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Correlates of subjective and functional outcomes in outpatient clinic attendees with schizophrenia and schizoaffective disorder

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Abstract Outcome in schizophrenia is multidimensional and, thus, consists of clinical, humanitarian, rehabilitative and cost domains. Accordingly, recovery is conceptualized as the ability to function in the community, socially and vocationally, as well as being relatively free of disease-related psychopathology. The present cross-sectional study examined the relationship of premorbid functioning, psychopathology, insight, attitudes toward medication and side-effects, as well as sociodemographic factors with treatment outcomes in terms of quality of life (QOL) and psychosocial functioning among 60 regular attendees of a specialized schizophrenia outpatient clinic. Both insight into the illness as well as attitudes toward treatment indicated satisfactory compliance. Premorbid school and social functioning were positively correlated with actual employment status, and premorbid social functioning was further positively correlated with QOL and global functioning. Attitudes toward treatment were positively associated with global QOL, and with the patients' living situation. Both positive and negative symptoms as well as asthenia were negatively associated with QOL, while cognitive symptoms negatively influenced occupational functioning. Older patients lived independently and/or in a partnership more often, but had a lesser likelihood of competitive employment. Our observations suggest that subjective and functional outcomes in highly compliant patients are mainly predicted by psychopathological symptoms and unchangeable sociodemographic variables.

Key words schizophrenia · outcome · quality of life · employment · psychosocial functioning

Introduction

Schizophrenia is a severe and disabling disorder which affects multiple functional domains adversely. There are major deficits in employability, independent living is rare, and frequency of marriage and having children is low [33, 40]. Accordingly, in recent years, there has been an increase in emphasis on clinical outcomes that are meaningful to patients, families, and clinicians, as well as a greater focus on functional recovery [4, 45].

If outcome in schizophrenia is measured exclusively in terms of remission of positive symptoms, most patients treated with antipsychotic medications are rated as much improved. However, patients with schizophrenia who experience reductions in psychotic symptoms when receiving treatment may still have marked impairments in a variety of other domains, including subjective outcome variables [e. g., quality of life (QOL)] as well as social and vocational functioning [11, 43]. Consequently, Weiden et al. [57] have proposed a hierarchy of long-term goals in the treatment of schizophrenia with maintenance of stability as the basic goal, followed by the improvement of QOL, again followed by the recovery of functioning.

Several factors can affect subjective and functional outcomes. Among them are premorbid functioning, psychopathological symptoms, insight, and attitudes toward and side-effects of medication. First-episode patients with premorbid social maladjustment or a protracted duration of untreated psychosis have been found to have a diminished QOL [13]. Furthermore, premorbid adjustment has been shown to predict objective outcome [8, 36] as assessed by the Strauss-Carpenter Outcome Scale [52]. With regard to psychopathological symptoms, depressed mood and anxiety seem to be associated with a worse QOL, whereas the association between positive or negative psychotic symptoms and sub-

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jective QOL is more uncertain [20, 26, 32, 54]. Correlations between positive symptoms and social disabilities tend to be weak [16, 45], while negative symptoms have been associated with reduced social functioning, as measured by community adjustment, and social skills [1, 10]. Both positive and negative symptoms have been found to predict employment status in some studies [9], but not in others [27, 44, 47].

There are conflicting findings about a potential association between insight and QOL. Several studies have shown that patients with diminished insight report negative subjective QOL [7, 18, 48], whereas Sim et al. [51], for example, have recently reported an inverse relationship between the degree of insight and overall QOL in first-episode schizophrenia patients with comorbid depression. Others have not found any relationship between insight and QOL [24, 59]. On the other hand, diminished insight has been associated with poor vocational performance [38].

A negative subjective response to antipsychotics has been shown to diminish QOL [7, 26], and employed patients might have less positive regard for medication than patients who are unemployed [21, 25]. With regard to medication side-effects, weight gain [2, 27], sexual dysfunction [26], and extrapyramidal symptoms – in particular akathisia and parkinsonism [21, 26, 56] – have been linked to reduced QOL, with parkinsonism being further associated with poor vocational performance [27].

Based on the findings described above, the current study attempted to examine the influence of premorbid functioning, psychopathology, insight, attitudes toward medication and side-effects, as well as sociodemographic factors on treatment outcomes in terms of QOL and psychosocial functioning among regular attendees of a specialized schizophrenia outpatient clinic. We hypothesized that poor premorbid functioning, depressed mood and anxiety, a negative subjective response to antipsychotics as well as the presence of antipsychotic-induced side-effects would be associated with poor QOL. Furthermore, we hypothesized that poor premorbid functioning, positive and negative symptoms, a negative subjective response to antipsychotics, and again antipsychotic-induced side-effects would be associated with poor functional outcome in this patient group.

Method

Subjects

From 2003 to 2005, we performed a cross-sectional study including 60 patients with schizophrenia or schizoaffective disorder between the ages of 19 and 60 from our specialized outpatient clinic. Altogether, this comprises about 50% of the patients who are regularly treated in this clinic. All subjects had a duration of illness of over 2 years. At the time of the interviews, patients had been clinically stable with a fixed medication regimen for a period of at least 6 months. The diagnostic criteria of a schizophrenic or schizoaffective disorder according to ICD-10 served as a basis for study inclusion after patients had consented in writing. The diagnoses were confirmed using chart infor-

mation and reports from clinicians as well as on-site psychiatrists. In order to render a homogenous sample, only those patients were included in the study who were known to be compliant with treatment. Accordingly, patients were recruited by the treating psychiatrists, while all ratings were performed by a single research team staff member trained in the use of the scales who was not involved in the treatment of the patients. The study was approved by the local Ethical Committee.

Premorbid functioning

Premorbid functioning was quantified with the Premorbid Adjustment Scale (PAS) [15], which provides a measure of premorbid symptoms at different stages of life and prior to the onset of psychotic symptoms. The PAS is divided into five sections. The first four sections assess four time periods: childhood (up to 11 years), early adolescence (12–15 years), late adolescence (16–18 years), and adulthood (19 years and above). The fifth section is a general section providing an overall indication of premorbid educational, occupational, social, and energy level. This nonspecific section was not considered as reliable as the other four and, therefore, not analyzed any further.

The PAS covers two discrete areas of functioning: school functioning (scholastic performance and adaption to school) and social functioning (sociability and withdrawal, peer relationships, and capacity to establish sociosexual relationships (the latter was not assessed for childhood)). Items are scored on a scale from 0 to 6, with 0 denoting the best level of functioning and 6 the worst. The range of scoring for each developmental period is the same, allowing for comparison scores across developmental periods.

The premorbid period, as defined by Andreasen et al. [5], ends 1 year before the first admission to hospital or the onset of florid psychotic symptoms. Therefore, in order to assure the assessment of premorbid development, the PAS was completed only for the developmental stages preceding the period of onset of illness. For example, if a patient was first admitted to hospital with psychotic symptoms at the age of 21, only the childhood, early adolescence and late adolescence developmental scales were completed.

Psychopathology

Psychopathological symptoms were rated by means of the Positive and Negative Syndrome Scale (PANSS) [30]. As in our previous studies [26–28], this instrument was divided into five dimensions following Lindenmayer et al. [34, 35]: (I) negative component (including the items 'blunted affect', 'emotional withdrawal', 'poor rapport', 'passive social withdrawal', 'lack of spontaneity', 'active social avoidance'); (II) excitement component ('excitement', 'hostility', 'uncooperativeness', 'poor impulse control'); (III) cognitive component ('conceptual disorganization', 'difficulty in abstract thinking', 'mannerisms and posturing', 'disorientation', 'poor attention'); (IV) positive component ('delusions', 'hallucinatory behavior', 'grandiosity', 'suspiciousness', 'stereotyped thinking', 'unusual thought content'); and (V) depression/anxiety component ('anxiety', 'guilt', 'tension', 'depression').

Insight

Insight was assessed with the Insight and Treatment Attitudes Questionnaire (ITAQ) [39]. It consists of 11 questions, each rated in terms of 0 = no insight; 1 = partial insight; 2 = good insight – thus, the higher the score, the better the patient's insight. Questions concern the presence of mental or (nervous) problems at the time of admission and currently, the need for admission, the possibility of future illness, the need for monitoring, the need for medication, and willingness to take medication.

Drug attitude

The patients' subjective response to antipsychotics and their attitudes toward medication were assessed by means of the Drug Attitude In-

ventory (DAI) [29], a self-report questionnaire consisting of statements about perceived effects and benefits of antipsychotics with which the patient can agree or disagree. It is divided into seven factors: (1) *subjective positive feelings* related to antipsychotics (e. g., feeling happier); (2) *subjective negative feelings* attributed to the drugs (e. g., feeling tired and sluggish); (3) *health/illness-dependent drug intake*: patients' model of health (e. g., believing it is unnatural to take medication); (4) patients' *confidence in physician* (e. g., believing it is up to the doctor when one stops taking medication); (5) *control*: patients' attitudes toward the locus of control in taking medication (e. g., feeling pressured to ingest medication); (6) *prevention*: patients' belief in the effect of antipsychotics in forestalling relapse (e. g., antipsychotics can prevent one's getting sick); and (7) *harm*: patients' concerns with potential toxic effects (e. g., believing medication is a slow-acting poison). Each item of the DAI is scored as 1 or 2, depending on whether the answer selected by the patient indicates a negative or positive view of medication.

■ Side-effects

To quantify side-effects, the UKU Side-Effect Rating Scale (UKU) [37] was used, which comprises a total of 48 symptoms, arranged into four groups: psychic, neurological, autonomic and other side-effects. Each symptom is scored on a severity scale from 0 to 3, and the rater assesses whether the report is best attributed to a side-effect (rated as improbable, possible or probable) or related to the disease. For the purpose of subsequent statistical analysis, only adverse effects with scores ≥ 1 on any UKU item and a causal relationship of possible or probable were considered as antipsychotic-induced side-effects.

■ Quality of life

QOL was assessed with the WHOQOL-BREF [53], which consists of 26 questions, scored in four domains: physical health (7 items), psychological (6 items), social relationships (3 items), and environment (8 items). Each item is self-rated on a 5-point scale and the domain scores are transformed to lie between 0 and 100. Two items are global indicators of quality of life and satisfaction with health, which are not included in the calculation of domain scores.

■ Functioning

Functional outcome was evaluated by assessing patients' marital and employment status, and by assessing their living situation. Furthermore, the Global Assessment of Functioning Scale (GAF) [3] was used for assessing patients' overall level of functional status across psychological, social, and occupational domains via a single anchored measure. The GAF Scale is divided into ten ranges of functioning. Each 10-point range contains a description with two components: (1) symptom severity and (2) functioning.

■ Statistical analysis

Data analyses were carried out using SPSS (Windows) Version 11.0

Subscales and total scores of the assessment instruments used (PAS, PANSS, ITAQ, DAI, UKU, WHOQOL-BREF) were calculated according to the instructions of the developers. To reduce the relatively large number of seven DAI subscales, they were condensed to three dimensions using the results of a previously performed factor analysis [25]: 'positive feelings and effects' [including the original subscales 'subjective positive feelings' (I), 'confidence in physician' (IV) and 'prevention' (VI)], 'negative feelings and effects' [including the subscales 'subjective negative feelings' (II), 'harm' (VII) and 'control' (V)] and 'health/illness-dependent drug intake' (consisting of the original subscale III).

Associations between potential predictor variables and outcome were studied on two different levels of complexity, firstly by correlational analyses (exploratory) and secondly by multiple regression analysis (confirmatory). Outcome variables considered were QOL

(subscales of the WHOQOL-BREF), employment status (competitive employment yes/no), existing partnership (yes/no), living situation (independent living yes/no), and global functioning (GAF). Independent variables (potential predictors of outcome) studied were sociodemographic and clinical patient characteristics, premorbid functioning (PAS), actual psychopathological symptoms (PANSS) and antipsychotic-induced side-effects (UKU). In order to limit the number of independent variables, level of insight (ITAQ) and attitude towards medication (DAI) were not considered in the multiple regression analysis, and only the total ITAQ and DAI scores (no subscores) were used in the correlational analyses. The rationale for this reduction was that all study participants could be expected to present fairly high DAI and ITAQ scores as they were all compliant with their medication; therefore, the effect of low DAI and/or ITAQ scores on outcome could not be tested. Moreover, omission of DAI and ITAQ in the regression analysis appears sensible as it is unclear how these variables interfere with psychopathology (DAI and ITAQ may indirectly affect psychopathology through medication compliance, but the latter may also affect the former) and regression methods cannot adequately deal with such situations.

For the first part of the analysis, Spearman rank correlation, the Mann-Whitney U-test and Fisher's exact test were used, depending on the type of the variables involved (ordinal/continuous x ordinal/continuous, binary x ordinal/continuous, binary x binary). This part of the analysis was considered as exploratory and hence no correction for multiple testing was made.

The second part of the analysis consisted of multiple linear and logistic regression to study the joint effect of the independent variables on outcome (linear regression in case of continuous outcome variables with a normalizing transformation if required; logistic regression in case of binary outcome variables). The independent variables were entered in a three-stage regression procedure. The total set of independent variables was split into three blocks according to the chronological order in which variables become available; the first consisting of the variables describing the premorbid state (PAS subscales), the second comprising the variables already given at study entry (age, sex, diagnostic group and duration of illness), the third including the PANSS subscales and antipsychotic-induced side-effects (UKU). The regression procedure starts with the first block of variables, using stepwise backward elimination for variable selection and retaining all variables with $p \leq 0.05$. The second and third block of variables are then added consecutively, applying the same method as above for variable selection. Corrected R^2 was used as a measure of determination of the models, change in R^2 serves as a measure of the improvement obtained by adding the variables of the second and third block. As there were usually very few significant predictors (if any) in the first and second block, the results of the first two analysis steps were combined in the presentation of the regression analysis (referred to as model I); the final model, after adding the third block of variables, is reported separately as model II.

Results

■ Patient characteristics

Demographic and clinical characteristics of the study sample are summarized in Table 1. The majority of patients were male, their mean age was 37.6 years, and the mean time from the onset of florid psychotic symptoms was approximately 10 years. The mean PANSS total score was 49.9 ± 12.3 , indicating fairly few symptoms. In all, 5 % of patients were treated with traditional antipsychotics, 86.7 % with second-generation drugs, and 8.3 % received combined treatment.

Premorbid school functioning, as measured by the PAS, deteriorated significantly from childhood (1.88 ± 1.20) to early adolescence (2.40 ± 1.16 , $p = 0.002$),

Table 1 Demographic and clinical characteristics of 60 patients

Age, mean \pm SD, years	37.6 \pm 8.6
Sex, %, female/male	28.3/71.7
Duration of illness, mean \pm SD, years	10.3 \pm 5.9
Diagnosis, N (%)	
Schizophrenia, paranoid type	21 (35)
Schizophrenia, residual type	30 (50)
Schizoaffective disorder	9 (15)
PANSS score, mean \pm SD	
Total score	49.9 \pm 12.3
Negative ^a (6 items)	12.7 \pm 5.1
Excitement ^a (4 items)	5.1 \pm 1.7
Cognitive ^a (5 items)	7.6 \pm 2.6
Positive ^a (6 items)	9.4 \pm 3.8
Depression/anxiety ^a (4 items)	7.4 \pm 2.8
Antipsychotic treatment, N (%)	
Traditional antipsychotics (monotherapy)	3 (5.0)
Second-generation antipsychotics (monotherapy)	52 (86.7)
Traditional + second-generation antipsychotic	2 (3.3)
Two second-generation antipsychotics	3 (5.0)
Housing, N (%)	
With original family	19 (31.7)
With own family	3 (5.0)
Alone	29 (48.3)
In a small group home	5 (8.3)
Others	4 (6.7)
Marital status, N (%)	
Single	50 (83.3)
Married/stable partnership	3 (5.0)
Divorced/widowed	7 (11.7)
Employment status, N (%)	
Full-time employment	4 (6.7)
Part-time employment	6 (10.0)
Supported employment	6 (10.0)
Training	6 (10.0)
Unemployed	38 (63.3)

PANSS Positive and Negative Syndrome Scale

^a PANSS components were defined according to the Lindenmayer 5-factor model (33,34) and scored on a 1 (= no symptom) to 7 (= extremely severe symptom) scale

and remained constant thereafter (late adolescence: 2.60 ± 1.27). There was no significant change of premorbid social functioning from childhood (1.76 ± 1.56) to early (1.78 ± 1.39) and late adolescence (1.84 ± 1.65). The PANSS total score was negatively correlated with social functioning during childhood ($p = 0.02$), early ($p = 0.008$) and late adolescence ($p = 0.005$). We did not find any association between diagnostic subgroups or current psychopathological symptoms and premorbid school functioning. On the other hand, patients with residual schizophrenia had worse social functioning during late adolescence than schizoaffective patients (2.29 ± 1.78 vs. 1.22 ± 1.72 , $p = 0.058$, trend level).

The mean ITAQ score was very high (19.70 ± 3.98 , range = 1–22). Table 2 shows an overview of the patients' attitudes towards antipsychotic medication, as assessed by the DAI. Generally, the subscales describing positive aspects of antipsychotics received much higher scores and, thus, a higher degree of consent than subscales characterizing negative aspects of medication.

The most frequently reported antipsychotic-induced side-effects (found in $\geq 30\%$ of patients) included tremor [50% ($N = 30$)], asthenia [45% ($N = 27$)], and functional sexual disturbances [41% of female patients ($N = 7/17$), 12% of male patients ($N = 5/43$); 20% of all patients]. Diminished sexual desire was reported in 31% of patients, and sedation in 30%. Moreover, hypersalivation was observed in 37% of patients, and orthostatic dizziness in 32%.

Outcomes

An overview of patients' QOL, as assessed by the WHO-QOL-BREF, is given in Table 3. Of the life domains assessed, 'environment' received the highest satisfaction ratings, while 'social relationships' had the lowest ratings. Patients' global QOL was generally positive, which is reflected by a mean WHOQOL-BREF score of 67.5 ± 19.8 on a scale from 0 (poorest QOL) to 100 (best QOL). Significant group differences included only the physical domain, with higher mean scores in schizoaffective

Table 2 Drug attitude inventory (DAI) scores

Subscale	Mean	SD	Proportion of patients with a score above 50	
			N	%
(I) Subjective positive feelings	80.0	26.8	51	85.0
(II) Subjective negative feelings	27.5	22.3	5	8.3
(III) Health/illness dependent drug intake	20.0	28.9	7	11.7
(IV) Confidence in physician	92.5	20.2	52	86.7
(V) Control	5.0	15.1	0	0.0
(VI) Prevention	94.2	20.8	55	91.7
(VII) Harm	20.8	32.3	5	8.3
Total score (best = 100, worst = 0)	81.5	13.4	59	98.3

Raw subscores of the DAI were converted to a range of 0 (no agreement) to 100 (total agreement) by linear transformation

Table 3 Quality of life scores according to the WHOQOL-BREF^a

Domain	Mean	SD
Physical health	69.3	14.2
Psychological	64.5	17.4
Social relationships	62.1	21.7
Environment	73.8	11.9
Global quality of life	67.5	19.8

^a Range: 0 (= poorest quality of life) to 100 (= best quality of life)

fective patients than in patients with residual schizophrenia (75.8 ± 13.9 vs. 65.4 ± 12.6 , $p < 0.05$).

A total of 10 patients (16.7%) were competitively employed (part-time or full-time employment) with 6 patients belonging to the paranoid subgroup, 3 to the schizoaffective subgroup, and 1 to the residual schizophrenia subgroup. This means that 28.6% of patients with paranoid schizophrenia, 33.3% of schizoaffective patients, and 3.3% of residual schizophrenia patients were able to attend to competitive work (paranoid vs. residual: $p = 0.007$; schizoaffective vs. residual: $p < 0.03$).

The three groups did not differ significantly with regard to marital status, living situation, or GAF score. In all, 60% of patients (36/60) were living independently with 5% having a stable partnership, while the others were attended by their original family or lived in a small group home (Table 1). The mean GAF score was 57.4 ± 14.3 (range = 1–100).

■ Association of patients' outcomes with sociodemographics, premorbid functioning, psychopathology, insight, drug attitude and side-effects

Sociodemographics

Among sociodemographic variables, age was negatively correlated with the patients' actual employment status

(lower probability of competitive employment with increasing age, $r = -0.42$, $p = 0.002$), and both age and duration of illness were positively correlated with the patients' living situation [higher probability of independent living with increasing age ($r = 0.35$, $p = 0.006$) and duration of illness ($r = 0.26$, $p < 0.05$)]. There was no association between sociodemographic variables and QOL, marital status, or global functioning.

Premorbid functioning

Premorbid school functioning was positively correlated with patients' employment status (higher probability of competitive employment with better school functioning during childhood, $r = 0.27$, $p < 0.05$), but not associated with QOL, marital status, or living situation. On the other hand, there was a positive correlation between the social relationships domain of the WHOQOL-BREF and social functioning during childhood ($r = 0.29$, $p < 0.03$) and early adolescence ($r = 0.28$, $p < 0.03$) and a further positive correlation between social functioning during late adolescence and patients' actual employment status (higher probability of competitive employment with better social functioning, $r = 0.39$, $p = 0.004$). In addition, the GAF score was positively associated with social functioning during childhood ($r = 0.43$, $p = 0.001$), early ($r = 0.53$, $p < 0.001$) and late adolescence ($r = 0.47$, $p < 0.001$). We did not find any correlation between premorbid social functioning and both the patients' marital status and living situation.

Psychopathology

Correlations of psychopathology and outcome are summarized in Table 4. Generally, there were distinct associations between actual psychopathological symptoms and outcome with the PANSS total score being negatively associated with all the outcome variables assessed.

Table 4 Spearman rank correlations of psychopathology and outcome (quality of life, employment, partnership, independent living, GAF-score)

	PANSS dimension ^a					
	Total score	Negative	Excitement	Cognitive	Positive	Depression/anxiety
WHOQOL physical health	-0.354**	-0.207	-0.332**	-0.122	-0.279*	-0.265*
WHOQOL psychological	-0.502**	-0.364**	-0.300*	-0.179	-0.355**	-0.328*
WHOQOL social relationships	-0.408**	-0.318*	-0.083	-0.206	-0.217	-0.203
WHOQOL environment	-0.431**	-0.305*	-0.225	-0.262*	-0.305*	-0.114
WHOQOL global	-0.439**	-0.262*	-0.322*	-0.295*	-0.319*	-0.155
Competitive employment ^b	-0.341*	-0.236	-0.113	-0.368**	-0.161	-0.175
Partnership ^b	-0.285*	-0.284*	-0.209	-0.204	-0.092	-0.058
Independent living ^b	-0.299*	-0.261*	-0.215	-0.113	-0.158	-0.015
GAF-score	-0.749**	-0.560**	-0.269*	-0.437**	-0.575**	-0.280*

* $p \leq 0.05$; ** $p \leq 0.01$

GAF Global Assessment of Functioning Scale

^a According to Lindenmayer et al. [33, 34]; ^b Yes (1) vs. no (0)

Insight, drug attitude, side-effects

Insight was not associated with any of the outcome variables. The patients' attitude towards antipsychotic medication, measured by the DAI total score, was positively correlated with global QOL (i.e., a more positive drug attitude was associated with better QOL, $r=0.31$, $p<0.02$), independent living ($r=0.43$, $p=0.001$), and the GAF score ($r=0.31$, $p<0.02$). Among side-effects, tremor was negatively associated with both global QOL ($r=-0.26$, $p<0.05$) and the environment domain of the WHOQOL-BREF ($r=-0.25$, $p<0.05$), and asthenia was negatively associated with global QOL ($r=-0.31$, $p<0.02$) as well as with the physical ($r=-0.30$, $p<0.02$), psychological ($r=-0.37$, $p=0.003$), and environment domains ($r=-0.25$, $p=0.05$), and the GAF score ($r=-0.26$, $p<0.05$). Furthermore, diminished sexual desire showed a negative correlation with the social relationships domain ($r=-0.29$, $p<0.03$), whereas sedation was negatively associated with the psychological domain ($r=-0.32$, $p<0.02$). None of the side-effects was associated with marital and/or employment status, and living situation.

■ Results of multiple linear and logistic regression analyses

The combined effects of premorbid adjustment, patient characteristics, psychopathology and side-effects on outcome were analyzed by multiple linear and logistic regression analyses, the results of which are summarized in Table 5. Regarding QOL, the extent to which premorbid adjustment, patient characteristics, psychopathology and side-effects together were able to predict the five WHOQOL-BREF domains was moderate at most, ranging from $R^2=0.143$ to 0.335 (i.e., 14%–33% of total variance was attributable to these variables). Premorbid social adjustment was found to be a significant predictor of the social relationships domain of the WHOQOL-BREF (higher PAS social adjustment scores predicted a better QOL in the social domain), while premorbid adjustment did not show a significant effect on any other QOL domains. Patient characteristics had a significant contribution to only one of the WHOQOL subscales: longer duration of illness was a predictor of lower QOL in the physical health domain. Among the five dimensions of the PANSS (according to Lindenmayer's definition), positive symptoms were found to be a significant predictor of lower QOL in all domains but one (social relationships). In addition, negative symptoms had a negative effect on the psychological, social relationships, and environmental domains. Among side-effects, only asthenia was found to be a significant predictor of QOL, having a negative effect on the WHOQOL-BREF scores in the physical and psychological domains. No further PANSS or UKU variable had a significant effect on QOL, once the other variables had been accounted for.

Good premorbid social adjustment in early and late adolescence proved to be a positive predictor of competitive employment (higher chance of competitive employment), whereas older age as well as residual type of schizophrenia were found to be significant negative predictors. The cognition subscale of the PANSS emerged as an additional predictor of competitive employment (poorer cognition scores reduce the probability of competitive employment), after adjusting for patient characteristics and premorbid adjustment. Higher PANSS negative symptoms scores predicted both a lower probability of stable partnership and a lower probability of independent living. The latter was also affected by age, with a higher chance of independent living with older age.

Regarding global assessment of functioning, premorbid social adjustment in early adolescence as well as three of the PANSS subscales (negative symptoms, positive symptoms and cognition) were found to contribute significantly to the GAF score, the first predicting higher levels of functioning, the latter lower levels.

Discussion

This study illustrates the complexity of factors that influence subjective and functional outcomes in stable outpatients with schizophrenia. It was conducted in order to determine an eventual impact of premorbid functioning, psychopathology, insight, drug attitude, antipsychotic-induced side-effects, and sociodemographic factors on QOL, employment status, living situation, marital status, and global functioning of patients in a naturalistic treatment setting. We chose to study regular attendees of a specialized outpatient clinic. This approach neglects a considerable number of patients who choose not to take advantage of specialized services regularly. Selecting a sample in this way clearly limits the generalizability of the collected data. Therefore, when interpreting our data, one has to consider that we have investigated a highly compliant sample, as indicated by very high ITAQ and DAI total scores. This is an advantage of the present study, since it eliminates the compliance problem from the analysis, which is known to be related to symptom severity, insight, drug attitude, and side-effects [50], which, in turn, have an important impact on outcomes [55].

As shown in Table 1, we studied a patient group with some residual symptoms living in a stable social environment, which we believe to be comparable with stable outpatients treated in similar outpatient settings in other countries.

Of the QOL domains, social relationships received the lowest satisfaction ratings, which corroborates the findings of earlier studies [31]. Furthermore, longer duration of illness was a predictor of lower QOL in the physical health domain. However, corresponding to our previous studies of independent samples [26, 27], patients indicated that they were satisfied with their lives

Table 5 Effects of premorbid adjustment, patient characteristics^a, psychopathology, and side-effects on patients' quality of life, employment and marital status, living situation, and global assessment of functioning (multiple linear or logistic regression analysis)

Dependent variable	Model ^b	Significant predictors ^c	Model information ^d		Change in R ^{2e}	Total R ^{2e}
			Test value	d.f.	p	
WHOQOL physical health	I: PAS + patient characteristics	Duration of illness ↓	F = 5.30	1.58	0.025	0.084
	II: I + psychopathology + side-effects	+ PANSS positive symptoms ↓ UKU asthenia ↓	F = 7.98	3.56	0.001	0.219
WHOQOL psychological	I: PAS + patient characteristics	–	–	–	–	0
	II: I + psychopathology + side-effects	PANSS negative symptoms ↓ PANSS positive symptoms ↓ UKU asthenia ↓	F = 9.40	3.56	< 0.001	0.335
WHOQOL social relationships	I: PAS + patient characteristics	Social adjustment childhood ↑	F = 8.01	1.58	0.006	0.109
	II: I + psychopathology + side-effects	PANSS negative symptoms ↓	F = 8.19	2.57	0.001	0.201
WHOQOL environment	I: PAS + patient characteristics	–	–	–	–	0
	II: I + psychopathology + side-effects	PANSS negative symptoms ↓ PANSS positive symptoms ↓	F = 6.40	2.57	0.003	0.183
WHOQOL global	I: PAS + patient characteristics	–	–	–	–	0
	II: I + psychopathology + side-effects	PANSS positive symptoms ↓	F = 9.65	1.58	0.003	0.143
Competitive employment (yes/no)	Ia: Premorbid adjustment (PAS)	Social adjustment early adolescence ↑ Social adjustment late adolescence ↑	χ ² = 13.85	2	0.001	0.234
	Ib: Ia + patient characteristics	+ Age ↓, diagnosis (residual type ↓)	χ ² = 28.50	4	< 0.001	0.422
Partnership (yes/no)	II: Ib + psychopathology + side-effects	+ PANSS cognition ↓	χ ² = 38.21	5	< 0.001	0.520
	I: PAS + patient characteristics	–	–	–	–	0
Independent living (yes/no)	II: I + psychopathology + side-effects	PANSS negative symptoms ↓	χ ² = 6.56	2	0.010	0.104
	I: PAS + patient characteristics	Age ↑	χ ² = 7.40	1	0.007	0.116
Global assessment of functioning	II: I + psychopathology + side-effects	+ PANSS negative symptoms ↓	χ ² = 12.45	2	0.002	0.188
	I: PAS + patient characteristics	Social adjustment early adolescence ↑	F = 16.79	1.58	< 0.001	0.206
	II: I + psychopathology + side-effects	+ PANSS negative symptoms ↓ PANSS positive symptoms ↓ PANSS cognition ↓	F = 29.08	4.55	< 0.001	0.663

PAS Premorbid Adjustment Scale; PANSS Positive and Negative Syndrome Scale; UKU UKU Side-Effect Rating Scale

^a Comprising age, sex, diagnostic group and duration of illness^b In accordance with the blockwise variable entry method, statistical information is displayed separately for the first step and for the second (final) step of the regression analysis, denoted by model I and model II, respectively^c All independent variables attaining a p-value ≤ 0.05 in the respective regression model are listed. The direction of the effect is denoted by arrows (↑ positive effect, ↓ negative effect on dependent variable). For model II, the + sign indicates that the variables listed are added to those entered in model I^d Summarizes statistical information for the global model (F-test in the case of linear regression, likelihood-ratio test in the case of logistic regression)^e In the case of logistic regression, standard R² is not available and was replaced by Cox and Snell's version of R²

in general. We hypothesize that the relatively long duration of illness of about 10 years may have enabled our patients to adjust to their state of health and to available resources. This explanation would be in line with our finding that older patients lived independently and/or in a stable partnership more frequently than younger ones.

Premorbid social functioning was positively associated with the social relationships domain of the WHOQOL-BREF, actual employment status, and global functioning as assessed by the GAF. These findings are in agreement with those of other researchers [8]. Similarly, feelings and attitudes towards antipsychotics correlated with patients' QOL, living situation, and global functioning. Again, these findings corroborate those of earlier reports suggesting that the subjective response to medication is associated with outcome [6, 7, 12]. On the other side, given the high ITAQ scores, we were not able to detect any associations between the assessed outcome variables and insight. Again, this may be a reflection of sample selection, as outlined above.

In the overall regression analysis, positive symptoms were negatively associated with the global and physical domains of the WHOQOL-BREF, while negative symptoms were negatively associated with the social relationships domain. Both positive and negative symptoms were negatively associated with the psychological and environment domains, while none of the remaining PANSS dimensions was associated with QOL. This finding seems surprising at first sight, since several authors have reported that negative QOL correlates more strongly with depression and anxiety than with psychotic symptoms [7, 20, 22, 26], thereby indicating that patients' QOL is related more to negative and affective states, and less to positive symptomatology. However, our findings are preceded by other investigations which have also shown that some positive symptoms, especially paranoid ideation or reality distortion, are inversely correlated with QOL [14, 48].

The most frequently observed side-effects in our sample were similar to those previously reported [25, 57]. Asthenia was the only one that adversely affected the physical health and psychological domains of the WHOQOL-BREF in a multiple linear regression analysis. However, although some side-effects did not influence QOL in the overall regression analysis, there were distinct relationships when analyzed separately. Tremor was associated with reduced global QOL, diminished sexual desire was inversely correlated with the social relationships domain of the WHOQOL-BREF, and sedation was negatively associated with the psychological domain. Again, the fact that these side-effects did not stay significant in the overall regression analysis may be a reflection of sample size and selection.

Not surprisingly, premorbid functioning during adolescence correlated with the patients' employment status at the time of the study: patients with a higher level of premorbid functioning had a higher probability of competitive employment. Moreover, as to be expected, competitive employment was less frequent in older and in

residual patients as well as in patients with a larger extent of cognitive dysfunction, the latter being further negatively associated with global functioning (GAF). These results are consistent with neuropsychological studies comparing the cognitive functioning of employed and unemployed patients [28, 42, 47], and suggest that our patients are comparable to other samples of patients with schizophrenia. This underscores the assumption that cognitive impairment contributes to the problem of unemployment in patients with schizophrenia [43].

We could also replicate earlier reports of negative associations between negative symptoms and the probability of living independently and/or in a stable partnership on one hand, and global functioning on the other [1, 10, 12, 17, 41].

In summary, this study provides further evidence for clinically relevant links of premorbid adjustment, psychopathological symptoms, and side-effects of medication with subjective and functional outcomes in patients with schizophrenia or schizoaffective disorder. Most patients had a monotherapy with second-generation antipsychotics, less likely to lead to dopamine D2 receptor occupancy related adverse events [19], which have been associated with diminished QOL [23, 26, 56] and poor vocational performance [27].

Altogether, our findings corroborate the hierarchical pyramid model of treatment outcomes described by Weiden et al. [58], which defines the maintenance of symptomatic stability as a foundation for achieving long-term improvements in QOL and level of functioning. Correspondingly, subjective and functional outcomes in our sample were mainly predicted by psychopathological symptoms and unchangeable sociodemographic variables (age, duration of illness). Therefore, these data suggest that both pharmacological and psychosocial interventions designed to specifically target psychopathological symptoms including cognitive deficits may have the greatest impact on QOL and functional outcomes in patients with schizophrenia spectrum disorders. However, as this was a cross-sectional study, it will be critical to generate longitudinal follow-up data, to determine how the associations or the determinants of subjective and functional outcomes interact and change over time.

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