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The impact of subjective well-being under neuroleptic treatment on compliance and remission

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The patients' perspective of antipsychotic treatment was largely neglected for a long period. It has only been during the last 10 years, with the development of atypical antipsychotics, that scientific interest in this issue has markedly increased. Numerous studies have shown that the majority of schizophrenic patients are able to fill out a self-rating scale in a meaningful way, and several self-report scales with sufficient internal consistency and good construct validity have been developed. The effects of antipsychotic treatment on psychopathology and on subjective well-being (SW) are not strongly related; the perspectives of the patient and his/her psychiatrist markedly differ. Recent research indicates that SW/quality of life, much more improved by atypical than by typical antipsychotics, has a strong impact on compliance, as well as on the chance of achieving remission. The data strongly suggest that a systematic evaluation of the patient's perspective of antipsychotic treatment is meaningful and necessary to increase compliance, functional outcome, and long-term prognosis.

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I nterest in the subjective well-being (SW) of psychiatric patients has significantly increased over recent years. While, for a long time, symptom reduction alone was the most essential outcome parameter, more detailed success criteria are now being implemented, approximately 50 years after the introduction of neuroleptic treatment. Considering the extensive use of typical neuroleptics over the last decades, surprisingly little evaluation of patients' subjective complaints while being medicated has been performed.¹⁻⁶ In terms of tolerability, investigators focused on motor symptoms when looking at drug-induced complaints and reasons for noncompliance. With the development of atypical antipsychotics, treatment goals became more ambitious, the patient's perspective was considered more, and complaints such as affective blunting and cognitive slowing, as well as volition and loss of spontaneity, received greater interest.⁷⁻¹² These emotional restrictions have been described as "neuroleptic dysphoria," "pharmacogenetic depression," "akinetetic depression," "neuroleptic depression," and "neuroleptic-induced anhedonia."¹³

The increased interest in subjective well-being was not only due to a conceptual shift in therapeutic outcome criteria:

- Studies on subjective well-being disproved the former belief that schizophrenic patients are not able to reliably assess their SW. The majority of schizophrenic patients, if not acutely psychotic or suffering from severe cognitive impairment, are able to complete self-rating scales in a consistent and reliable manner.¹⁴⁻¹⁷

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Selected abbreviations and acronyms

PANSS	<i>Positive and Negative Syndrome Scale</i>
SOHO	<i>Schizophrenia Outpatient Health Outcomes study</i>
SUD	<i>substance use disorder</i>
SW	<i>subjective well-being</i>
SWN	<i>Subjective Well-being under Neuroleptic treatment</i>

- The impact of antipsychotic drugs on SW, together with the quality of the doctor–patient relationship, is one of the two agreed major determinants for medication compliance.^{18,23}

Despite significant advances in the pharmacotherapy of schizophrenia, noncompliance, particularly in long-term treatment, remains a major problem. Rates of noncompliance vary because of inconsistent definitions and heterogeneous samples; studies show that 25% to 70% of all schizophrenic patients are noncompliant.^{18,20,24} Although compliance somewhat improved under treatment with atypical antipsychotics, adherence rates at 6 and 12 months were only moderately higher compared with patients receiving typical agents.²⁵ Since noncompliance is one of the most important risk factors for relapse,¹⁸ enhanced medication adherence is an urgent task.

Due to the advances in psychopharmacological as well as in psychosocial/psychoeducational treatments, chances for better long-term prognosis have been improved, and remission has become a major goal in the treatment of schizophrenia. Most recently, the Remission in Schizophrenia Working Group published a consensus statement on definition criteria and time thresholds of remission in schizophrenia.³⁰ The European Schizophrenia Outpatient Health Outcomes (SOHO) study^{26–29} was one of the first to assess these criteria, including a self-rating, in a large sample of patients.

Measurement of subjective well-being

Subjective well-being is a major component of quality of life,³¹ influenced by the pharmacological and/or psychosocial treatment as well as by the illness itself. A multitude of components, for example patients' attitudes toward medication or other nonpharmacological factors, possibly interfere when their subjective experience of neuroleptic drugs is investigated.

Naber suggested a model consisting of five dimensions of SW: emotional regulation, self-control, mental functioning, social integration, and physical functioning.¹⁵ Lambert et al¹⁴ combined this concept with six influenc-

ing factors: psychopathology and symptomatic improvement, physical side effects and associated distress, attitudes toward pharmacological treatment and insight, psychosocial factors, phase, and severity of illness. One major impetus for this research was the sometimes marked subjective improvement, when patients were switched from typical antipsychotics to clozapine.³² Similarly to the first trial, quality of life was an outcome criterion to assess the improvement by clozapine.³³

The Subjective Well-being under Neuroleptic treatment (SWN) is a self-rating Likert scale with 20 items (10 positive, 10 negative) and good psychometric properties.^{18,34} Recently, an algorithm has been developed to exclude patients who are unable to understand the items or to reliably fill out the scale, based on analyzing mean differences between negative and positive items for the individual subscores (S. Moritz, unpublished data). Starting with the pioneer work of the Drug Attitude Inventory of Hogan et al,³⁵ there now exist, together with the SWN, several self-rating instruments to investigate the patients' perspective of antipsychotic treatment.³²

Psychopathology and subjective well-being

The relationship between psychopathology, as shown with the Positive and Negative Syndrome Scale (PANSS), and the subjective well-being, as measured with the SWN, was investigated in several trials.^{15,35–37} The total score, as well as the subscales were only moderately correlated with the PANSS scores ($r=-0.1$ to -0.5) with stronger relationships to the negative and global score than to the positive score. The highest correlations ($r=-0.4$ to -0.5) were related to the severity of depression and anxiety. Regarding the impact of side effects, Lambert et al³⁸ found, in a study in 213 patients treated with typical neuroleptics, that sexual dysfunctions and extrapyramidal and psychic side effects were rated as subjectively more distressing than vegetative side effects and sedation.

In a study by de Haan et al³⁹ it was shown that dosage of medication leading to dopamine (D_2) receptor blockade should be carefully evaluated, since it is most likely responsible for neuroleptic dysphoria, even in the absence of motor side effects.^{40,41} The relationship between SWN and striatal D_2 receptor occupancy was investigated in 22 schizophrenic patients, clinically stable under either 14.7 mg of olanzapine or 4.1 mg of risperidone. It was demonstrated that in the absence of extrapyramidal symptoms, higher striatal D_2 -receptor

occupancy as measured by single photon-emission computed tomography (SPECT) was related to reduced SWN, negative symptoms, and depression ($P < 0.01$).

Atypical antipsychotics, subjective well-being, and compliance

Naber¹⁵ investigated the subjective perception of neuroleptic treatment with the SWN and found it to be significantly related to noncompliance. Forty-eight patients rated their SWN prior to discharge from inpatient treatment. Six months later, 14 patients were noncompliant. Compared with 34 patients who remained compliant, their SWN at discharge was significantly lower ($P < 0.05$). However, the psychiatrists did not see a difference between future compliant or noncompliant patients; the PANSS scores did not differentiate between both groups. In another patient population, it was shown that the SWN of 28 patients treated with the atypical antipsychotic clozapine because of therapy resistance or motor side effects was, despite negative selection, significantly better than the SWN score of 38 patients under classical neuroleptics ($P = 0.03$).

In a later study, olanzapine and clozapine were compared in a double-blind, controlled trial in 114 patients, over a 26-week period.³⁷ Regarding SWN, the total score—as well as all subscores, excluding mental functioning—showed a significant relationship between low SWN and non-compliance ($P < 0.005 - P < 0.01$). Again, this study showed that the improvement of SWN and of PANSS are not strongly related ($r = -0.3$ to -0.4).

The SOHO study also found a relevant relationship between subjective well-being and compliance. It is a 3-year investigation of the health outcomes associated with antipsychotic treatment in Europe.²⁶⁻²⁹ 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. In the German study population with 2960 patients, SWN was used to assess the patients' perspective. At baseline, patients and physicians categorized compliance as "almost always compliant," "partly compliant," or "almost never compliant." The relationship between changes in compliance (improvement $n = 225$, no change $n = 1366$, worsening $n = 78$) and clinical variables were assessed by factor analysis. This revealed the strongest correlations for SWN ($r^2 = 0.866$), followed by symptoms ($r^2 = 0.772$) and side effects ($r^2 = 0.480$) (Karow et al,

unpublished data). SW seems to be of potent influence on adherence during maintenance treatment, but not in the acute phase, as Mutsatsa et al⁴³ did not find a significant relationship between SWN and early medication adherence in 101 first-episode patients.

Numerous studies show the advantages of atypical versus typical antipsychotics, and these advantages are most prominent from the patients' perspectives: Atypical antipsychotics improve subjective quality of life more than typical antipsychotics,^{44,45} subjective response is significantly better under atypical compared with typical drugs,⁴⁶ and, not surprisingly, switching from a typical to atypical antipsychotic is associated with a marked subjective improvement.^{47,48}

Subjective well-being as a remission criterion in the SOHO study

In the SOHO study, SWN was used as an important single component of the complete remission criterion, according to the new consensus statement on criteria and the time frame of remission in schizophrenia published by the Remission in Schizophrenia Working Group.³⁰ In contrast to previous definitions, the consensus included the incorporation of subjective rating next to sustained symptomatic (ie, positive, negative, and cognitive symptoms) as well as functional remission (ie, activities of daily living, employment).⁴⁹⁻⁵⁷

Remission criteria and predictor variables were assessed at baseline, at 3, 6, 12, 18, and 24 months with standardized scales. Complete remission was defined as patients fulfilling all criteria for (i) symptomatic, (ii) functional, and (iii) subjective well-being over a period of at least 6 months (ie, at the 18-month and 24-month visits). Symptomatic remission was defined as receiving a Clinical Global Impressions Scale (CGI)-Schizophrenia score⁵⁸ of no worse than "mild" (≤ 3) in assessments of overall severity, positive, and cognitive subscores and a score of no worse than "moderate" (≤ 4) in the negative subscore. Functional remission was defined as a positive occupational/vocational status, ie, paid or unpaid, full- or part-time employment, being an active student or head of a household with an employed partner, and independent living, ie, living alone, living with a partner, living with peers. Subjective well-being was met if a SWN total score of ≥ 80 points was achieved.

Predictor variables were (i) baseline predictors, (ii) early course of treatment predictors defined as fulfilled remis-

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sion criteria at 3 months, and (iii) course of treatment predictors defined as variables assessed continuously throughout the complete 24-month period.

The baseline predictors were (i) age, gender, and duration of illness, (ii) symptomatic status assessed with the expanded version of the CGI-Schizophrenia including an overall severity of illness score and 4 subscores for the severity of positive, negative, cognitive, and depressive syndromes, (iii) functional variables included the occupational/vocational status and independent living assessed in yes/no categories, (iv) subjective well-being assessed with the SWN. The early course of treatment predictors were early symptomatic, functional, and subjective well-being remission at 3 months. The course of treatment predictors were compliance with antipsychotic medication, (noncompliance was defined as missing $\geq 50\%$ of medication over at least 4 weeks) and comorbid substance use disorder (SUD) according to *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* criteria, categorized into (i) no SUD; (ii) remitted SUD (remission during follow-up with SUD at baseline); and (iii) persistent SUD.

Lambert et al (unpublished data) found that 50% of the patients achieved symptomatic remission and about 40% subjective well-being remission, whereas only one third sustained functional remission. Including symptomatic and functional criteria, 19% achieved complete remission in the SOHO study; following the consensus statement including the subjective quality of life, remission rate decreased to 14%. It is of particular interest that 32% of all patients achieved none of the three remission criteria. First antipsychotic treatment proved to be a predictor of

all remission criteria. Similarly to the study by Robinson,⁵² the functional remission criterion of 24.5% was the main barrier in achieving complete remission. Consistent with previous studies,^{52,56} early remission within the first 3 months predicted all remission criteria including complete remission. Therefore, early detection of incomplete remission or treatment resistance and subsequent treatment adaptation are mandatory in the treatment of multiple-episode patients as well as first-episode patients.⁶¹ Lambert et al found specific predictors of remission components in the SOHO analysis. Persistent SUD when compared with no SUD was associated with a decreased probability of symptomatic remission, while baseline SUD was not found to have significant influence on symptomatic remission, consistent with previous findings.⁶⁰ Similar to findings from many previous studies, medication noncompliance was associated with symptomatic nonremission.

Conclusion

For a long period, many psychiatrists believed that they knew their patients well enough not to need additional self-ratings by the patients. However, numerous trials have revealed that both perspectives differ markedly regarding the relevance of side effects or success of antipsychotic treatment. Subjective well-being is at least a valuable addition to objective (?) psychopathology, and should become an integral part of shared decision-making. A better consideration of the patients' perspective can improve therapeutic alliance, medication adherence, and, finally, the long-term prognosis. □

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El proyecto MATRICS del NIMH para desarrollar agentes que mejoren la cognición en la esquizofrenia

El Instituto Nacional de Salud Mental de los Estados Unidos ha financiado una iniciativa para facilitar el desarrollo de psicofármacos para mejorar la neurocognición en pacientes con esquizofrenia. Esto se ha llevado a cabo mediante un proceso consensuado en que se han incluido representantes del mundo académico, de la industria farmacéutica y del gobierno. El grupo ha señalado los obstáculos para el desarrollo de fármacos, los que incluyen: (i) la falta de un instrumento bien aceptado para medir la neurocognición en los ensayos clínicos, (ii) la falta de consenso respecto al mejor o los mejores objetivos moleculares para el desarrollo de fármacos, (iii) la falta de consenso respecto al diseño de ensayos óptimos tanto para la comedición que mejore la cognición cuando se asocia a un antipsicótico como para un fármaco de amplio espectro que mejore la cognición y trate la psicosis y (iv) los procedimientos de las agencias reguladoras, como la FDA de los Estados Unidos, para aprobar y clasificar un nuevo fármaco.

Impact sur l'observance et la rémission du bien-être subjectif ressenti sous traitement neuroleptique.

Le point de vue du patient sur le traitement antipsychotique a été très négligé pendant une longue période. C'est seulement depuis ces 10 dernières années, avec le développement des antipsychotiques atypiques, que l'intérêt scientifique sur cette question s'est accru considérablement. De nombreuses études ont montré que la majorité des patients schizophrènes est capable de remplir une échelle d'auto-appréciation de façon intelligible et plusieurs échelles de ce type avec une cohérence interne suffisante et une bonne validité de construction ont été développées. Les effets du traitement antipsychotique sur la psychopathologie et sur le bien-être subjectif (BS) sont peu rapportés; les points de vue du patient et de son psychiatre diffèrent sensiblement. Des recherches récentes montrent que le rapport BS/qualité de vie, plus amélioré par les antipsychotiques atypiques que typiques, influe beaucoup sur l'observance comme sur la probabilité de rémission. Les données suggèrent fortement que l'évaluation systématique du traitement antipsychotique par le patient est significative et nécessaire pour augmenter l'observance, le résultat fonctionnel et le pronostic à long terme.

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