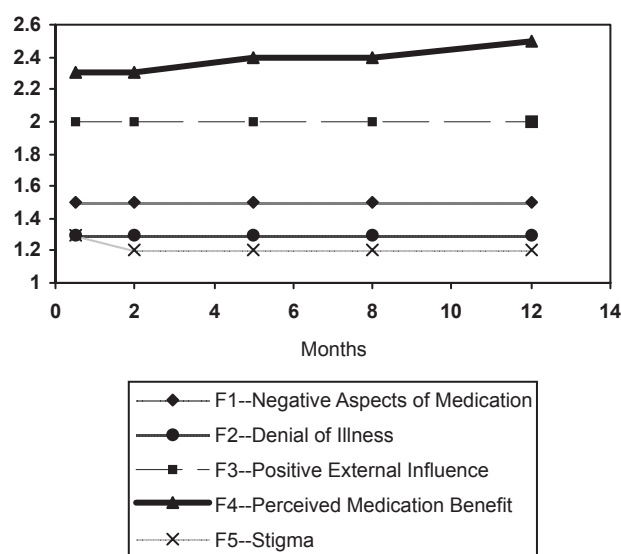
Figure 1 Post-baseline longitudinal course of ROMI factors from 2 weeks through 1 year. Perceived medication benefit was the only factor that significantly improved over the course of treatment (2 weeks to 1 year: p < 0.001).
F3-Positive external influence and F4-Perceived medication benefit: reasons for compliance – 1 (none), 2 (mild), 3 (strong); greater score indicates greater compliance attitude.
F1-Negative aspects of medication, F2-Denial of illness and F5-Stigma: reasons for noncompliance – 1 (none), 2 (mild), 3 (strong); lower score indicates greater compliance attitude.

limited. Medication persistence in the current study is similar to medication adherence in usual clinical practice since patients could switch medications while remaining in the study. Thus study/treatment discontinuation would primarily result from patient choice similar to adherence. Data from the current study suggest perceived benefit from medication, including preventing relapse, relieving side effects, and fulfilling life goals, was significantly associated with psychiatric treatment persistence. This is consistent with a previous study of adherence in patients with schizophrenia, which reported that relapse prevention, prevention of symptom exacerbation, and daily benefit of medication were the most frequently cited patient reasons for adherence (Loffler et al 2003). It is also consistent with a recent qualitative examination of factors influencing medication adherence behavior in patients with schizophrenia, where medication efficacy and attitudes toward medication were 2 of 5 clinically relevant themes identified that influence medication adherence (Kikker et al 2006). The findings also concur with a recently published study on patients recovering from a first episode of schizophrenia (Perkins et al 2006). In that study, the likelihood of becoming medication non-adherent was greater in patients who believed medication was of low benefit.

The Health Belief Model considers treatment nonadherence as a decision made by patients after weighing medication benefits against risks and costs. Although previous research reported negative aspects of medication including adverse events as strong predictors of treatment nonadherence (Kampman and Lehtinen 1999), the present study did not find a significant association between negative aspects of medication and treatment persistence. These findings are consistent with a previous study that reported the medication benefits were a more important factor of persistence than adverse events (Perkins et al 2006). Furthermore, another study found that poor treatment response along with worsening symptoms was the most frequently given reason for discontinuing the treatment, which was substantially more common than discontinuation due to the poor tolerability of the medication (Liu-Seifert et al 2005).

More severe positive symptoms (Kamali et al 2006), deficit symptoms (Freudenreich et al 2004), depression (Elboqen et al 2005), cognitive disorganization, and hostility (Marder et al 1983) have been previously associated with poor adherence attitude and behavior. The present study reported that better attitude toward medication adherence based on beliefs about medication benefit was associated with better psychopathology in a broad spectrum of clinical symptoms. This positive adherence attitude was also found to be associated with greater improvement in clinical symptoms. These associations between greater beliefs in medication and better state of psychopathology, as well as greater improvement in psychopathology, persisted throughout the 1-year study.

In addition, the current study suggested patient attitude favoring treatment adherence based on perceived medication benefit was positively associated with subjective quality of life and satisfaction with overall well-being. There has been limited knowledge of how quality of life and treatment adherence relate to each other. While no direct relation could be discerned between subjective quality of life and adherence to medication by Puschner and colleagues (2006), other studies have found that subjective well-being and quality of life had a strong impact on treatment adherence (Coldham et al 2002; de Millas et al 2006). In addition, a recent analysis of observational data from German patients from the Schizophrenia Outpatient Health Outcomes study showed a strong association between subjective well-being and adherence with antipsychotic medication (Karow et al 2007).

The correlation between patient perception of medication benefit and clinical symptom psychopathology and quality of life in the present study does not necessarily suggest the direction of causality. It is likely that perceived medication benefit leads to motivation to adhere to treatment and ultimately to better clinical and functional outcomes. Alternatively,

Table 5 Pearson's correlation coefficients between ROMI factors and LQLI subscales at 2 months

Correlation coefficient (p value)	F1 negative aspects of medication	F2 denial of illness	F3 positive external influence	F4 perceived medication benefit	F5 stigma
Objective scale					
Amount of money spent on self	0.027	0.0777	−0.0637	−0.0571	−0.0254
	(0.596)	(0.129)	(0.193)	(0.223)	(0.616)
Arrests	−0.0569	−0.0417	0.0332	−0.014	0.0132
	(0.204)	(0.352)	(0.441)	(0.734)	(0.766)
Current employment	0.0655	0.0199	−0.0523	0.0436	0.0824
	(0.143)	(0.656)	(0.222)	(0.290)	(0.063)
Daily activities	0.0095	−0.0019	−0.0306	−0.186	−0.0071
	(0.830)	(0.965)	(0.472)	(<0.001)	(0.872)
Family contact	−0.0264	−0.0892	0.2787	0.1783	0.0159
	(0.559)	(0.048)	(<0.001)	(<0.001)	(0.722)
Financial adequacy	0.0316	0.0413	−0.0537	−0.139	0.0116
	(0.480)	(0.356)	(0.210)	(<0.001)	(0.795)
Social contact	0.009	−0.0654	0.1018	0.2242	0.0076
	(0.840)	(0.140)	(0.016)	(<0.001)	(0.863)
Victimization	−0.0166	0.042	−0.1304	−0.0656	0.0593
	(0.709)	(0.346)	(0.002)	(0.109)	(0.179)
Subjective scale					
Daily activities	−0.1007	0.0206	0.1884	0.3237	−0.1176
	(0.023)	(0.643)	(<0.001)	(<0.001)	(0.007)
Family contact	−0.008	0.0509	0.197	0.1908	−0.0474
	(0.861)	(0.263)	(<0.001)	(<0.001)	(0.293)
Finances	−0.1021	−0.0162	0.1472	0.2062	−0.0923
	(0.022)	(0.716)	(<0.001)	(<0.001)	(0.036)
Health	−0.0449	0.0176	0.1516	0.277	−0.1409
	(0.313)	(0.692)	(<0.001)	(<0.001)	(0.001)
Job	−0.1595	−0.1257	0.0673	0.0824	−0.161
	(0.113)	(0.201)	(0.475)	(0.369)	(0.102)
Living situation	−0.1555	−0.0639	0.2466	0.2036	−0.1174
	(<0.001)	(0.149)	(<0.001)	(<0.001)	(0.007)
Safety	−0.1325	−0.0829	0.0963	0.1301	−0.0986
	(0.003)	(0.061)	(0.023)	(0.001)	(0.025)
Satisfaction with general life	−0.0563	0.0139	0.1602	0.2359	−0.1127
	(0.204)	(0.754)	(<0.001)	(<0.001)	(0.010)
Social relations	−0.0102	0.0545	0.1815	0.2698	−0.0387
	(0.823)	(0.230)	(<0.001)	(<0.001)	(0.391)

Abbreviations: ROMI, Rating of Medication Influences; ROMI Factor 1, 2, and 5: greater score indicates poorer compliance attitude; Factor 3 and 4: greater score indicates greater compliance attitude; QOLI, Quality of Life Interview; greater score in subjective subscales indicates greater level of functioning and satisfaction. Greater score in objective subscales indicates lower level of functioning, except in Family contact, Social contact, and Amount of money spent on self, where greater score indicates greater level of functioning.

patients may recognize the better psychopathology symptoms and better quality of life as the beneficial effects of medication and establish beliefs in medication benefits. These results underline the important role of effective symptom control in patient's perception of medication use and in turn their adherence and persistence to treatment. Further, the links between perceived medication benefit and improved psychopathology and quality of life over the period of 1 year suggest the importance of continuous monitoring of patient symptoms, feelings about treatment, as well as satisfaction with life during treatment.

In the present study, ROMI data were not available at baseline; thus it was not possible to assess the early change in patient's perception of medication use. A previous study found that patient perception of medication benefit improved significantly within a week of initiation of treatment and was a key driver of the improved adherence attitude in a population of acutely ill, noncompliant patients (Liu-Seifert et al 2007). The study also found that the acute improvement in perceived medication benefit was associated with the acute improvement in psychopathology. The present study on a relatively more stable and more compliant patient

group showed that patient perception of medication benefit continued to improve for up to a year after treatment initiation and remained congruent with improvement in psychopathology and quality of life over time.

A limitation of the study is that differences in the number and content of specific items in different versions of the ROMI make direct comparison of the 5 factors identified from the 19 item ROMI in the current study with ROMI factors identified in other studies somewhat difficult. PCA analysis of the 7 compliance items and 13 noncompliance items of the original version of the ROMI scale developed by Weiden, yielded 3 compliance factors and 5 noncompliance factors (Weiden et al 1994). Comparison of these factors to the factors identified in our study is not possible since the specific ROMI items differed and our PCA analysis combined both compliance and noncompliance items. The 5 factors derived from the ROMI items in the current study are largely consistent with a PCA analysis of the same 19 item ROMI version used with a different patient population (Liu-Seifert et al 2007). In that study, 7 factors were identified, 4 of which directly correspond with factors identified in the current analysis: perceived medication benefit, positive external influence, denial of illness, and negative aspects of medication. In addition, the identified factors are consistent with 4 constructed factors (need for treatment, benefits of medication, negative aspects of medication, and external support factors) based on a combined analysis of ROMI and the Insight and Treatment Attitudes Questionnaire (ITAQ) in first episode schizophrenia patients (Perkins et al 2006).

An additional limitation of the present study was that it was a clinical trial and may not reflect completely the real world patient treatment setting. The current study was designed to reflect the usual clinical practice in the treatment of schizophrenia, including dosing according to clinician's discretion, enrolling patients with comorbid conditions such as substance abuse and the open-label design. However, patients who are willing to enter a clinical trial might have different motivation and beliefs about treatment than patients in other settings. With these caveats, data from the present study may still provide useful information in developing interventions to improve patient treatment persistence and long-term prognosis.

Conclusions

Patient perception of an effective and beneficial treatment was found to be the only significant predictor of treatment persistence among the 5 underlying factors of medication influence. Effective treatment can maximize the benefit-to-risk ratio and influence patient beliefs about the value of medication. Current findings highlight the role of effective symptom control and patient perception of treatment efficacy in medication persistence and may offer strategies for interventions to improve patient outcome.

Competing interests

Authors' contributions

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References

Ayuso-Gutierrez JL, del Rio Vega JM. 1997. Factors influencing relapse in the long-term course of schizophrenia. *Schizophr Res*, 28:199–206.

Becker MH, Maiman LA. 1975. Sociobehavioral determinants of compliance with health and medical care recommendations. *Med Care*, 13:10–24.

Coldham EL, Addington J, Addington D. 2002. Medication adherence of individuals with a first episode of psychosis. *Acta Psychiatr Scand*, 106:286–90.

Davis JM, Chen N. 2001. The effects of olanzapine on the 5 dimensions of schizophrenia derived by factor analysis: combined results of the North American and international trials. *J Clin Psychiatry*, 62:757–71.

de Millas W, Lambert M, Naber D. 2006. The impact of subjective well-being under neuroleptic treatment on compliance and remission. *Dialogues Clin Neurosci*, 8:131–6.

Elboqen EB, Swanson JW, Swartz MS, et al. 2005. Medication nonadherence and substance abuse in psychotic disorders: impact of depressive symptoms and social stability. *J Nerv Ment Dis*, 193:673–9.

Fenton WS, Blyler CR, Heinssen RK. 1997. Determinants of medication compliance in schizophrenia: empirical and clinical findings. *Schizophr Bull*, 23:637–51.

Freudenreich O, Cather C, Evins AE, et al. 2004. Attitudes of schizophrenia outpatients toward psychiatric medications: relationship to clinical variables and insight. *J Clin Psychiatry*, 65:1372–6.

Kamali M, Kelly BD, Clarke M, et al. 2006. A prospective evaluation of adherence to medication in first episode schizophrenia. *Eur Psychiatry*, 21:29–33.

Kampman O, Lehtinen K. 1999. Compliance in psychoses. *Acta Psychiatr Scand*, 100:167–75.

Karow A, Czekall J, Dittmann RW, et al. 2007. Association of subjective well-being, symptoms, and side effects with compliance after 12 months of treatment in schizophrenia. *J Clin Psychiatry,* 68:75–80.

Kay SR, Fiszbein A, Opler LA. 1987. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*, 13:261–76.

Kikkert MJ, Schene AH, Koeter MW, et al. 2006. Medication adherence in schizophrenia: exploring patients', carers' and professionals' views. *Schizophr Bull*, 32:786–94.

Lehman AF. 1988. A quality of life interview for the chronically mentally ill. *Eval Program Plann*, 11:51–62.

Lieberman JA, Stroup TS, McEvoy JP, et al. 2005. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*, 353:1209–23.

Liu-Seifert H, Adams DH, Kinon BJ. 2005. Discontinuation of treatment of schizophrenic patients was driven by poor symptom response: a pooled post-hoc analysis of four atypical antipsychotic drugs. *BMC Med*, 3:21.

Liu-Seifert H, Houston JP, Adams DH, et al. 2007. Association of acute symptoms and compliance attitude in noncompliant patients with schizophrenia. *J Clin Psychopharmacol*, 27:392–4.

Loffler W, Kilian R, Toumi M, et al. 2003. Schizophrenic patients' subjective reasons for compliance and noncompliance with neuroleptic treatment. *Pharmacopsychiatry*, 36:105–12.

Marder SR, Mebane A, Chien CP, et al. 1983. A comparison of patients who refuse and consent to neuroleptic treatment. *Am J Psychiatry*, 140:470–2.

McEvoy JP, Lieberman JA, Stroup TS, et al. 2006. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry*, 163:600–10.

Perkins DO. 1999. Adherence to antipsychotic medications. *J Clin Psychiatry*, 60:25–30.

Perkins DO. 2002. Predictors of noncompliance in patients with schizophrenia. *J Clin Psychiatry*, 63:1121–8.

Perkins DO, Johnson JL, Hamer RM, et al. 2006. Predictors of antipsychotic medication adherence in patients recovering from a first psychotic episode. *Schizophr Res*, 83:53–63.

Puschner B, Born A, Giessler A, et al. 2006. Adherence to medication and quality of life in people with schizophrenia: results of a European multicenter study. *J Nerv Ment Dis*, 194:746–752.

Stroup TS, Lieberman JA, McEvoy JP, et al. 2006. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry*, 163:611–22.

Stroup TS, Lieberman JA, McEvoy JP, et al. 2007. Effectiveness of olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia after discontinuing perphenazine: a CATIE study. *Am J Psychiatry*, 164:415–27.

Tunis SL, Faries DE, Nyhuis AW, et al. 2006. Cost-effectiveness of olanzapine as first-line treatment for schizophrenia: results from a randomized, open-label, 1-year trial. *Value Health*, 9:77–89.

Valenstein M, Copeland LA, Blow FC, et al. 2002. Pharmacy data identify poorly adherent patients with schizophrenia at increased risk for admission. *Med Care*, 40:630–9.

Weiden P, Rapkin B, Mott T, et al. 1994. Rating of medication influences (ROMI) scale in schizophrenia. *Schizophr Bull*, 20:297–310.