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Association between symptoms and quality of life in patients with schizophrenia: A pooled analysis of changes over time

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ABSTRACT

Quality of life is an important outcome in the treatment of patients with schizophrenia. It has been suggested that patients' quality of life ratings (referred to as subjective quality of life, SQOL) might be too heavily influenced by symptomatology to be a valid independent outcome criterion. There has been only limited evidence on the association of symptom change and changes in SQOL over time. This study aimed to examine the association between changes in symptoms and in SQOL among patients with schizophrenia. A pooled data set was obtained from eight longitudinal studies that had used the Brief Psychiatric Rating Scale (BPRS) for measuring psychiatric symptoms and either the Lancashire Quality of Life Profile or the Manchester Short Assessment of Quality of Life for assessing SQOL. The sample comprised 886 patients with schizophrenia. After controlling for heterogeneity of findings across studies using linear mixed models, a reduction in psychiatric symptoms was associated with improvements in SQOL scores. In univariate analyses, changes in all BPRS subscales were associated with changes in SQOL scores. In a multivariate model, only associations between changes in the BPRS depression/anxiety and hostility subscales and changes in SQOL remained significant, with 5% and 0.5% of the variance in SQOL changes being attributable to changes in depression/anxiety and hostility respectively. All BPRS subscales together explained 8.5% of variance. The findings indicate that SQOL changes are influenced by symptom change, in particular in depression/anxiety. The level of influence is limited and may not compromise using SQOL as an independent outcome measure.

1. Introduction

Quality of life is regarded as a relevant outcome criterion in the treatment of patients with schizophrenia (Priebe and Fakhoury, 2008). There are objective and subjective indicators of quality of life, and patients' rating of their own quality of life (referred to as subjective quality of life, SQOL) are widely used in research. The US Food and Drug Administration (US FDA, 2009) explicitly referred to it when underlining the importance of using patient reported outcomes in trials. Whilst there is no universal consensus on its precise definition, several scales are based on Lehman's (Lehman, 1996) approach of measuring SQOL as satisfaction with life in general and major life domains.

Many research studies and evaluations of routine care have found symptomatology to be associated with SQOL scores (Priebe and Fakhoury, 2008). Numerous cross-sectional studies, including meta- and pooled analyses (Eack and Newhill, 2007; Vatne and Bjorkly, 2008; Priebe et al., 2011), have reported that higher symptom levels are associated with less favourable SQOL ratings. These findings have led to suggestions that SQOL ratings in patients with schizophrenia might be too heavily influenced by symptoms and therefore not a valid independent outcome criterion (Atkinson et al., 1997; Katschnig, 1997).

However, treatment effects are commonly evaluated by investigating changes over time. For assessing whether SQOL can be used as an outcome criterion independent of symptoms, evidence is required on how changes in symptoms and changes in SQOL over time are associated. Cross-sectional associations can either overestimate or underestimate the extent of associations of changes over time. Only a few studies have investigated the association of symptom change and change in SQOL in a longitudinal design (Kaiser and Priebe, 1998; Fakhoury et al., 2002). These studies had small sample sizes and produced inconsistent

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findings. While Kaiser and Priebe (1998) reported an association between change in anxiety and depressive symptoms, symptoms of hostility, and change in SQOL, there was no evidence of such an association for general psychopathology and other types of symptoms. Further, Fakhoury et al. (2002) even found an absence of evidence of an association of changes in SQOL with changes in general psychopathology and depression/anxiety symptoms.

Using a pooled analysis of individual patient data from several studies, we aimed to study the association of changes in psychopathological symptoms and changes in SQOL in patients with schizophrenia. A pooled analysis considers both studies and individual patients as the unit of analysis and has several advantages compared to a conventional meta-analysis of aggregate data sets: it enables a more precise estimate of the effects of influential factors; allows for controlling of confounding factors including heterogeneity across studies at the patient level; and reduces effects of heterogeneity from aggregation of methodologically diverse studies by using the same statistical model (Blettner et al., 1999; Reininghaus and Priebe, 2007).

2. Methods

In a pooled analysis, linear mixed models were applied to individual patient data from samples of patients with schizophrenia, with SQOL change scores as the dependent variable.

2.1. Sample

The pooled data set was collected within a project on factors influencing SQOL in different patient samples (Priebe et al., 2011). To identify relevant data sets we contacted experts in the field and conducted a literature search of academic databases. For the current study, we included data sets with at least one follow-up assessment of both psychopathological symptoms and SQOL. For studies with more than two time points the first and last one were used. These long time periods were taken to have a greater chance of obtaining substantial changes in patients' SQOL that can be tested for their association with symptom change. For avoiding problems of heterogeneity of measurement methods (Vatne and Bjorkly, 2008), only data sets using Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) or Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1988) for assessing psychiatric symptoms and the Lancashire Quality of Life Profile (Oliver et al., 1997) or its short version, the Manchester Short Assessment of Quality of Life (MANSA) (Priebe et al., 1999) for measuring SQOL were included. We included only patients with documented diagnoses of schizophrenia, schizotypal, or delusional disorders (ICD-10F2) (World Health Organization, 1992).

2.2. Measures

Studies used either the Lancashire Quality of Life Profile or MANSA for measuring SQOL, which use Lehman's approach of assessing SQOL (Lehman, 1996) and contain very similar items on satisfaction with life in general and different life domains rated from 1 (couldn't be worse) to 7 (couldn't be better). The two scales have been shown to yield practically identical SQOL scores with a correlation between mean scores of $r = 0.94$ (Priebe et al., 1999), and are widely used in mental health service research in Europe. Their reliability and validity has been demonstrated in several studies (Kaiser et al., 1997; Priebe et al., 1999; Gaite et al., 2000; van Nieuwenhuizen et al., 2001). Limiting the analysis to these two measures ensured consistent data and fully utilised the advantages of a pooled analysis of individual patient data. We computed change scores of SQOL between baseline and follow-up assessments.

Symptoms were assessed on the BPRS or PANSS. Both scales contain identical items and allowed for computing BPRS-18 total and subscales: anxiety/depression (somatic concern, anxiety, guilt feelings, depressive mood), anergia (emotional withdrawal, motor retardation, blunted affect, disorientation), thought disorder (conceptual disorganisation, grandiosity, hallucinatory behaviour, unusual thought content), activity (tension, mannerisms and posturing, excitement), and hostility (hostility, suspiciousness, uncooperativeness). We computed change scores of symptoms between baseline and follow-up assessments.

2.3. Statistical analysis

Stata 10 for Windows was used for all data analyses (Stata, 2007). Mean differences in symptom and SQOL scores were tested using paired t-tests. Test–retest reliability coefficients were computed to examine the stability of SQOL and symptom ratings over time. Linear mixed models were computed to examine the association between symptom change and change in SQOL, whilst controlling for heterogeneity across studies using `xtreg` in Stata 10 (Rabe-Hesketh et al., 2002; Stata, 2007). In this two-level model, patients (level 1) were treated as nested within studies (level 2). The modelling proceeded through several stages. (1) Mixed models were fitted with SQOL change scores as dependent variable and fixed effects for BPRS change scores. (2) In the analysis of change in BPRS subscales, all fixed effects identified as statistically significant in stage (1) were entered into a multivariate mixed model. In the multivariate model the BPRS total score was not entered since the score is dependent on the subscales. In all stages, heterogeneity of findings across the included study samples was controlled for by including a random intercept for the study variable into the model.

In trials, outcomes are commonly evaluated using end of treatment scores adjusted for baseline scores. This type of analysis also reflects change although strictly speaking not using change scores. We tested whether the findings of the analysis of change scores also applied when analysing follow-up scores adjusted for baseline scores. In a sensitivity analysis, SQOL at follow-up adjusted for SQOL at baseline was taken as the dependent variable, and residual gain scores of symptoms were used as independent variable to adjust for patients' symptom level at baseline.

3. Results

3.1. Included studies and samples

Eight studies (Roder-Wanner and Priebe, 1998; Priebe et al., 2002, 2007, 2009; Ruggeri et al., 2002; Slade et al., 2006; Kallert et al., 2007), including one unpublished study (Junghan, 2009, unpublished data), were included (see Table 1). Five were prospective observational and three randomised controlled trials. From these 8 studies,BPRS and SQOL change scores were available for a total of 886 patients with schizophrenia, schizotypal, or delusional disorders. The follow-up periods ranged from 6 to 36 months.

3.2. Patient characteristics

Patient characteristics are shown in Table 2. The mean age of patients was 40.2 years, with an approximately equal gender distribution. About a third of patients were unemployed. Most patients were not married or living in partnership. About half of the patients were educated to school level.

3.3. Changes of symptoms and SQOL over time

While overall symptom levels decreased from baseline to follow-up (mean difference = −5.65, 95% CI −6.39 to −4.92, $P<0.001$; Cohen's $d = 0.51$), SQOL levels improved (mean difference = 0.20, 95% CI 0.26 to 0.14, $P<0.001$, Cohen's $d = 0.23$). Test–retest reliability was broadly similar for SQOL ($r_{tt} = 0.55$, 95% CI 0.50 to 0.60) and BPRS scores (total

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Table 1
Study characteristics of the 8 included studies and samples.

Study	Study sites	Sample size[1]	Research design	SQOL measure[2]	Time to follow-up (month)
		n			
Roder-Wanner and Priebe (1998)	Berlin (Germany)	49	Prospective–observational	LQOLP	9
Priebe et al. (2002)	Berlin (Germany)	83	Prospective–observational	LQOLP	18
Ruggeri et al. (2002)	Verona (Italy)	55	Prospective–observational	LQOLP	36
Slade et al. (2006)	London (UK)	37	RCT	MANSA	7
Priebe et al. (2007)	London (UK) Granada (Spain) Groningen (Netherlands) Lund (Sweden) Mannheim (Germany) Zuerich (Switzerland)	336	RCT	MANSA	12
Kallert et al. (2007)	Dresden (Germany) London (UK) Wroclaw (Poland) Michalovce (Slovakia) Prague (Czech Republic)	123	RCT	MANSA	12
Priebe et al. (2009)	London (UK) Bristol (UK) Nottingham (UK)	144	Prospective–observational	MANSA	12
Junghan (unpublished data)	Bern (Switzerland)	29	Prospective–observational	LQOLP	6

[1] Sample size refers to included patients with an ICD-10 clinical diagnosis of schizophrenia, schizotypal, or delusional disorders, for which BPRS-18 and SQOL change scores were available.
[2] LQOLP, Lancashire Quality of Life Profile; MANSA, Manchester Short Assessment of Quality of Life.

score, $r_{tt}=0.51$, 95% CI 0.46 to 0.56; depression/anxiety subscale, $r_{tt}=0.48$, 95% CI 0.43 to 0.53; anergia subscale, $r_{tt}=0.56$, 95% CI 0.52 to 0.61; thought disorder subscale, $r_{tt}=0.45$, 95% CI 0.39 to 0.50; activation subscale, $r_{tt}=0.44$, 95% CI 0.39 to 0.49; hostility subscale, $r_{tt}=0.30$, 95% CI 0.24 to 0.36). SQOL ratings at follow-up were not significantly higher in RCTs compared to observational studies (Standardised coefficient 0.042, Unstandardised coefficient 0.037, 95% CI −0.064 to 0.137, P = 0.477).

3.4. Associations between symptom change and change in SQOL

Associations between symptom change and change in SQOL as a dependent variable controlling for SQOL at baseline and heterogeneity of findings across studies are shown in Table 3.

All symptom change scores were significantly associated with change in SQOL. However, when all BPRS-18 subscale symptom change scores were entered into a multivariate model, only change in BPRS depression/anxiety and hostility remained significantly associated with change in SQOL, with 5% and 0.5% of variance being attributable to BPRS depression/anxiety and hostility, respectively. In this final model, BPRS subscales overall explained 8.5% of variance.

These findings broadly held in the sensitivity analysis with SQOL at follow-up as dependent variable and residual gain scores of symptoms as independent variable adjusted for SQOL at baseline. In this analysis, depression/anxiety (Standardised coefficient −0.262, Unstandardised coefficient −0.069, 95% CI −0.084 to -0.054, P<0.001) and hostility (Standardised coefficient −0.121, Unstandardised coefficient −0.053, 95% CI −0.077 to −0.029, P<0.001) were the only types of symptoms significantly associated with SQOL in the multivariable model and explained 5.3% and 1.2% of the variance of SQOL, respectively.

Table 2
Patient characteristics.

	Total sample (n = 886)
Age[a], mean (s.d.)	40.2 (12.0)
Female, n (%)	415 (46.8)
Educated to school level[b], n (%)	242 (48.5)
Married/partnership[c], n (%)	121 (17.3)
Unemployed[d], n (%)	248 (36.0)
Outpatient care, n (%)	458 (51.7)

Missing values [a]1, [b]387, [c]185, [d]197.

4. Discussion

After controlling for heterogeneity of findings across studies in linear mixed models, a reduction in symptoms was associated with improvements of SQOL scores. In univariate analyses, changes in each BPRS subscale were associated with changes in SQOL scores. Only associations of depression/anxiety and hostility subscales and SQOL change scores remained significant in a multivariate model. Whilst these associations were statistically significant in a large sample, the shared variance of symptom change and SQOL change was small. All scales together explained 8.5% of the variance of changes of SQOL. Change in the most important type of symptoms, i.e. depression/anxiety, explained only 5% of the variance in SQOL change.

4.1. Strengths and limitations

The analysis used a sufficiently large sample to detect effects of clinical relevance, adjusted for the heterogeneity of studies and considered individual patient data in a pooled analysis. Symptoms and SQOL improved over time as it may be expected in research trials and routine treatment. The inter-individual distribution of symptoms and SQOL showed similar stability over time, reducing the risk of unreliable correlations due to substantial differences in the variability of the correlated parameters. Also, the sensitivity analysis which reflected a common method for the analysis of trial results produced similar results as the main analysis.

The samples might not be representative for all patients with schizophrenia in the given service. A potential selection bias may have affected the absolute levels of symptoms and SQOL. Yet, associations between such variables may be assumed to be more robust and less influenced by a selection bias. Data were taken from different studies that had been conducted in different countries. Although all studies used the same scales and trained raters, the rating of scales may still have been inconsistent across languages and settings.

4.2. Comparisons with previous research

Compared to findings in cross-sectional studies, for which an average effect size of r = −0.35 ($R^2=0.1225$) (Eack and Newhill, 2007) has been reported, we found a considerably attenuated association between symptoms and SQOL. Cross-sectional associations might be higher because of the influence of response biases that influence the

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Table 3
Mixed models analysis of symptom and SQOL change scores as dependent variable (8 studies, 886 patients)[a].

	Bivariate model				Adjusted for BPRS-18 subscales[b]			
	Standardised coefficient	Unstandardised coefficient (95% CI)	P	R^2	Standardised coefficient	Unstandardised coefficient (95% CI)	P	ΔR^2
BPRS-18 total score	−0.235	−0.018 (−0.023 to −0.013)	<0.001	0.060	–	–	–	–
Depression/anxiety subscale[c]	−0.300	−0.056 (−0.010 to −0.042)	<0.001	0.073	−0.272	−0.051 (−0.065 to −0.036)	<0.001	0.050
Anergia subscale	−0.106	−0.028 (−0.045 to −0.011)	0.001	0.012	−0.044	−0.011 (−0.028 to 0.005)	0.184	0.002
Thought disorder subscale	−0.086	−0.018 (−0.031 to −0.004)	0.010	0.013	−0.014	−0.003 (−0.017 to 0.012)	0.702	0.0002
Activation subscale	−0.077	−0.027 (−0.050 to −0.005)	0.017	0.008	−0.001	−0.000 (−0.023 to 0.023)	0.982	0.000
Hostility subscale	−0.155	−0.042 (−0.060 to −0.024)	<0.001	0.028	−0.085	−0.023 (−0.043 to −0.003)	0.024	0.005

[a] Estimates are adjusted for and heterogeneity of findings across studies.
[b] Overall $R^2 = 0.085$.

SQOL ratings and also impact on the reporting of symptoms in a clinical interview at the same time. Such response biases can be linked to personality traits (Eid and Diener, 2004), and have less influence on changes over time. Whatever the exact explanation is for the lower longitudinal associations, the evaluation of treatments requires assessments of changes over time rather than cross-sectional data, and our study indicates that the overall impact of symptom change on SQOL change in patients with schizophrenia is lower than cross-sectional studies may have suggested.

All types of symptoms showed associations with SQOL in univariable analyses. The scores of all BPRS subscales are correlated with each other and reflect the overall severity of symptoms which is correlated with SQOL. In the multivariable analysis all subscales were considered at the same time so that specific associations of each type of symptoms with SQOL were tested, and these specific associations were not explained by an effect of the overall symptom severity. In this analysis, only changes in anxiety/depression and hostility remained significantly associated with SQOL changes. The finding suggests that other symptoms, beyond reflecting the overall symptom severity, do not have a specific association with SQOL.

The particular relevance of affective symptoms has been suggested before. Patients who are more depressed at the time of the rating tend to report a lower satisfaction with life. A negative view of life as it is captured in SQOL ratings may be part of a depressive syndrome. Less existing research has pointed towards the importance of hostility. Some cross-sectional studies also suggested that hostility is inversely associated with SQOL (Priebe et al., 2011). Patients with high levels of hostility tend to provide more negative SQOL ratings. Both hostility and negative satisfaction ratings may be linked to dysphoria and a wish to demonstrate dissatisfaction in the interview situation.

The findings add to an analysis of the influence that symptoms may have on the rating of single items of SQOL measures in patients with schizophrenia. In a study on so called differential item function, patients with the same underlying SQOL but higher levels of depressive symptoms were less likely to endorse positive 'life as a whole' and 'mental health' ratings (Reininghaus et al., 2011). This suggested that depressive symptoms may influence the ratings of two individual SQOL items, although the magnitude of the effect was also identified as small and unlikely to be of clinical relevance.

4.3. Conclusions

The findings of this study suggest that in patients with schizophrenia symptom levels and SQOL are sensitive to change over longer periods of time. The mean scores of symptoms and SQOL improved, and changes of the two criteria were associated with each other. However, the extent of the association was so small, that SQOL can be regarded as an independent outcome criterion that is not dominated by symptoms. The existing associations, specifically with depression/anxiety may not compromise the validity of the SQOL ratings.

The weak association of symptom change and SQOL changes also suggests that a treatment effect on symptoms is only to a limited extent reflected in changes of SQOL. Treatments aiming to improve SQOL through symptom reduction should clearly target depression and anxiety. However, the small amount of shared variance between changes of depression/anxiety and SQOL changes indicates that an effective pharmacological or psychological treatment of depression/anxiety may not automatically lead to a substantial improvement of patients' SQOL. On a group level, the impact of such a treatment on changing SQOL is likely to be small. This however does not rule out a substantial impact in individual cases, particularly in patients with marked symptoms of depression and anxiety and low SQOL.

At the same time, interventions to improve SQOL may be effective without achieving symptom change. For example, in a cluster-randomised trial in six European countries an intervention to structure the patient–clinician communication in community care of patients with psychosis led to significant SQOL improvements without impacting on patients' symptom levels (Priebe et al., 2007).

Should symptom levels nevertheless be controlled for when SQOL changes are considered as outcome criterion in trials and other longitudinal research studies? The answer is likely to depend on the nature and purpose of the given evaluation. In studies with large samples aiming to detect small effect sizes this can make sense and help increase the power and sensitivity of the study for identifying an effect. In smaller studies that try and detect larger effect sizes adjusting the analysis of SQOL changes for symptom change may not be essential.

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Contributors
SP designed the study and had overall responsibility for completion. UR conducted the literature searches and managed the data. SP, RM, UJ, TK, MR, and MS took each responsibility for at least one of the data sets in the analysis. UR and SP analysed the data. All authors contributed to and have approved the manuscript.

Conflict of interest
None of the authors reported potential conflicts of interests.

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