Measurement-Based Psychiatry: Definitions of Response, Remission, Stability, and Relapse in Schizophrenia

Stefan Leucht, M.D., and John M. Kane, M.D.

Clinical trials and clinical practice rely on the assessment of change. In the former, assessments are made utilizing rating scales, whereas that is rarely the case in clinical practice. At the same time, there are terms that are used in both contexts that become particularly important in translating the results of clinical trials into clinical practice, e.g., *response*, *remission*, *stability*, and *relapse*. This column will discuss some important issues that surround the definitions of these terms. We believe these issues take on greater significance as clinical practice and clinical decision-making become more "measurement-based."

Response

Response can be defined as a clinically meaningful improvement of the patient's psychopathology irrespective of whether he or she is still symptomatic. Current antipsychotic drug trials usually apply cutoffs in terms of percentage reduction in score from baseline on rating scales such as the Brief Psychiatric Rating Scale (BPRS)[1] or the Positive and Negative Syndrome Scale (PANSS)[2] as response criteria. However, one problem is that there is no consensus as to what the cutoff to define response should be. In the literature, thresholds of more than 20%, 30%, 40%, 50%, or 60% reduction of the BPRS or the PANSS score have all been used, but in individual studies the choice of a cutoff is often made rather arbitrarily, or even post-hoc.

In 3 recent publications based on more than 1000 patients, we tried to clarify some of these issues.[3–5] Using equipercentile linking—a method for the comparison of the results of different scales—we found that a 25% reduction in score from baseline on the BPRS or the PANSS corresponded approximately to "minimal improvement" in terms of the Clinical Global Impressions scale (CGI),[6] while a 50% reduction corresponded to "much improvement." Since nonrefractory, acutely ill people with schizophrenia generally respond well to antipsychotic drugs,[7] we feel that from a clinical perspective the 50% cutoff is more relevant as a primary outcome than lower cutoffs.

In treatment refractory patients, however, even small improvements of symptoms may be meaningful, thus justifying the use of the ≥ 25% BPRS/PANSS reduction cutoff, while we advised against the use of the 20% cutoff.[3–5] In addition, instead of showing the results of 1 or several arbitrarily chosen cutoffs, the results could be displayed in a simple table in which the numbers and percentages of patients with a < 25%, 25% to < 50%, 50% to < 75%, and ≥ 75% reduction of PANSS/BPRS score are shown. This way of presenting the data is frequently used in Chinese antipsychotic drug trials (e.g., reference 8). The advantage of displaying the data in this way is to present the distribution of the various response levels and thus the complete picture.

In pragmatic trials, when investigators try to randomize large numbers of patients with broad inclusion criteria and utilize minimal inexpensive assessment methods, it might not be appropriate or feasible to employ comprehensive scales such as the BPRS or the PANSS. Such studies may use the CGI, which consists of 2 scales: 1 rating the severity of illness and the other rating participants' overall change on a 7-step scale.[6] The advantage of the CGI is its simplicity and that it can be understood intuitively by clinicians. However, the psychometric properties of the CGI have never been well examined, and there are no good anchors for the ratings; thus, clinicians may have quite different opinions as to what, for example, "much improved" means. If the CGI were chosen as an outcome measure, a new version with validated psychometric properties that is specific for schizophrenia should be used.[9]

Remission

Instead of considering mere response, definitions of *remission* of schizophrenia have been discussed and have recently been proposed by international working groups.[10,11] According to these criteria, a patient is in symptomatic remission if 8 items of the PANSS are rated mild or better. The remission is considered sustained if this threshold is maintained for at least 6 months. In proposing this definition of remission, the characteristic signs and symptoms utilized in making a diagnosis of schizophrenia were matched with items on the major rating scales (the PANSS was chosen as the lead example).

The difference between response and remission is that response, utilizing percentage reduction from baseline, does not provide information on how symptomatic the patient is at endpoint. A reduction in PANSS score from 120 to 60 is a 50% reduction, as is a change from 80 to 40; however, the patient with a score of 60 is far more symptomatic than the patient with a score of 40, despite having a change score of 60 as compared to 40. The remission criteria provide information about where patients end up, i.e., are they still symptomatic? At the same time, the remission criteria do not provide the measure of change (other than to document the proportion of patients in remission at baseline versus endpoint in, for example, a long-term maintenance trial). We believe that the choice of remission or response criteria may depend on the study objectives, and many studies would benefit from the inclusion of both measures as it is current practice in depression trials.

Relapse

The term *relapse* is even more problematic, because to date a consensus as to what a schizophrenic relapse is has not been presented. For example, in a recent review[12] comparing the relapse prevention potential of atypical antipsychotics with that of typical antipsychotics and placebo, 11 different criteria were used in 17 studies. Those studies that applied the same criteria were usually organized by the same pharmaceutical company.[12] Some of the criteria such as "hospitalization for psychopathology" are pragmatic and intuitively meaningful, but similar to the debate on the use of the PANSS/BPRS versus the CGI, the problem is that whether or not a patient is hospitalized will depend on the treating psychiatrist, the health care system, and many other factors ranging from psychosocial to economic.

Other criteria are much more sophisticated and complex (e.g., ≥ 2-point increase in CGI rating and a ≥ 2-point increase in 2 BPRS positive items for 3 days, or the same level of deterioration for 24 hours and requiring hospitalization, or a CGI rating of severely ill for 24 hours[13]), but they are less intuitive and much more difficult to apply. Again, other criteria included symptoms such as suicidal ideation that are not specific for schizophrenia[14] or defined relapse as a percentage increase in the BPRS score from baseline.[15] Relapse criteria might also differ depending on whether a study involves a placebo-treated group, in which case, the intent may be to identify the early and less severe phase of relapse.

Stability of Symptoms

Studies on relapse prevention usually require a certain level of stability at baseline as an inclusion criterion. This procedure is warranted, because if a patient is not stable, it does not appear appropriate to speak of preventing a relapse or of maintaining a response. Again, there is no consensus as to how stability should be defined. Some studies do away with any requirement of stability whatsoever by simply following up the responders of the acute phase without further randomization.[16,17] This procedure is problematic because it is not consistent with the concept of randomization. For example, the characteristics of responders to placebo may be quite different from those of responders to an antipsychotic drug. The required duration of stability also varies substantially.

In the early literature comparing antipsychotic drugs with placebo, in some studies, the patients were described to have been stable for 1 year,[18] while in others they were only stable for 4 weeks or even less. As a criterion, patients may be required to have been on a stable dose of an antipsychotic drug for a certain period of time or to have simply had no significant improvement or worsening of symptoms according to the judgment of the treating doctor. This vagueness of the criteria leads to somewhat contradictory situations in which patients were stable but were still quite symptomatic according to the average PANSS or CGI at baseline.[19] The development of widely acceptable criteria of relapse and stability will be an important challenge to the field for the near future.

Conclusion

We believe that these definitions are important for investigators and clinicians. We need clinical trials to provide clinically meaningful information to clinicians, and the routine treatment process would benefit from better defined and documented measurement-based decision making.

Dr. Leucht is with Technische Universität München, Klinikum rechts der Isar, Munich, Germany. Dr. Kane is with The Zucker Hillside Hospital, Glen Oaks, and The Albert Einstein College of Medicine, Bronx, N.Y.

Dr. Leucht serves as a consultant to and/or speaker for Sanofi-Aventis, Bristol-Myers Squibb, Eli Lilly, Janssen, Lundbeck, and Pfizer; and has received grant/research support from Sanofi-Aventis and Eli Lilly. Dr. Kane serves as a consultant to Abbott, AstraZeneca, Bristol-Myers Squibb, Wyeth, Pfizer, Eli Lilly, Janssen, and Lundbeck and on the speakers or advisory boards for Janssen and Bristol-Myers Squibb.

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