Validation of Remission Criteria for Schizophrenia

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Objective: Remission criteria for schizophrenia have been proposed, consisting of a time criterion and a symptomatic remission criterion. With longitudinal data of a representative patient group (N=317; median follow-up: 1,132 days), validity of the symptomatic remission criterion was investigated.

Method: In a group of 145 patients meeting the symptomatic remission criterion at baseline and a group of 172 patients not meeting it at baseline, change over time in remission status was examined in relation to changes in various functional outcomes.

Results: In both groups, change over time with the symptomatic remission criterion was associated with substantial changes in unmet needs, Global Assessment of Functioning scale scores, satisfaction with services and, to a lesser extent, quality of life. Changing the symptomatic remission criterion to include depression and suicidality did not affect the results.

Conclusions: The proposed symptomatic remission criterion has clinical validity and represents the right balance between parsimony and inclusiveness.

The recently introduced concept of remission criteria for schizophrenia (1) represents a major opportunity for clinicians and consumers. The proposed remission criteria consist of two components: a symptom-based criterion (low scores on diagnostically relevant symptoms) and a time criterion (duration of 6 months). Using longitudinal data from a local health technology assessment database in a geographically defined area, we attempted validation of the symptom-based criterion in terms of 1) cross-validation with clinician-reported and patient-reported functional outcomes and 2) sensitivity analysis with regard to the exclusion of depression and suicidality from the remission criteria.

Method

Data were collected in a local catchment area (N=250,000) from the local Cumulative Needs for Care Register for patients with severe mental illness, which had been in operation since 1998 (2). Conforming to current legal requirements, patients were informed that anonymized routine clinical data may be used for the purpose of regional health technology assessment and given the choice to “opt out,” in which case their data were not used. We used the Camberwell Assessment of Need of (3), the Brief Psychiatric Rating Scale (BPRS) (4), the Global Assessment of Functioning Scale (GAF) split into its psychopathology (GAF symptoms: group range=1–95) and impairment (GAF symptoms, group range=1–95) components (5), a single item on satisfaction with services (satisfaction), two items on quality of life with housing and social relationships (combined into a single item: social quality of life), and two items on quality of life with physical and mental health (combined into a single item: health quality of life). The Camberwell Assessment of Need, the BPRS, and the GAF were scored by clinicians; satisfaction, social quality of life, and health quality of life were scored by the patient on 7-point Likert scales and have been validated previously (2). The number of Camberwell Assessment of Need unmet needs was used in the analysis (group range=0–9).

After the first assessment, the assessments were repeated whenever there was an important change in the treatment plan or, if no such change was present, with intervals of 1 to 2 years. We report here on 317 subjects with a clinical diagnosis of nonaffective psychotic disorder (DSM codes 295, 297, and 298) in the register, who since 1998 had had at least two assessments (median number of postbaseline assessments: 3.0, interquartile range: 2–4; median follow-up: 1,132 days; interquartile range: 521–1,757), and who could be classified at baseline and at least one follow-up according to the symptomatic remission criterion. The median interval between assessments was 462 days (interquartile range: 315–736 days, range: 34–2,034), and this was not associated with whether or not the symptomatic remission criterion was met at the time of the assessment (multiple regression B=18.2, p=0.62). Compared to the other 661 subjects in the register with severe mental illness who were not included in the analyses because of different diagnostic grouping, single assessments only, or missing data at remission, our study group of 317 was similar in terms of the Camberwell Assessment of Need unmet needs (multiple regression B=0.29, p=0.18), GAF psychopathology (multiple regression B=−1.49, p=0.53), and GAF impairment (multiple regression B=−0.94, p=0.67).

The cross-validation assessed whether a change in remission status over time would be associated with important changes in clinician-reported and patient-reported functional outcomes. To this end, the patients were identified who at baseline did (N=145, 46%) and did not (N=172, 54%) fulfill the symptomatic remission criterion according to the seven items of the BPRS (1). These two groups were followed up for change in remission status, and those who had changed were compared with nonchanged individuals for change in functional outcomes. For that purpose, regression models were constructed with various functional outcomes (e.g., the number of Camberwell Assessment of Need unmet needs and the social quality of life score) as the dependent variable and remission status (0: not meeting criterion; 1: meeting criterion) as the independent variable, with adjustment for the baseline value of the functional outcome. Because there was more than one observation per individual, compromising the statistical independence of observations, the STATA XTREG multilevel random regression procedure (6) was used to conservatively adjust standard errors in p values for clustering within individuals. The 317 indi-
that did not move into symptomatic remission, as well as nearly 11 points more on the GAF psychopathology scale and 8 points more on the GAF impairment scale. Similar differences were apparent for the patient-reported functional outcomes. Changing the remission criterion to include the BPRS items of depression and suicidality did not introduce large or consistent changes to the results. Of the patient-reported outcomes, satisfaction with services was sensitive to change in remission status, whereas quality of life outcomes appeared to be somewhat less sensitive.

Discussion

The results suggest that change in the symptomatic remission criterion of the recently proposed concept of remission was associated with large and clinically relevant changes in clinician-reported and, to a lesser extent, patient-reported functional outcomes. A further observation was that change in symptomatic remission over time is not rare: about 30% in either direction (i.e., moving in and moving out of remission). It should be noted that the analyses did not take into account the time criterion: patients could have moved in and out of remission between assessment periods. The data nevertheless suggest that the symptomatic criterion is valid and suitable for use in research such as randomized controlled trials. Similarly, the data presented here suggest that the inclusion of BPRS symptoms that are most relevant for the diagnosis of schizophrenia represent the right mix between parsimony and inclusiveness because the addition of mood items to the definition did not affect the rate of change in the symptomatic remission criterion over time or the association with functional outcomes. The fact that patient-reported quality-of-life outcomes were less sensitive indicates that criteria focusing more on recovery in schizophrenia are also in need of further development. In the meantime, use

| TABLE 1. Cross-Validation and Sensitivity Analyses of Symptomatic Remission Criterion and Extended Remission Criterion, Including Depression and Suicidality, in Individuals With Schizophrenia |
|---|---|---|---|
| Functional Outcome Measure | Analyses Remission Criterion | Analyses Extended Criterion |
| Camberwell Assessment of Need unmet needs | Bc | Bc | Bc | Bc |
| Global Assessment of Functioning psychopathology scale | 18.6 | 148.224 | 18.3 | 138.227 |
| Global Assessment of Functioning impairment scale | 14.0 | 10.3, 17.7 | 12.6 | 8.3, 16.9 |
| Social quality of life | 1.0 | 0.1, 1.9 | 0.6 | -0.4, 1.6 |
| Health quality of life | 1.3 | 0.3, 2.3 | 1.1 | 0.1, 2.2 |
| Satisfaction with services | 0.5 | 0.2, 0.9 | 0.5 | 0.1, 0.8 |
| | | | | |
| Analyses Extended Criterion | Analyses Extended Criterion |
| Bc | Bc | Bc | Bc |
| Bc | Bc | Bc | Bc |
| Bc | Bc | Bc | Bc |
| Bc | Bc | Bc | Bc |

\*Change in functional outcome associated with remission status (0=not meeting criterion, 1=meeting criterion), expressed as the regression coefficient from multilevel random regression procedure.

\*Remission criterion also included the Brief Psychiatric Rating Scale items depression and suicidality.

\*Regression coefficient from multilevel random regression procedure.

Individuals Meeting Criterion at Baseline (N=145), of Whom 51 (35%) Changed Over the Follow-Up Period (effect size remission criterion on functional outcome)  
Individuals Not Meeting Criterion at Baseline (N=172), of Whom 53 (31%) Changed Over the Follow-Up Period (effect size remission criterion on functional outcome)

Individuals provided 841 postbaseline observations for the regression analyses, 6% provided one postbaseline observation, 34% two postbaseline observations, 26% three postbaseline observations, and 34% four or more postbaseline observations.

The sensitivity analysis assessed how stable the cross-validation was in terms of changing the remission criterion to include BPRS depression and suicidality. To this end, the same cross-validation analyses were carried out, with the additional requirement of including the BPRS depression and suicidality items in the symptomatic remission criterion (extended symptomatic remission criterion).

Results

Of the 145 patients who did fulfill the symptomatic remission criterion at baseline, 35% moved out of remission over the follow-up. Conversely, of the 172 patients who did not fulfill the symptomatic remission criterion at baseline, 31% moved into remission. For the extended symptomatic remission criterion, including BPRS depression and suicidality, these rates were, respectively, 37% of the 120 patients meeting the criterion at baseline and 29% of 193 patients not meeting the criterion. Associations between change in remission status in the two groups and functional outcomes are summarized in Table 1. For both the group that did and the group that did not meet the symptomatic remission criterion at baseline, change in remission status was associated with strong differences in functional outcome compared to group members who did not change. For example, in meeting the symptomatic remission criterion at baseline, remaining in remission was associated with adjustment for any baseline differences, with 1.5 unmet needs less than the group that moved out of symptomatic remission, as well as nearly 20 points more on the GAF psychopathology scale and 14 points more on the GAF impairment scale. Similarly, for those not meeting the criterion at baseline, moving into symptomatic remission was associated—with adjustment for any baseline differences—with around one unmet need less than the group...
An Inverse Relationship Between Perceived Harm and Participation Willingness in Schizophrenia Research Protocols

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Objective: This study attempted to clarify how people with schizophrenia evaluate the potential harm associated with various research-related procedures and how these assessments relate to participation willingness.

Method: The authors conducted a semistructured interview among participants with schizophrenia.

Results: Sixty participants with schizophrenia rated four procedures as harmful (e.g., symptom induction), five procedures as moderately harmful (e.g., being given a placebo), and six procedures as not harmful (e.g., undergoing a physical examination). Rated willingness to participate was inversely related to the participants’ perceptions of harmfulness for all procedures.

Conclusions: In this study, people living with schizophrenia perceived different research procedures as posing different levels of possible harm. Potential harm appears to be an important consideration in protocol enrollment decisions. This work reaffirms the value of clarifying the strengths of seriously ill people who may choose to participate in research.

The serious nature of schizophrenia creates a motivating force for pursuing clinical research to understand this devastating neuropsychiatric disease affecting 1% of the world’s population. However, the same features of the illness that inspire us to study its origins and treatment also give rise to ethical challenges. As protocol volunteers, people with schizophrenia have potential sources of vulnerability because cognitive impairments, symptoms, and other factors may interfere with informed consent for research participation (1–2). Regulatory and ethical safeguards for the protection of human subjects have been designed to facilitate nonexploitative studies on potentially vulnerable persons (3–5). Nevertheless, controversy still surrounds key ethical issues in schizophrenia research, including whether people living with serious mental illnesses are able to discern harm associated with protocol participation (2, 5).

Data are necessary to provide a scientific foundation for ethical safeguards in psychiatric research. Efforts to improve the informed consent process could be enhanced by knowing whether people with schizophrenia logically assess the risks of protocols and make decisions about participation that take those assessments into account (6–8). Few studies have explored these issues. More than two decades ago, Stanley et al. (9) found that psychiatric and medical hospital patients were generally similar...