Prediction of Remission as a Combination of Symptomatic and Functional Remission and Adequate Subjective Well-Being in 2960 Patients With Schizophrenia

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Objective: Recently, the Remission in Schizophrenia Working Group proposed symptomatic remission criteria and pointed to the lack of data regarding functional remission and quality of life in schizophrenia. This post hoc analysis of data from German patients in the Schizophrenia Outpatient Health Outcomes study assessed rates and predictors of symptomatic and functional remission as well as adequate subjective well-being/quality of life in a large cohort of patients with schizophrenia.

Method: Data were collected in an observational 24-month follow-up study of 2960 patients with DSM-IV–defined schizophrenia recruited between January and December 2001. Complete remission required that patients achieved symptomatic remission mirroring the Remission in Schizophrenia Working Group criteria, functional remission, and a level of adequate subjective well-being over at least 6 months.

Results: At endpoint, 47.2% of the patients achieved symptomatic remission, 26.6% achieved functional remission, and 42.2% achieved adequate subjective well-being. At endpoint, 12.8% were in complete remission. In 35.1% of patients, none of the 3 remission criteria were achieved. Only 8.7% of early nonremitted cases achieved remission at endpoint. Each single remission component as well as complete remission was mainly predicted by early remission within the first 3 months. First-line treatment with atypical antipsychotics increased the likelihood of complete remission compared to conventional antipsychotics.

Conclusions: Despite advances in pharmacologic and psychosocial treatments in schizophrenia, close to 90% of the patients in this study did not fulfill the combined remission criteria. This was in part attributable to the low functional remission rate, particularly the low employment rate. The finding that the course of the disorder depends on early outcome not only in previously untreated but also in more chronically ill patients points toward a critical "window of opportunity" in the course of treatment.

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Recent advances in understanding and treatment of schizophrenia have renewed and extended the questions (1) how is remission defined? (2) how many patients achieve remission? and (3) which parameters predict remission? Several prospective and retrospective studies in first-[1–4] and multiple-episode patients[5–8] provided definitions for remission using a wide range of criteria and time periods during which the criteria must be maintained.[9,10] The lack of consistent definitions of remission and the heterogeneity of assessed populations thereby hampered cross-study comparisons and limited the generalizability of these results.[9]

Most recently, in accordance with previous studies,[1–8] the Remission in Schizophrenia Working Group published a consensus statement on the criteria and the time frame of remission in schizophrenia.[9] Remission was defined as a state of no greater than low-to-mild intensity in core symptoms, sustained for a minimum duration of 6 months. These criteria were recently applied in a 1-year

study of long-acting risperidone injection.[7] Furthermore, aside from sustained symptomatic remission (i.e., positive, negative, and disorganized/cognitive symptoms), the Expert Consensus Guidelines[10] considered the incorporation of functional indicators of remission (i.e., independent living, occupation/education, peer relationships). The Remission in Schizophrenia Working Group also explicitly considered the incorporation of functional outcomes including quality of life into the definition of remission. The group, however, did not find an adequate knowledge base regarding the course of psychosocial and cognitive outcomes and their potential association with changes in symptom patterns and severity.[9] Therefore, data on both symptomatic remission as defined by the recent expert groups[9,10] and functional remission as well as adequate quality of life/well-being are valuable resources for clinicians and researchers in the process of extending the definition of remission and recovery in schizophrenia.

The first aim of this post hoc analysis of the European Schizophrenia Outpatient Health Outcomes (SOHO)[11–14] study was to assess rates and predictors of symptomatic and functional remission as well as adequate subjective well-being/quality of life. Symptomatic remission criteria used in this study mirrored the criteria recommended by the Remission in Schizophrenia Working Group, although these criteria were not literally applied. The second aim was to analyze rate and predictors of complete remission, defined as simultaneous fulfillment of criteria for symptomatic and functional remission as well as adequate subjective well-being/quality of life.

METHOD

Context and Sample

Data were collected in a prospective, nonrandomized observational study of 10,972 patients with schizophrenia recruited in 10 European countries between January and December 2001. Participating psychiatrists offered enrollment to patients who met the following inclusion criteria: DSM-IV diagnosis of schizophrenia,[15] age of at least 18 years, IQ > 70, and switch to or new initiation of antipsychotic treatment. Exclusion criteria were DSM-IV diagnoses of other schizophrenia spectrum disorders, bipolar I disorder with psychotic features, substance-induced psychosis, or psychotic disorder due to a medical condition.

Analyses presented here were restricted to patients recruited in Germany (N = 2960) because (1) the mental health system, including standards and elements of care, is more homogeneous than in the total SOHO study population[16]; (2) subjective well-being, an important single component of the complete remission criterion, was assessed only in the German study population; and (3) functional outcomes such as employment and independent living are strongly influenced by the socioeconomic status of a country.[17] These 2960 patients were included in the analysis.

At initial documentation, all patients were outpatients treated by office-based psychiatrists. These consultant psychiatrists had completed at least 5 years of hospital-based training, and most of them had completed long-term training in either cognitive behavioral or dynamic psychotherapy. All ratings were performed by these consultant psychiatrists. Apart from the study visits, patients received intensive outpatient treatment throughout the 24-month study period. Subjects were treated according to the German schizophrenia clinical practice guidelines.[16] The local ethics research committees approved the study.

Assessments and Measures

Assessments were carried out at baseline and at 3, 6, 12, 18, and 24 months with standardized scales. The predictor variables assessed, in chronological order, were (1) predictors at baseline; (2) predictors in the early course of treatment, defined as fulfilled cross-sectional remission criteria at 3 months without the 6-month duration requirement; and (3) predictors during the course of treatment, defined as variables assessed continuously throughout the complete 24-month period.

The baseline predictor variables were as follows. (1) Age, gender, and duration of illness. (2) Symptomatic status assessed with the expanded version of the Clinical Global Impressions-Severity of Illness scale (CGI-Schizophrenia)[18,19] including an overall severity of illness score and 4 subscores for the severity of positive, negative, cognitive, and depressive symptoms. With regard to concurrent validity, the CGI-Schizophrenia subscales were reported to correlate satisfactorily with most of their respective Positive and Negative Syndrome Scale (PANSS) subscales (Pearson correlations: PANSS-positive = 0.86, PANSS-negative = 0.80, PANSS-cognitive/disorganized = 0.78) and less with PANSS-depressive (0.61).[19] (3) Functional variables including "occupational/vocational" status and "independent living" assessed by means of simple 1-item questions with yes/no categories; a positive occupational/vocational status required working full- or part-time or attending school/university. (4) Subjective well-being assessed with the Subjective Well-being Under Neuroleptic Treatment Scale, short version (SWN-K).[20] The SWN-K, a self-rating Likert scale with 6 response categories (absent to very much) covers 20 statements (10 positive and 10 negative) on 5 subscales with a minimum total score of 20 and a maximum total score of 120; higher scores indicate better well-being. In addition to the SWN-K, health-related quality of life (HRQoL) was assessed using the EuroQoL-5D,[21] which is not specific to schizophrenia. SWN-K and EuroQoL-5D total scores were sufficiently correlated (Spearman correlation coefficient = 0.644, 95% confidence interval = 0.622 to 0.665, $p < .001$). The SWN-K

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was found to be sensitive to treatment changes in schizophrenia[22] and highly correlated with one of the most commonly used HRQoL scales, the Short-Form 36.[23,24] (5) Variables related to antipsychotic treatment (all yes/no categories): first antipsychotic treatment, defined as no treatment with antipsychotics before baseline; presence of neurologic side effects, defined as extrapyramidal motor symptoms and/or tardive dyskinesia; and type of initial antipsychotic medication, separated into atypical antipsychotics (i.e., olanzapine, risperidone, amisulpride, quetiapine, or clozapine) and conventional antipsychotics (i.e., oral or depot antipsychotics).

The predictors early in the course of treatment were symptomatic and functional remission as well as adequate subjective well-being at 3 months, omitting the temporal requirements as defined below.

The predictors throughout the course of treatment were comorbid substance use disorder (SUD) assessed according to DSM-IV criteria[15] and categorized into no SUD (no SUD at baseline and throughout follow-up), remitted SUD (SUD at baseline and remission at all follow-up visits), and persistent SUD (SUD reported at any postbaseline visit). Similar to the criterion proposed by Kane et al.,[10] noncompliance with antipsychotic medication was defined as missing ≥ 50% of medication over at least 4 weeks.

Definition of Remission Criteria

Remission required fulfillment of the following criteria over a period of at least 6 months until the end of the observational period, i.e., at least at both the 18- and 24-month follow-up visits. Subjects who fulfilled criteria over a 6-month period earlier in the study with subsequent relapse were not considered remitted in this study.

Symptomatic remission was defined as receiving a CGI-Schizophrenia severity score of absent to mild (score ≤ 3) in assessments of overall severity and positive, negative, and cognitive subscores.

Functional remission was defined as a positive occupational/vocational status, i.e., paid or unpaid full- or part-time employment; being an active student in university or head of household (with employed partner); and independent living, i.e., living alone, with partner, or with peers.

The criterion for adequate subjective well-being was met if an SWN-K total score of ≥ 80 was achieved. This total score corresponds to an average rating of "marked" positive subjective well-being in the positive SWN-K items and an average rating of only "mild" impairment of subjective well-being in the negative SWN-K items.

Complete remission required that subjects simultaneously fulfilled criteria for symptomatic and functional remission as well as adequate subjective well-being.

Data Analysis

All analyses were carried out using SAS version 8.2 (SAS Institute Inc., Cary, N.C.). Following the intent-to-treat principle, we included all German SOHO patients in the analyses, and last observation carried forward (LOCF) was used to impute missing values before determining fulfillment of the above mentioned remission criteria.

Patients' baseline, early course of treatment, and course of treatment variables were described using means and standard deviations (SDs), or relative frequencies based on nonmissing observations. The association of SWN-K total score and the EuroQoL-5D visual analog scale was evaluated by Spearman correlation coefficient. The 95% confidence interval for the correlation coefficient was computed using Fisher's z-transformation.

Length of time in which patients were treated with the initial antipsychotic was analyzed using Kaplan-Meier estimates and the log-rank test. Confidence intervals are reported for the lower quartile of time on treatment with the initial antipsychotic and for the percentage of patients still on treatment with the initial antipsychotic after 24 months.

The influence of baseline, early course of treatment, and course of treatment predictors on the 3 remission components and on the complete remission criterion was investigated in 3 steps: First, the impact of the baseline predictors was assessed by means of logistic regressions (SAS procedure LOGISTIC) using a model that included all baseline predictors (block 1). Second, all early course of treatment predictors were additionally included into the logistic regression model (block 2). Third, the full model was achieved by adding the course of treatment predictors (block 3). Thus, the odds ratios resulting from the logistic regressions of blocks 2 and 3 were adjusted for the previous blocks of predictors.

Forward and backward selection models, using $p = .1$ as threshold for single variables, were performed for the combined remission criterion using all variables (blocks 1, 2, and 3) and yielded a reduced model. Confidence intervals and p values were based on Wald test.

RESULTS

Subject Characteristics

The demographic and clinical characteristics of the 2960 subjects with schizophrenia are outlined in Table 1. Most subjects had a long history of illness (median = 7.6 years), with only 20.6% receiving their first antipsychotic trial. More than half of the subjects were treated with olanzapine, and only 13.6% were treated with conventional antipsychotics.[11–14] The treating psychiatrists reported that patients were switched to another antipsychotic (a mandatory inclusion criterion in patients who were not antipsychotic-naive) due to, among other reasons, lack of efficacy in 42.1%, intolerance to previous antipsychotic treatment in 28.6%, and noncompliance in 12.7%. The mean CGI-Severity of Illness overall score and subscores point to a moderate severity of illness, as

Table 1. Patients' Baseline, Early Course of Treatment, and Course of Treatment Variables (N = 2960)

Variable	Value for Total Sample[a]
Premorbid and baseline variables	
Age, mean (SD), y	42.3 (13.9)
Age, N (%)	
< 30 y	558 (19.3)
30 to < 40 y	871 (30.1)
40 to < 50 y	707 (24.5)
≥ 50 y	756 (26.1)
Sex, N (%), male	1430 (49.4)
Duration of illness, median (quartiles), y	7.6 (1.7, 16.7)
CGI-Schizophrenia severity score, mean (SD)	
Overall score	4.4 (1.0)
Positive subscore	3.7 (1.4)
Negative subscore	4.0 (1.3)
Cognitive subscore	4.0 (1.2)
Depressive subscore	3.6 (1.3)
Functioning, N (%)	
Employed	1254 (42.6)
Independent living	1907 (64.6)
SWN-K total score, mean (SD)	63.9 (17.1)
First antipsychotic treatment, N (%)	593 (20.6)
Extrapyramidal motor symptoms and/or tardive dyskinesia, N (%)	1079 (37.5)
First-line antipsychotic, N (%)	
Atypical antipsychotic	2492 (86.4)
Conventional antipsychotic	394 (13.6)
Early course of treatment variables (at month 3)	
Early symptomatic remission, N (%)	971 (32.9)
Early functional remission, N (%)	847 (28.7)
Early adequate subjective well-being, N (%)	975 (33.6)
Course of treatment variables	
Substance use disorder (SUD), N (%)	
No SUD	2199 (80.3)
Remitted SUD	314 (11.5)
Persistent SUD	227 (8.3)
Noncompliance, N (%)	1056 (36.5)

[a]Ns vary due to missing data.
Abbreviations: CGI-Schizophrenia = Clinical Global Impressions-Severity of Illness scale, expanded version; SWN-K = Subjective Well-being Under Neuroleptic Treatment Scale, short version.

expected in an outpatient sample. While 19.7% of the subjects were reported to have comorbid substance use disorder (SUD) at baseline, only 8.3% had persistent SUD throughout the 24-month study period. Subjects stayed on treatment with their respective first atypical longer than with their first conventional antipsychotic (lower quartile of time to first switch of antipsychotic medication: 550 days [95% CI = 455 to 644 days] vs. 358 days [95% CI = 271 to 582 days], respectively; log-rank test p = .040). After 24 months, 70.7% (95% CI = 68.6% to 72.9%) of the subjects still received their initial atypical antipsychotic, and 66.0% (95% CI = 60.4% to 71.6%), their initial conventional antipsychotic. The main reasons for switching from a first to a second antipsychotic trial were lack of efficacy in 54.4%, intolerance to previous antipsychotic treatment in 19.6%, and noncompliance in 17.2% of cases.

Applying the remission criteria at baseline (omitting temporal requirements) resulted in the following rates:

Table 2. Combinations of Symptomatic and Functional Remission and Adequate Subjective Well-Being at 24 Months

Symptomatic Remission	Functional Remission	Adequate Subjective Well-Being	Subjects (N = 2905)[a]	
			N	%
No	No	No	1019	35.08
Yes	No	No	323	11.12
No	Yes	No	209	7.19
No	No	Yes	241	8.30
Yes	Yes	No	127	4.37
Yes	No	Yes	548	18.86
No	Yes	Yes	65	2.24
Yes	Yes	Yes	373	12.84

[a]Includes all subjects for whom data were available.

9.6% of subjects met the symptomatic remission criterion, 28.1% met the functional remission criterion, and 17.5% exhibited adequate subjective well-being. Only 2.1% (N = 59) fulfilled the cross-sectional combined remission criterion at baseline. As displayed in Table 1, the symptomatic remission rate increased about 3-fold at month 3, and the rate of subjects with adequate subjective well-being almost doubled, while the functional remission rate remained nearly unchanged.

Remission Rates

Remission criteria (including the 6-month duration criterion) at 24 months are presented in Table 2. At 18 and 24 months, 2316 subjects (78.2%) and 2210 subjects (74.7%), respectively, were still participating in the study, necessitating LOCF procedures in about a quarter of subjects. Additionally, for 55 subjects (1.9%), data on at least 1 of the remission criteria were not available (48 [1.6%] of those never completed the SWN-K scale throughout the study). At 24-month follow-up assessment, 47.2% of subjects had achieved symptomatic remission, 42.2% adequate subjective well-being, and 26.6% functional remission. Only 12.8% of the subjects met the complete remission criterion at 24 months, while 35.1% fulfilled none of the 3 remission criteria.

The independent living criterion was fulfilled by 62.6% of subjects, and the vocational/occupational criterion, by 62.6% of subjects, but only 28.5% met both functional remission criteria. Both symptomatic remission and adequate subjective well-being were achieved by 31.7% of subjects. Only 17.2% met both symptomatic and functional remission criteria.

The biggest obstacle in achieving complete remission was the vocational/occupational criterion: 23.4% of the subjects would have achieved complete remission if the occupational/vocational status criterion were omitted.

Predictors of Remission

The same set of variables was used in the 4 logistic regression analyses in order to compare predictors across

Table 3. Predictors of Symptomatic and Functional Remission and Adequate Subjective Well-Being

	Symptomatic Remission			Functional Remission			Adequate Subjective Well-Being		
Predictor	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value
Block 1—baseline predictors (N = 2345)									
Age			.828			< .001			.411
< 30 y[a]	…	…	…	…	…	…	…	…	…
30 to < 40 y	1.05	0.81 to 1.36	.733	0.91	0.65 to 1.27	.562	0.86	0.66 to 1.11	.250
40 to < 50 y	0.94	0.71 to 1.25	.665	0.78	0.54 to 1.14	.201	0.78	0.59 to 1.04	.093
≥ 50 y	1.02	0.75 to 1.40	.880	0.38	0.25 to 0.60	< .001	0.82	0.60 to 1.13	.220
Sex (male vs female)	0.90	0.75 to 1.07	.223	0.75	0.59 to 0.95	.019	0.99	0.83 to 1.19	.956
Duration of illness (years)	0.99	0.98 to 1.00	.073	0.99	0.97 to 1.00	.085	0.99	0.98 to 1.00	.168
CGI-Schizophrenia severity score									
Overall score ≤ 3	3.02	2.14 to 4.25	< .001	1.22	0.79 to 1.88	.374	1.25	0.90 to 1.73	.178
Positive subscore ≤ 3	1.22	1.01 to 1.49	.044	1.21	0.92 to 1.59	.176	0.90	0.74 to 1.10	.323
Negative subscore ≤ 3	1.45	1.16 to 1.82	.001	1.19	0.88 to 1.61	.252	1.19	0.95 to 1.49	.125
Cognitive subscore ≤ 3	1.21	0.96 to 1.53	.102	0.89	0.65 to 1.23	.485	0.87	0.69 to 1.09	.227
Depressive subscore ≤ 3	1.21	0.98 to 1.50	.069	1.04	0.78 to 1.39	.796	1.19	0.97 to 1.47	.102
Functioning									
Employed	1.29	1.07 to 1.55	.008	11.72	9.08 to 15.13	< .001	1.15	0.96 to 1.39	.129
Independent living	1.46	1.20 to 1.77	< .001	14.44	10.22 to 20.41	< .001	1.53	1.26 to 1.87	< .001
SWN-K total score[b]	0.87	0.77 to 0.98	.018	0.91	0.77 to 1.07	.258	1.87	1.66 to 2.12	< .001
First antipsychotic treatment	1.64	1.29 to 2.09	< .001	1.59	1.16 to 2.18	.004	1.49	1.17 to 1.89	.001
Extrapyramidal motor symptoms and/or tardive dyskinesia	1.00	0.8 to 1.21	.990	1.11	0.85 to 1.45	.449	1.16	0.96 to 1.41	.130
First-line antipsychotic (typicals vs atypicals)	0.71	0.55 to 0.91	.008	0.65	0.45 to 0.93	.019	0.57	0.44 to 0.74	< .001
Block 2—early course of treatment predictors (N = 2345)									
Early functional remission	1.23	0.90 to 1.70	.199	7.71	5.34 to 11.15	< .001	1.20	0.87 to 1.65	.274
Early symptomatic remission	5.84	4.61 to 7.40	< .001	1.11	0.82 to 1.52	.489	1.76	1.39 to 2.22	< .001
Early adequate subjective well-being	1.74	1.36 to 2.21	< .001	1.33	0.97 to 1.82	.072	6.04	4.79 to 7.61	< .001
Block 3—course of treatment predictors (N = 2191)									
Substance use disorder (SUD)			.003			.438			.025
No SUD[a]	…	…	…	…	…	…	…	…	…
Remitted SUD	1.01	0.74 to 1.37	.962	0.79	0.52 to 1.19	.254	0.84	0.62 to 1.15	.280
Persistent SUD	0.52	0.35 to 0.76	.001	0.83	0.51 to 1.35	.458	0.59	0.40 to 0.88	.009
Noncompliance	0.73	0.59 to 0.89	.002	1.01	0.76 to 1.32	.971	0.78	0.63 to 0.96	.018

[a]Reference category.
[b]SWN-K total score was rescaled in units of 20 points.
Abbreviations: CGI-Schizophrenia = Clinical Global Impressions-Severity of Illness scale, expanded version; SWN-K = Subjective Well-being Under Neuroleptic Treatment scale, short version.

the 3 remission criteria as well as for complete remission. In this large observational study, data on several potential predictor variables were not available for all subjects. As mentioned above, of the 2960 subjects, data on remission criteria were available in 2905 subjects, data on baseline predictors and early course of treatment predictors were available in 2345 subjects across all remission criteria, and the complete set of predictors was available in 2191 subjects. A significant difference in the rate of complete remission was noted between the subjects with and without at least 1 missing predictor variable (10.5% vs. 13.6%; $\chi^2 = 4.6$, df = 1, p = .032). In particular, missing data on SUD and noncompliance were indicators for a significantly lower complete remission rate.

The 3 models for the prediction of symptomatic and functional remission and adequate subjective well-being are presented in Table 3. Among the most relevant predictors of symptomatic remission were a lower overall severity of illness and a better subjective well-being at baseline as well as early symptomatic remission and early adequate subjective well-being at 3 months. With regard to the "course of treatment" predictors, persistent substance use and noncompliance were associated with symptomatic nonremission. Younger age, female gender, functioning at baseline, and early functional remission at 3 months predicted functional remission. Adequate subjective well-being was mainly predicted by better subjective well-being and functioning level at baseline as well as early symptomatic remission and early adequate subjective well-being at month 3.

Consistently across all remission criteria, subjects receiving their first antipsychotic treatment and those initially treated with atypical antipsychotics were more likely to achieve symptomatic and functional remission and adequate subjective well-being.

The prediction models of complete remission are displayed in Table 4. Both forward and backward selection algorithms resulted in selecting the same predictors for the models, with robust estimates for the odds ratios. Younger age, better overall functioning at baseline, and

Table 4. Prediction Models (full model and reduced model resulting from forward and backward selection algorithm) of Complete Remission Defined as Fulfilled Criteria for Symptomatic and Functional Remission and Adequate Subjective Well-Being

	Full Model			Reduced Model		
Predictor	OR	95% CI	p Value	OR	95% CI	p Value
Block 1—baseline predictors (N = 2345)						
Age			.001			< .001
< 30 y[a]	…	…	…	…	…	…
30 to < 40 y	0.77	0.54 to 1.11	.159	0.70	0.48 to 1.03	.067
40 to < 50 y	0.65	0.43 to 0.99	.046	0.61	0.40 to 0.94	.023
≥ 50 y	0.33	0.19 to 0.56	< .001	0.26	0.15 to 0.44	< .001
Sex (male vs female)	0.90	0.68 to 1.19	.459			
Duration of illness (years)	0.99	0.97 to 1.01	.564			
CGI-Schizophrenia severity score						
Overall score ≤ 3	1.59	0.99 to 2.57	.057			
Positive subscore ≤ 3	1.03	0.75 to 1.42	.857			
Negative subscore ≤ 3	1.11	0.80 to 1.56	.531			
Cognitive subscore ≤ 3	0.88	0.61 to 1.27	.496			
Depressive subscore ≤ 3	1.19	0.85 to 1.66	.308			
Functioning						
Employed	5.78	4.20 to 7.96	< .001	2.74	1.75 to 4.27	< .001
Independent living	8.69	5.51 to 13.71	< .001	4.43	2.58 to 7.59	< .001
SWN-K total score[b]	1.12	0.93 to 1.34	.235			
First antipsychotic treatment	1.81	1.29 to 2.55	.001	1.67	1.20 to 2.31	.002
Extrapyramidal motor symptoms and/or tardive dyskinesia	1.10	0.80 to 1.52	.545			
First-line antipsychotic (typicals vs atypicals)	0.45	0.27 to 0.73	.001	0.39	0.23 to 0.67	.001
Block 2—early course of treatment predictors (N = 2345)						
Early functional remission	2.92	1.84 to 4.64	< .001	2.76	1.74 to 4.37	< .001
Early symptomatic remission	2.36	1.69 to 3.29	< .001	2.06	1.49 to 2.83	< .001
Early adequate subjective well-being	2.47	1.76 to 3.46	< .001	2.29	1.66 to 3.14	< .001
Block 3—course of treatment predictors (N = 2191)						
Substance use disorder (SUD)			.333			
No SUD[a]	…	…	…	…	…	…
Remitted SUD	0.71	0.44 to 1.15	.166			
Persistent SUD	0.81	0.44 to 1.48	.489			
Noncompliance	0.75	0.54 to 1.04	.085	0.73	0.53 to 1.01	.061

[a]Reference category.
[b]SWN-K total score was rescaled in units of 20 points.
Abbreviations: CGI-Schizophrenia = Clinical Global Impressions-Severity of Illness scale, expanded version; SWN-K = Subjective Well-being Under Neuroleptic Treatment Scale, short version.

first antipsychotic treatment predicted complete remission. Furthermore, early symptomatic and functional remission and adequate subjective well-being independently predicted complete remission. At 24 months, 57.2% of the subjects with early complete remission fulfilled complete remission criteria, while only 8.7% of early nonremitted cases achieved remission at endpoint. With regard to antipsychotic treatment, those receiving their first antipsychotic trial and initially treated with atypical antipsychotics were more likely to achieve complete remission at 24 months.

DISCUSSION

Expectations in treating schizophrenia have expanded beyond just controlling psychotic symptoms to the inclusion of all domains that may be affected by the disease, such as psychosocial functioning and quality of life/subjective well-being. Most early studies on outcomes in schizophrenia focused solely on sustained symptomatic improvement.[25] More recent studies on outcome of first- and mainly multiple-episode patients[4,8] have assessed symptomatic and functional remission/recovery criteria. These studies have reported that a significant proportion of patients achieve favorable outcome with either symptomatic or functional improvement, but rarely fulfill symptomatic and functional criteria simultaneously.[4,8] To our knowledge, the present SOHO study is the first to assess remission in 3 domains, symptomatic and functional remission as well as adequate subjective well-being.

Key Findings

With regard to remission rates, a substantial proportion, almost 50%, of the patients achieved symptomatic remission, and about 40% achieved adequate subjective well-being, but less than a third of the subjects sustained functional remission. When only symptomatic and functional criteria were combined, 17% of subjects achieved complete remission. With the inclusion of adequate subjective quality of life, the remission rate further decreased to 13%. Notably, 35% of patients achieved none of the 3 remission criteria. Direct comparisons of these rates with

previous studies are limited by substantial differences in the definition of remission criteria and the time frames used for maintenance of these criteria.[8,9] The complete remission rate in this study is apparently low. This may be partly explained by the long mean duration of illness and therefore more chronic course of illness of patients in the sample. In line with this assumption, receiving the first antipsychotic treatment was positively associated with all remission criteria. Furthermore, similar to the study by Robinson et al.,[4] the functional remission criteria, in particular the vocational/occupational status, were found to be a major obstacle in achieving complete remission. Twenty-three percent of the subjects would have achieved complete remission if the occupational/vocational status criterion were omitted. The low occupational/vocational functioning of patients with schizophrenia is probably determined by several components: the direct impairment caused by the illness, stigmatization, and common social and economic barriers of the general public in a given country.[17] The latter may also be reflected in the finding that older subjects were less likely to achieve functional remission. By showing that various factors, not all of which are intrinsic to schizophrenia, contribute to occupational/vocational functioning, these results question the applicability of using low occupational/vocational functioning as a criterion for measuring schizophrenia outcomes.[17,26]

Consistent with previous studies,[4,8] early remission (within the first 3 months in this study) predicted later fulfillment of the respective remission criteria and complete remission. Accordingly, only 9% of those without early complete remission achieved complete remission at endpoint. Therefore, early detection of incomplete remission or treatment resistance and subsequent treatment adaptations are mandatory in the treatment of first- as well as multiple-episode patients.[27]

We found specific predictors of remission components. In line with Lambert et al.,[28] persistent SUD was associated with a decreased probability of symptomatic remission. Importantly, baseline SUD was not found to have significant influence on symptomatic remission. Traditionally, clinicians have been pessimistic toward treating patients with comorbid psychosis and SUD. However, the above results suggest that clinicians may adopt a more optimistic approach. Our result that medication noncompliance was associated with symptomatic nonremission is consistent with findings from many previous studies.[29] Accordingly, people with schizophrenia and comorbid substance use should be offered integrated treatment that addresses both disorders and includes interventions to improve adherence.[29] With regard to predictors of functional remission, the high odds ratios of baseline employment and independent living imply highly stable social and vocational functioning throughout the study.[30] In line with previous research,[31,32] an adequate subjective well-being/quality of life was predicted by, among others, independent living and early remission of symptoms and subjective well-being.

Limitations

As this was a large observational study in daily clinical practice, several methodological limitations such as the lack of assessment of interrater reliability and availability of more differentiated measures such as PANSS or neuropsychological assessments for the detailed assessment of cognitive deficits were unavoidable. Furthermore, generalizability of the results to epidemiologic samples is clearly limited by the selection of an outpatient population with a long mean duration and only moderate severity of illness and inclusion criteria requiring a first initiation or switch of antipsychotic treatment. In the analyses of predictors of remission, subjects with missing data on SUD and noncompliance had lower rates of complete remission. Therefore, the odds ratios for these predictors need to be replicated in future studies. The most important limitation is probably the lack of assessment of other relevant predictors of remission, most importantly premorbid adjustment, duration of untreated psychosis, and prestudy treatment conditions and response. Strengths of the study include the large sample size, which allowed for the analysis of a large number of predictors and the assessment of 3 domains of remission in schizophrenia in an otherwise understudied population treated by outpatient psychiatrists.

Clinical Implications

Despite advances in pharmacologic and psychosocial treatments in schizophrenia, close to 90% of the patients in this study did not fulfill the combined remission criteria. In detail, just over 50% of the patients were still symptomatic, almost 60% still had impairment in subjective well-being, nearly 60% neither had a job nor attended school/university, and nearly 40% were not living independently, i.e., alone, with a partner, or with peers. Across studies,[4,8] the high prevalence of incomplete remission regardless of the criteria used is common. Factors that contribute to this unfavorable outcome may be the illness disability itself, a long duration of untreated illness before initial presentation, and insufficient quality of treatment. However, the finding that the course of the disorder depends on early outcome not only in previously untreated but also in more chronically ill patients points toward a critical "window of opportunity" in the course of treatment. Nevertheless, our results also suggest that there may be a subgroup of patients with traitlike incomplete remission in all or single outcome domains. The question remains to be answered whether the current strategies for the treatment of incomplete remission improve long-term outcome considerably in this subgroup of patients with schizophrenia.

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

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