Association of Subjective Well-Being, Symptoms, and Side Effects With Compliance After 12 Months of Treatment in Schizophrenia

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Objective: Subjective well-being is considered important for compliance with antipsychotic treatment. The objective of this post hoc analysis of data from German patients in the Schizophrenia Outpatient Health Outcomes study was to investigate subjective well-being and compliance, with consideration of clinical symptoms and side effects, in outpatients diagnosed with schizophrenia.

Method: In a multicenter observational study of 2960 patients with DSM-IV–defined schizophrenia recruited between January and December 2001, subjective well-being was measured during 12 months with the Subjective Well-Being Under Neuroleptic Treatment Scale, short version (SWN-K). Compliance was self- and physician-rated. The association of compliance with clinical parameters was assessed by logistic regression.

Results: Factor analysis resulted in 3 factors: SWN-K ($r^2 = 0.867$), clinical symptoms ($r^2 = 0.744$), and side effects ($r^2 = 0.420$). The odds for being compliant were 1.363 times higher if the SWN-K score increased by 20 points. Changes in positive symptoms (OR = 0.773) and changes in extrapyramidal symptoms (OR = 0.830) were found to be associated with compliance.

Conclusion: Compliance with antipsychotic medication was strongly associated with subjective well-being; further factors were clinical symptoms and side effects.

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Long-term pharmacotherapy in schizophrenia implies a high risk for medication noncompliance.[1] Rates ranged from 24% to 90%.[2–4] Noncompliance with antipsychotic treatment and the associated greater risk for relapses and hospitalizations often result in negative personal, social, and occupational consequences and strategies. Therefore, therapeutic interventions to enhance compliance with antipsychotic treatment have been repeatedly investigated.[5–10] Although an individualized approach is reasonable to address the specific reason for medication noncompliance, different authors suggest that the impact of antipsychotic drugs on subjective well-being is one of the major determinants.[9,11–16]

The measurement of subjective well-being is increasingly viewed as a useful extension of the classical clinical outcome measures, e.g., measures of psychopathology, in patients with schizophrenia.[12,13,15–20] Previous studies have shown that subjective well-being is inversely correlated with symptom severity, especially negative symptoms, depression, and in recent analyses also anxiety.[21–26] Various antipsychotic side effects, most importantly extrapyramidal symptoms (EPS), sexual dysfunction, and psychological side effects, are associated with reduced well-being.[26–30] Current research indicates that negative

subjective well-being is possibly predictive of a less favorable symptomatic outcome and associated with an increased prevalence of comorbid substance abuse.[30–32]

Few studies have investigated the long-term association between subjective well-being and compliance with consideration of relevant clinical variables so far.[9,11,19,33] The European Schizophrenia Outpatient Health Outcomes (SOHO) study is a prospective, naturalistic long-term study delivering data on the association between 12-month changes in subjective well-being and compliance with antipsychotic treatment with consideration of clinical symptoms and side effects in a large number of outpatients diagnosed with schizophrenia.

METHOD

Study Design

The SOHO study is an ongoing, 3-year, prospective observational study of the treatment of schizophrenia in Europe. The primary objective of the study is to assess the outcomes and costs of antipsychotic treatment of schizophrenia. The study was designed to observe a sample of approximately 50% of patients initiated on olanzapine treatment and the remaining 50% initiated on other antipsychotic therapy as given during clinical practice.

The study is being conducted in 10 European countries and involves more than 1000 psychiatrists and over 10,000 patients. Patients who met the following criteria were allowed to participate: (1) initiating or switching antipsychotic medication for the treatment of schizophrenia; (2) presenting within the normal course of care in the outpatient setting or in the hospital when admission was planned for the initiation or change of antipsychotic medication, with discharge planned within 2 weeks; (3) being at least 18 years of age; and (4) not participating in any interventional study.

Patients documented at baseline continued to be observed regardless of their current antipsychotic treatment, i.e., changes in antipsychotic medication were no reason for study discontinuation. The observation therefore represents a description of current antipsychotic treatment in Europe. A more detailed description of the methodology of the SOHO study is offered by Haro and coworkers.[34]

Assessments

The focus of the SOHO study was on measures such as compliance, quality of life (e.g., EuroQoL-5D), clinical symptoms, and side effects. In the current analysis, SOHO data from Germany were used to evaluate the effect of clinical and nonclinical factors on compliance and subjective well-being of patients. Subjective well-being was assessed exclusively in the German study population by the Subjective Well-Being Under Neuroleptic Treatment Scale (SWN). This validated scale was developed to measure subjective well-being under neuroleptic treatment. The original scale included 38 items and 5 subscales.[35] In this study, the short form SWN (Subjective Well-Being Under Neuroleptic Treatment Scale, short version [SWN-K], 20 items) was used, which resembles the long form in its structure.[36] Both versions assess 5 domains on a 6-category Likert response scale: emotional regulation, self-control, mental functioning, social integration, and physical functioning. The scale was successfully used in different samples of patients with schizophrenia, e.g., in brain imaging trials under double-blind conditions.[36–38]

Clinical symptoms (overall, positive, negative, cognitive, depressive) were rated based on the expanded version of the Clinical Global Impressions-Severity of Illness scale (CGI-Schizophrenia[39]; 7-point Likert scales) as categorical variables at baseline and 3, 6, and 12 months after the start of new antipsychotic treatment.

Data on issues relevant to safety were collected not by standard adverse event questioning, but by soliciting specific typical side effects of antipsychotic treatment that were to be reported only if they were "adverse events considered as related to antipsychotic treatment." Extrapyramidal symptoms (EPS) and tardive dyskinesia were assessed separately as present versus not present. Sexual side effects (loss of libido, sexual dysfunction, menstrual disturbance, galactorrhea, gynecomastia) were classified as yes or no if any of these were present. Weight was assessed at every visit, and weight gain was measured in kilograms compared to baseline (i.e., treatment initiation).

Patients' compliance with antipsychotic medication was separately assessed by the patient and the physician. Compliance was categorically assessed as "almost always compliant," "partly compliant," and "almost never compliant" with antipsychotic medication. Change of compliance from baseline to 12 months was assessed in terms of improved, unchanged, and worsened compliance based on the patient assessment. For logistic regressions, patients were considered as compliant with antipsychotic medication if the patient and the physician rated the patient as "almost always compliant" at the 12-month visit.

Data Analysis

All analyses presented are post hoc analyses performed to explore and describe the data obtained. The correlations of changes in SWN-K total score and subscores, CGI-Schizophrenia scores, and side effects were analyzed by a factor analysis to assess their interdependence. The factor analysis was performed using SAS 8.02 (SAS Institute Inc., Cary, N.C.) and applying a varimax rotation. Robustness checks were performed to assess whether 3 or 4 factors led to a better fit of the data and whether the inclusion of the SWN-K total score or the subscores led to better results.

The associations of the resulting 3 factors and the included variables with patient compliance were further analyzed by descriptive statistics and by logistic regres-

sion models. The compliance was dichotomized at 12 months as described above for the logistic regressions. Adjusted and unadjusted odds ratios together with confidence intervals and p values were obtained. Furthermore, the change in SWN-K total score was explored by change in compliance (patient assessment) from baseline to 12 months by means of descriptive statistics. The agreement between patient and physician compliance assessments at 12 months was assessed using a weighted kappa considering the ordinal nature of the 3 categories.

RESULTS

Sample Characteristics

A total of 2960 subjects, of whom 50.7% were female, were eligible for evaluation at baseline. After 12 months of treatment, 2414 patients (81.6%) remained in the study (1204 female, 49.9%). The demographic characteristics of subjects eligible for the 12-month analysis were as follows. Subjects' mean ± SD age at start of documentation (i.e., initiation/change of antipsychotic treatment) was 42.6 ± 13.7 (median = 40.5) years, and the mean age at first psychiatric contact was 31.6 ± 11.6 (median = 30) years. Evaluations of the patient population based on the CGI-Schizophrenia revealed a mean score of 2.7 ± 1.4 for positive symptoms, 3.0 ± 1.3 for negative symptoms, and 3.4 ± 1.0 for overall symptoms. The 2414 subjects for whom 12-month data were available received the following antipsychotic medication at baseline: 52.5% olanzapine, 13.2% risperidone, 7.4% quetiapine, 6.6% amisulpride, 3.0% clozapine, and 0.6% other atypical antipsychotics. The remaining subjects (16.8%) received typical antipsychotics (7.5% oral and 6.8% depot medication), and 2.4% were started on treatment with 2 or more antipsychotics at baseline. Some of the subjects in this cohort had received further antipsychotic medications at baseline that were initiated prior to the start of the study. A further description of antipsychotic medications, including treatment changes during the study period, is out of the scope of this article and has been reported elsewhere.[40,41] Results revealed no compliance differences regarding gender or age. Subjects with an improvement in compliance after 12 months had a mean duration of illness of 10.4 years, which was similar to patients with no change in compliance (10.7 years), while patients with a worsening in compliance showed a duration of illness of 7.3 years.

Subject- and Physician-Rated Compliance

At the 12-month visit, 82.9% (2000/2414) of the subjects were considered as compliant by the physician, and 88.3% (2131/2414) rated themselves as compliant. Results revealed 93.2% identical answers when subjects' and physicians' ratings were compared, while 6.8% differed. The weighted kappa for congruence of subjects' and physicians' compliance assessments was 0.6152 (95% CI for κ: 0.5579 to 0.6725). Of the 2183 subjects with complete compliance assessments (by both subjects and physicians) at month 12, 1915 (87.7%) were reported as almost always compliant by both raters.

Table 1. Absolute Changes in Antipsychotic Medication Compliance (patient assessment) by Changes in the SWN-K Total Score Between Baseline and Month 12 (LOCF for SWN-K values)

		Change in SWN-K Total Score				
Compliance	N	Minimum	25th Percentile	Median	75th Percentile	Maximum
Improved	225	–39	4.0	15.9	28.0	64.0
Unchanged	1366	–39	2.0	13.0	25.0	81.0
Worsened	78	–40	–2.0	7.5	18.0	58.1

Abbreviations: LOCF = last observation carried forward, SWN-K = Subjective Well-Being Under Neuroleptic Treatment Scale, short version.

Relation Between Changes in Subjective Well-Being and Changes in Compliance

Mean changes in the SWN-K total score between baseline and month 12 (in case of missing SWN-K data at month 12, values at month 6 or month 3 were considered) were calculated for each of the available compliance rating categories (improved, changed, worsened) at month 12 (Table 1).

Results revealed the strongest relative improvement in the SWN-K total score for subjects with an improvement in compliance (mean change 45.7% ± 38.9%, median change 25%). Less pronounced relative SWN-K improvements were seen in subjects with unchanged compliance (27.9% ± 36.9%, median change 20%) and for those with a worsening in compliance between baseline and month 12 (17.9% ± 32.1%, median change 12.5%).

Factor Analysis of Clinical Symptoms, Subjective Well-Being, and Side Effects

A factor analysis with the aim of classifying the clinical parameters influencing changes in compliance was conducted. Results revealed 3 different factors, which can be interpreted as the following: factor 1, subjective well-being (SWN-K total score and all subscores); factor 2, clinical symptoms (CGI-Schizophrenia scores of positive, negative, depressive, and cognitive symptoms); and factor 3, side effects (EPS, tardive dyskinesia, weight gain, sexual problems). The eigenvalues for SWN-K subscores (factor 1) and CGI-Schizophrenia scores (factor 2) were high. The eigenvalues for side effects (factor 3) were high for EPS and tardive dyskinesia but low for sexual problems and weight gain. Results of the squared multiple correlations of all variables showed the strongest correlation for factor 1 (SWN-K, $r^2 = 0.867$), followed by factor 2 (clinical symptoms $r^2 = 0.744$) and factor 3 (side effects $r^2 = 0.420$).

Table 2. Unadjusted Odds Ratios for Compliance With Respect to Absolute and Relative Improvements of the SWN-K Total Score and the SWN-K Subscore Self-Control Between Baseline and Month 12

		95% CI	
SWN-K Score	OR	Lower	Upper
SWN-K total			
20-point improvement	1.363	1.217	1.530
25% improvement	1.218	1.133	1.314
SWN-K self-control			
4-point improvement	1.179	1.084	1.287
25% improvement	1.251	1.105	1.418

Abbreviation: SWN-K = Subjective Well-Being Under Neuroleptic Treatment Scale, short version

Table 3. Unadjusted Odds Ratios for Compliance With Respect to CGI Positive Symptoms at Baseline, Changes in CGI Positive Symptoms, and Changes in EPS Between Baseline and Month 12

		95% CI	
Variable	OR	Lower	Upper
CGI positive symptoms			
Baseline	0.873	0.808	0.944
Change	0.773	0.689	0.868
EPS change	0.830	0.682	1.011

Abbreviations: CGI = Clinical Global Impressions scale, EPS = extrapyramidal symptoms.

Regression Models Investigating the Association Between Subjective Well-Being, Symptoms, Side Effects, and Compliance

Separate regression models were calculated to investigate the association between SWN-K, clinical symptoms, side effects, and compliance. The logistic regression model including the 3 factors SWN-K, symptoms, and side effects revealed a significant association with compliance for factor 1, SWN-K (OR = 1.311, p = .0001, 95% CI for OR: 1.143 to 1.505); factor 2, clinical symptoms (OR = 0.883, p < .0338, 95% CI for OR: 0.787 to 0.990); and factor 3, side effects (OR = 0.853, p = .0331, 95% CI for OR: 0.737 to 0.987).

The odds for being compliant were 1.363 (95% CI for OR: 1.217 to 1.530) times higher if the SWN-K total score showed an absolute increase of 20 points and 1.218 (95% CI for OR: 1.133 to 1.314) times higher if the SWN-K score showed a relative increase of 25%. Considering the impact of all SWN-K subscales, self-control showed the highest association with compliance (Table 2). The influence of the subscale self-control decreased when the total score was included in the regression model, while the odds ratio for the SWN-K total score did not change.

Further, these regression analyses investigated the association of the different symptoms (positive, negative, depressive, cognitive, total score), changes in symptoms (positive, negative, depressive, cognitive, total score), and changes in side effects (improvement, no change, worsening) for EPS, tardive dyskinesia, weight gain, and sexual problems with compliance. Of all CGI-Schizophrenia scores, positive symptoms were found to have the strongest impact on compliance. The regression models demonstrated that the severity of positive symptoms at baseline (OR = 0.873, p = .0006, 95% CI for OR: 0.808 to 0.944) and changes in positive symptoms (OR = 0.773, p < .0001, 95% CI for OR: 0.689 to 0.868) were significantly negatively correlated with compliance (based on difference/change of 1 category of the CGI-Schizophrenia scale). Furthermore, a trend for a negative correlation with compliance was found for changes in EPS (OR = 0.830, p = .0646, 95% CI for OR: 0.682 to 1.011). The above mentioned unadjusted odds ratios for the independent variables did not change in the adjusted model. Therefore, the effect of positive symptoms at baseline, changes in positive symptoms, and EPS on compliance should be interpreted as independent in this sample (Table 3).

DISCUSSION

In this observational, naturalistic long-term study, compliance with antipsychotic medication in outpatients with schizophrenia was strongly associated with changes in patients' subjective well-being. Results showed a marked improvement in subjective well-being for patients with an increase in compliance and only a minor improvement in patients with a decrease in compliance during the observation period of 1 year. The domain "self-control" of the SWN-K showed the strongest association with compliance. The subscale self-control is represented by statements such as "I feel powerless and not in control of myself" and "I find it easy to draw a line between myself and others." These results suggest that self-control and personal responsibility for treatment are important for the patient's adherence to medication. It is likely that patients who feel personally responsible for their treatment are more willing to comply with long-term pharmacotherapy. Accordingly, shared decisions between patient and doctor might improve patients' self-control and thereby treatment adherence. Note that the logistic regression models do not imply a causal relationship between improvement in compliance and improvement in subjective well-being. Our results provide evidence for interrelatedness between the course of compliance and subjective well-being. Most likely, both variables influence each other reciprocally.

The factor analysis revealed 3 factors, i.e., subjective well-being, clinical symptoms, and side effects. A logistic regression analysis showed that, apart from subjective well-being, positive symptoms at baseline and changes in positive symptoms were found to have the strongest impact on compliance. Overall, side effects showed a moderate correlation with compliance, whereas changes in

EPS demonstrated the strongest association. Different reasons might account for the unexpected moderate association between side effects and compliance. The factor "side effects" was the most incongruent factor in the statistical analysis. This might be explained by the diversity of antipsychotic drugs used in the study, which were chosen according to the treating psychiatrist's clinical judgment. Therefore, those patients with the highest risk for a particular side effect were most likely primarily assigned or switched to another medication, thereby possibly obscuring the effect of side effects on compliance. Other studies indicated that high scores on side effect rating scales, especially EPS or sexual side effects, strongly predict noncompliance, and patients often cited current side effects as a primary reason for noncompliance.[6] The subjectively most distressing side effects might be psychological side effects, often referred to as "neuroleptic induced dysphoria" or "pharmacogenic depression." These side effects are, in addition to social, physical, and cognitive aspects of well-being, represented in the SWN-K. In consequence, the strong association of subjective well-being with compliance might be explained partly by psychological side effects. Tolerability of antipsychotics was rated as "good" in most patients in this trial. The small number of patients with severe side effects might be another reason for an overall lower association of side effects with compliance.

Limitations

As this was a large observational study in daily clinical practice, several methodological limitations such as the lack of more differentiated measures of psychopathology (e.g., Positive and Negative Syndrome Scale) and compliance (e.g., blood levels, electronic measures, pill counts) were unavoidable. Furthermore, generalizability of the results to epidemiologic samples may be limited by the selection of an outpatient population and the patients' only moderate severity of illness, with inclusion criteria requiring a switch of antipsychotic treatment. Additionally, the rate of compliance (87.7%) in our analysis is higher compared to other studies that found mean antipsychotic compliance rates of 50.5%, varying from 24% to 90%.[3,42–44] This high compliance rate may be related to the rate of loss to follow-up of 20%, since it can be speculated that a large proportion of these patients were noncompliant in an observational study. In addition, physicians might have preferentially chosen patients for the study whom they considered as collaborative regarding compliance, especially since they were expecting a 3-year duration of the study. Lower compliance rates were reported in controlled studies, and compliance was lower in recently discharged patients and improved longitudinally.[2,43]

As expected, lower compliance rates were found when assessed by means of pill counts, electronic measures, or blood level data compared to self-reports.[43,45] The appropriate measurement remains a fundamental issue when determining medication adherence. Expert ratings and self-reports, while straightforward and inexpensive, are clearly limited by their subjective nature. Pill counts and electronic monitors provide detailed information regarding medication administration, but both measures might not reflect the actual medication consumption. However, blood and urine medication levels, while direct measures of adherence, are invasive, expensive, and unpopular in the majority of patients, thereby introducing another source of potential sample bias. Presently, there is no measure of compliance accepted as the "gold standard."[2,43] Although our analysis might not provide the exact and objectively measured rate of compliance, noncompliance, as defined here, can be considered as clinically relevant to physicians and patients and was measured in those patients who still had a therapeutic relationship to their physician. The observational nature of the study might also account for the relatively high percentage of female participants, as the proportion of females in other observational studies of schizophrenia was similar.[46–48] The analysis revealed no compliance differences regarding gender or age.

CONCLUSION

In summary, the high association of compliance with patients' subjective well-being indicates that the decision to take an antipsychotic is based on how patients weigh costs and benefits. This decision is made not simply by considering symptom reduction, but by evaluating the level of distress caused by symptoms, the degree of symptom reduction, and the presence of side effects and their impact on subjective well-being.[13,33] The psychiatrists' beliefs about the effectiveness and tolerance of a particular antipsychotic drug do not necessarily reflect patients' well-being and attitude toward medication.[1] In consequence, the assessment of the subjective response to antipsychotic treatment in schizophrenia will contribute to the understanding of the complex relationship between treatment, clinical symptoms, side effects, and medication adherence.

Drug names: clozapine (Fazaclo, Clozaril, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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