Measurements of Response, Remission, and Recovery in Schizophrenia and Examples for Their Clinical Application

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Different definitions of response, remission, and recovery are used in schizophrenia research, which makes comparing and applying results in clinical practice difficult. Response criteria are often based on reductions in rating scale scores (eg, ≥ 20% reduction from baseline). However, when reduction scores from rating scales, such as the Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS), are linked to Clinical Global Impressions (CGI) scores, which are more easily understood, rating scale scores have better clinical application. This linking process also reveals that the widely used response cutoff of 20% does not reflect clinically meaningful improvement in patients with acute, nonrefractory schizophrenia. This article provides suggestions for selecting response criteria, displaying responder rates, and using standard definitions (eg, remission, recovery) in research studies. The ultimate goal of recovery in schizophrenia treatment includes sustained symptom resolution and a return to full functioning.

(J Clin Psychiatry 2014;75[suppl 1]:8–14)

Treatment for a patient with acute schizophrenia ideally progresses through the steps of 1) response to treatment, 2) resolution of symptoms, 3) remission, and 4) recovery. Rating scales can be used to document baseline symptoms and track the patient's progress through these steps. Response to treatment means that the patient is showing symptom improvement, and remission indicates that symptoms have been mostly alleviated. Recovery focuses on patients' social and vocational functioning rather than on symptoms.

Although the terms *response*, *resolution*, *remission*, and *recovery* are widely used in clinical trials and practice, definitions often vary. In addition, the clinical application of rating scale results is often limited by a lack of understanding of what the results mean. By examining issues related to the definitions of these terms, clinicians can gain a better understanding of how to apply the results from rating scales like the Positive and Negative Syndrome Scale (PANSS)[1] and the Brief Psychiatric Rating Scale (BPRS)[2] to their treatment of patients with schizophrenia. This report will present an update based on older and more recent findings on these issues.

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This article is derived from the planning teleconference series "Measurement-Based Strategies to Assess and Manage Schizophrenia," which was held in August 2013 and supported by an educational grant from Genentech.

Dr Leucht is a consultant for Janssen, has received grant/research support from Eli Lilly, and is a member of the speakers/advisory boards for Roche, Lundbeck, Eli Lilly, Pfizer, Janssen, Bristol-Myers Squibb, Johnson & Johnson, and Sanofi-Aventis. In the last 3 years, Dr Leucht has received honoraria for lectures from AbbVie, AstraZeneca, Bristol-Myers Squibb, ICON, Eli Lilly, Janssen, Johnson & Johnson, Roche, Sanofi-Aventis, Lundbeck, and Pfizer and for consulting/advisory boards from Roche, Eli Lilly, MedAvante, Bristol-Myers Squibb, Alkermes, Janssen, Johnson & Johnson, and Lundbeck. Eli Lilly has provided medication for a study with Dr Leucht as primary investigator.

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doi:10.4088/JCP.13049su1c.02

RESPONSE

Standard response criteria in treatment studies use rating scales like the PANSS and BPRS and typically require at least a 20% reduction from the baseline score. Unfortunately, the cutoff to determine response is often chosen arbitrarily or even post hoc in schizophrenia studies and varies from a 20%–50% reduction in score.[3] Nevertheless, rating scales can be useful for measuring response if clinicians know how best to use the results.

The advantage of using validated rating scales to measure symptomatology before and during treatment is their psychometric properties. Both the PANSS and BPRS have been validated and show strong reliability and sensitivity. The PANSS has 30 items rated on a 7-point scale, with 1 being "absent" and 7 being "extreme," and takes about 45 minutes for the clinician to complete.[1] The BPRS assesses 18 symptoms, also using a 7-point scale (from "not present" to "extremely severe"), based on clinical observation and patient report. The BPRS takes about 20 minutes to administer, depending on the clinician's experience.[2] A 0–6 version is also used, although frequently not reported, making interpretation even more difficult. A 0–6 rating system has also been applied for the PANSS,[4] but this is very rare.

Understanding Rating Scale Results

A problem with rating scales is that their results must be interpreted in terms of clinical significance.[3] For example, what does a PANSS total score of 90 mean from a clinical perspective? What is the clinical significance when a patient experiences a 20% or more reduction in PANSS score from baseline? One solution is to link results of rating scales like the PANSS or BPRS to the Clinical Global Impressions (CGI) scales,[2] which clinicians understand intuitively.[3,5] The CGI-Severity (CGI-S) instrument rates the current severity of illness on a 7-point scale from "normal" to "extremely ill," while the CGI-Improvement (CGI-I) instrument tracks patients' overall improvement from baseline. The CGI-I

Table 1. Linking CGI Scores With BPRS/PANSS Scores[a]

CGI-Severity	BPRS Total Score	PANSS Total Score
1 = Normal, not at all ill		31–32
2 = Borderline mentally ill		41–47
3 = Mildly ill	30–36	55–62
4 = Moderately ill	40–45	71–78
5 = Markedly ill	52–55	88–96
6 = Severely ill	64–70	105–118
7 = Among the most extremely ill	83–89	126–149
CGI-Improvement	**BPRS Reduction, %**	**PANSS Reduction, %**
1 = Very much improved	71–85	71–82
2 = Much improved	44–58	40–53
3 = Minimally improved	23–30	19–28
4 = No change	5–8	2–3
5 = Minimally worse		–15 to –20
6 = Much worse		–44 to –51
7 = Very much worse		

[a]Data from Leucht et al[3,5,8] and Levine et al.[10]
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale, PANSS = Positive and Negative Syndrome Scale.

Clinical Points

- Rating scale cutoffs for response in schizophrenia trials should be 50% for acutely ill, nonrefractory patients and 25% for treatment-resistant patients to identify clinically meaningful improvement.
- Studies should display PANSS/BPRS and CGI response rates in a table with 25% intervals to capture the distribution of results and provide clinical applicability to rating scale results.
- The RSWG remission criteria are being applied in research settings and should make studies more comparable and applicable in clinical practice. The number of participants who reached (symptomatic) remission should also be presented in a table.
- Recovery is the ultimate goal in schizophrenia treatment, but a consensus definition has yet to be created.

uses a 7-point scale with 1 being "very much improved" and 7 being "very much worse." Although the CGI provides a helpful impression of the patient's overall clinical state, a disadvantage is its lack of established psychometric properties.[3] This problem has been resolved by the development of a CGI scale specific for schizophrenia (CGI-SCH)[6] with key anchor points. It covers not only overall symptoms but also the positive, negative, cognitive, and depressive symptoms common in schizophrenia, and the psychometric properties were acceptable.[6] Unfortunately, this refined scale is too rarely used, although it is a clear improvement compared with the original CGI, and other specific CGIs (such as for bipolar disorder)[7] also exist. By examining the correlations between rating scale scores and the CGI throughout patients' treatment, clinicians can readily understand not only specific symptom changes from baseline but also the patient's overall improvement.

Linking CGI scores with absolute reduction in rating scale scores. The primary outcome in antipsychotic drug trials is often given as the mean absolute reduction in BPRS/PANSS scores. Therefore, it could be one option to define an absolute degree of reduction of these rating scales to define response. My colleagues and I[8] linked the absolute reduction of PANSS and BPRS total scores from baseline with the CGI ratings to help translate study results into practice. Absolute reductions of 10 points in BPRS scores and 15 points in PANSS scores were associated with a CGI-I rating of "minimally improved" and with a decrease to the next-lower level of severity on the CGI-S.[8]

However, when examining the effects of illness severity at baseline on the linking results, my colleagues and I identified an important problem. Because the absolute change in BPRS/PANSS score was linked with CGI-I scores after the patients were split into 2 groups according to the median of the BPRS/PANSS scores at baseline, less severely ill patients required less absolute reduction in BPRS/PANSS total scores to obtain the same CGI-I score as more severely ill patients.[8] This result indicates that when clinicians use the CGI-I, they tend to rate patients in relative (percentage) terms rather than in absolute terms. For instance, if a patient who is severely ill has an absolute decrease in the PANSS total score of 10 points (eg, 100 to 90), clinicians do not believe that change is very clinically significant because the patient is still very ill. But if a patient who is only slightly ill at baseline has an absolute decrease of 10 points in the PANSS total score (eg, 50 to 40), clinicians rate this change as a subjectively greater improvement than in the severely ill patient even though the changes are objectively the same.[8] This severity-at-baseline effect was observed in an analysis linking the Hamilton Depression Rating Scale (HDRS) and the CGI severity score.[9] It thus seems to be universal in psychiatric rating scales.

The severity-at-baseline effect was not found when the percentage BPRS or PANSS total score reduction was linked with the CGI-I score. Cutoffs in terms of a minimum percentage reduction of these scores can therefore be more uniformly applied to define response.

Linking CGI scores with percentage reduction in total scores. To provide clinically meaningful application of rating scale results, the CGI-S and CGI-I ratings can be linked to the BPRS or PANSS scores using equipercentile linking.[8,10,11] This technique identifies scores on both measures that have the same percentile rank.[5] Table 1[3,5,8,10] presents the results of the first studies that applied this approach to the BPRS and the PANSS. The first study[5] that linked BPRS scores and CGI ratings from 7 drug trials in patients with schizophrenia (N = 1,979) found that a "mildly ill" rating on the CGI-S corresponded to a BPRS total score of 30 to 32, "moderately ill" corresponded to a score of 40 to 44, and "markedly ill" corresponded to a score of 52 to 55. The BPRS score reductions of 23%–30% corresponded to a CGI-I rating of "minimally improved," while reductions of 44%–58% corresponded to the CGI-I rating of "much improved." These results can help clinicians understand BPRS total scores and reduction percentages in clinically meaningful terms.[5]

The first study[3] that compared PANSS total scores and percentage of score reductions with CGI ratings in 7

antipsychotic drug trials in patients with schizophrenia (N = 4,091) found that "mildly ill" according to the CGI-S corresponded to a PANSS total score of 57–61, "moderately ill" corresponded to a PANSS score of 73–78, and "markedly ill" corresponded to a PANSS score of 93–96. In terms of improvement since baseline, the CGI-I rating of "minimally improved" corresponded to PANSS score reductions of 19%–28%, while "much improved" was associated with PANSS score reductions of 40%–53%.[3]

Several studies[8,10–13] have replicated the linking functions between the PANSS/BPRS and the CGI in various settings. While there was more variability at the lower end of minimal CGI improvement, the association of CGI "much improvement" and 50% BPRS/PANSS reduction was rather consistent except for studies in stable patients with few symptoms at baseline.[13,14] It could be expected that the linking results in such relapse prevention studies in stable patients were different. Because substantial improvement was associated with BPRS/PANSS score reductions of around 50%, studies might ideally use at least a 50% reduction from baseline as the cutoff for response in patients with acute exacerbations of schizophrenia rather than lower cutoffs like 20% or 25%, which represent only minimal improvement.[3,5] However, in treatment-resistant patients, a 25% cutoff may be a better option, because even small improvements can be clinically significant.[3,5]

Issues With the Calculation and Use of Percentage Response Cutoffs

Scale-derived cutoffs are significant because they are used to define response in antipsychotic drug trials. Researchers and clinicians must be aware of several problems with response cutoffs to avoid misinterpreting or misunderstanding trial results.

Correctly calculating the BPRS/PANSS percentage reduction. When researchers calculate percentage reduction of BPRS or PANSS scores from baseline, they must remember to subtract the minimum scores of 30 for PANSS and 18 for BPRS first.[15] Because both the PANSS and BPRS are rated on a 1–7 scale, their minimum scores (no symptoms) are 30 and 18, respectively, not 0. When the minimum scores are not subtracted, the percentage of score reduction will be incorrect. For example, a reduction of the PANSS score from 120 to 60 is not a 50% reduction but rather a 67% reduction (ie, 120 – 30 = 90 and 60 – 30 = 30, so the change from 90 to 30 is a 67% reduction). If results are calculated without subtracting the minimum score, the drug effect will be underestimated. Unfortunately, the use of uncorrected scores is common. It has therefore been recommended to rescale both the PANSS and BPRS from 1–7 to 0–6 to avoid this problem.[16] Because many studies on second-generation antipsychotics have not made the subtraction, the effects of antipsychotics have been underestimated.

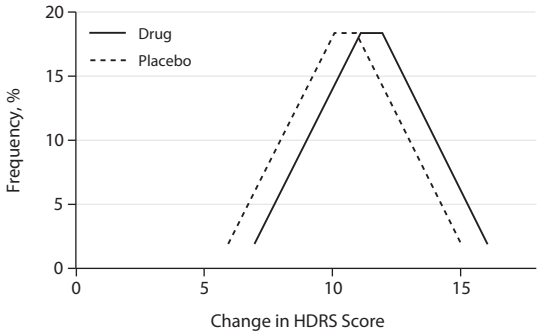
Choosing response cutoffs a priori versus post hoc. The problem with choosing a cutoff post hoc is that trial results vary depending on the cutoff chosen.[15] When randomized controlled trials are analyzed using different response cutoffs, the statistical significance of results changes. For example, a study[15] that analyzed results from randomized controlled trials of amisulpride found that, in one trial, the *P* value for a ≥ 30% reduction in BPRS scores was statistically significant (*P* = .0095) while the *P* value for the ≥ 50% response cutoff was not (*P* = .37), and another study[15] showed statistical significance for the ≥ 50% cutoff (*P* = .03) but not for the ≥ 40% cutoff (*P* = .24).

Choosing a cutoff post hoc should never be done because this manipulates research results.[15] Instead, researchers should select the response cutoff a priori based on clinical relevance (≥ 25% BPRS/PANSS score reduction corresponds to the CGI score of "minimally better," while the ≥ 50% cutoff corresponds to "much better").

Selecting the most sensitive cutoff. In certain situations it might be important to choose the response cutoff that is the most sensitive to detect a difference between an antipsychotic and placebo. Moncrieff and Kirsch[17] have shown that for depression trials the most sensitive response cutoff might be the one that maximally separates the normal distribution curves of drug and placebo (Figure 1). Where this point of maximum separation lies depends on the population. In major depression trials it may be around a 50% HDRS reduction. In schizophrenia trials, which are now usually conducted in chronic patients, it may often be around 20%, which explains why this cutoff has been used so often. However, in the analysis[15] of amisulpride studies, lower cutoffs were not more sensitive to differences between the drug and the comparator, possibly because the patients were overall more responsive than in other trials. Choosing the most sensitive cutoff is not recommended because for clinical trials to be informative for practice, clinically meaningful cutoffs are important, and the primary outcome in a study is the mean PANSS or BPRS total score change from baseline anyhow.

Presenting meaningful study results. Following tradition may be a reason for selecting a 20% response cutoff, such as copying the pivotal Kane et al study[18] demonstrating clozapine's superiority for treatment-resistant patients, or using the same cutoff as in previous trials to show consistency.

Figure 1. Normal Distribution of Hamilton Depression Rating Scale (HDRS) Scores for Depression[a,b]



[a]Reprinted with permission from Moncrieff and Kirsch.[17]
[b]Mean score of 11.5 for antidepressant treatment and 10.5 for placebo.

Table 2. Sample Table for Displaying BPRS-/PANSS-Derived Response Rates[a]

		BPRS/PANSS Reduction					
	Total N	≤ 0	1%–24%	25%–49%	50%–74%	75%–100%	Remission
Intervention group	N	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Control group	N	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

[a]Reprinted with permission from Leucht et al.[15]
Abbreviations: BPRS = Brief Psychiatric Rating Scale, PANSS = Positive and Negative Syndrome Scale.

Table 3. Sample Table for Displaying CGI-Derived Response Rates[a]

CGI-Improvement	Total N	Very Much Worse	Much Worse	Minimally Worse	Unchanged	Minimally Better	Much Better	Very Much Better
Score		7	6	5	4	3	2	1
Intervention group	N	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Control group	N	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
CGI-Severity	Total N	Extremely Ill	Severely Ill	Markedly Ill	Moderately Ill	Mildly Ill	Borderline Mentally Ill	Normal, Not at All Ill
Score		7	6	5	4	3	2	1
Intervention group	N	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Control group	N	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

[a]Reprinted with permission from Leucht et al.[15]
Abbreviation: CGI = Clinical Global Impressions scale.

Another reason is the hope of showing maximum separation between drug and placebo. A widely held belief is that low response cutoffs are more sensitive for detecting differences between drugs and placebo than higher cutoffs are.[15] As mentioned, many different response cutoffs are used in schizophrenia studies.[3] The 20% improvement cutoff has been the standard change from baseline used to define response, partly due to a landmark study by Kane et al,[18] which demonstrated that clozapine was more efficacious than chlorpromazine in treatment-refractory schizophrenia. Although the study's use of a 20% improvement from baseline in BPRS scores was appropriate for treatment-resistant patients, the 20% cutoff has been applied in studies of acutely ill patients with nonrefractory schizophrenia.[15]

To solve these problems with determining appropriate cutoffs, researchers could present BPRS or PANSS responder rates in increments of 25% up to 100% reduction from baseline scores in a table to display the distribution of the results (Table 2).[15] Such a table would show the intervention and control group results and could also display the number of patients who were in remission.[15] While comparing all the rates between groups in the table is beneficial for seeing the distribution of results, a primary cutoff should be chosen a priori. A simple table could also be used to display the overall distribution of CGI-S and CGI-I response rates for drug versus placebo results (Table 3).[15]

RESOLUTION AND REMISSION

After response, the next step in the treatment of schizophrenia—and an outcome measure for many trials—is resolution and remission. *Remission* entails maintaining a state without clinically important symptoms over a certain period of time. If only the severity criterion but not the time component is met, this state is called either *resolution*[19] or, probably more frequently, *symptomatic remission*. A uniformly accepted definition of remission helps clinicians and researchers improve and interpret study design, compare trial results, follow treatment algorithms, and create long-term goals with patients and their families.[20]

Definition of Remission

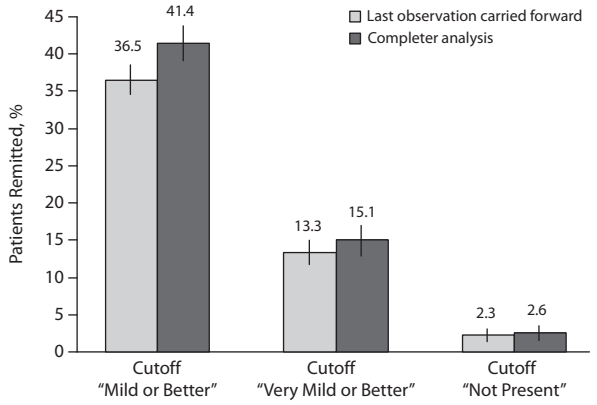
The Remission in Schizophrenia Working Group (RSWG) met in 2003 to develop a consensus definition of symptomatic remission in patients with schizophrenia. They proposed criteria for remission based on 3 symptom domains from factor analysis studies, 5 key symptoms of schizophrenia from the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*),[21] and 8 symptoms present in the most widely used assessment scales (Table 4).[20] The symptoms must all have a severity score of mild or less for at least 6 months to meet remission criteria.[20] These criteria are useful because they reflect the heterogeneous nature and long-term course of schizophrenia. Patients may experience minor changes in symptoms over time and still remain in remission as long as no symptom is more severe than mild. A definition of remission that used a rating scale cutoff score would not work as well because, in contrast to major depressive disorder, schizophrenia has many different symptoms, which vary in occurrence over time. Positive symptoms are mainly prevalent in the acute phase; negative symptoms characterize the time between episodes. Therefore, a definition based on a PANSS total score would be problematic because if, for example, a cutoff of 50 were chosen, patients might yet have a high degree of negative symptoms. Nevertheless, the remission criteria have been criticized several times because they combine a relatively relaxed symptom criterion (mild symptoms are allowed) with a relatively severe time criterion.[22] Similar to definitions of remission in other psychiatric disorders (such as anxiety),[23] some mild symptoms are allowed to remitted patients, which should not interfere too much with functioning, and using more stringent cutoffs (eg, very mild, not present) would

Table 4. Proposed Criteria by the Remission in Schizophrenia Working Group[a,b]

		Proposed Remission Criteria Items					
		SAPS and SANS Items		PANSS Items		BPRS Items[c]	
Dimension of Psychopathology	*DSM-IV* Criterion	Criterion	Global Rating Item Number	Criterion	Item Number	Criterion	Item Number
Psychoticism (reality distortion)	Delusions	Delusions (SAPS)	20	Delusions	P1	Grandiosity	8
						Suspiciousness	11
				Unusual thought content	G9	Unusual thought content	15
	Hallucinations	Hallucinations (SAPS)	7	Hallucinatory behavior	P3	Hallucinatory behavior	12
Disorganization	Disorganized speech	Positive formal thought disorder (SAPS)	34	Conceptual disorganization	P2	Conceptual disorganization	4
	Grossly disorganized or catatonic behavior	Bizarre behavior (SAPS)	25	Mannerisms/posturing	G5	Mannerisms/posturing	7
Negative symptoms (psychomotor poverty)	Negative symptoms	Affective flattening	7	Blunted affect	N1	Blunted affect	16
		Avolition-apathy (SANS)	17	Social withdrawal	N4	No clearly related symptom	
		Anhedonia-asociality (SANS)	22				
		Alogia (SANS)	13	Lack of spontaneity	N6	No clearly related symptom	

[a]Reprinted with permission from Andreasen et al.[20]
[b]For symptomatic remission, maintenance over a 6-month period of simultaneous ratings of mild or less on all items is required. Rating scale items are listed by item number.
[c]Use of BPRS criteria may be complemented by the use of the SANS criteria for evaluating overall remission.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, PANSS = Positive and Negative Symptom Scale, SANS = Scale for Assessment of Negative Symptoms, SAPS = Scale for Assessment of Positive Symptoms.

Figure 2. Short-Term (4 Weeks) Pooled Results for Symptom Severity Remission Criteria[a]



[a]Reprinted with permission from Leucht et al.[24]

allow very few patients to meet the severity criterion (Figure 2).[24] The 6-month criterion, however, poses a problem for clinical trials that need to be sufficiently long and need frequent measurements. A more balanced time criterion would be 3 months.

Circumstances for Remission

How possible is remission in patients with schizophrenia? Two circumstances in which patients with schizophrenia may reach remission are soon after the recognition of the illness and after long-term follow up.

Early in the illness. The incidence of remission is described in 2 studies of first-episode populations, although both studies predated the RSWG definition of remission. Lieberman and colleagues[25] conducted a randomized, double-blind, 52-week trial comparing chlorpromazine and clozapine in previously untreated Chinese patients with first-episode schizophrenia or schizophreniform disorder (N = 160). A high percentage (approximately 80%) of patients remitted within 1 year. The remission criteria in this study were a 50% reduction in total BPRS score from baseline, no score greater than mild on 5 BPRS psychosis items, and a CGI-S rating of mild or less.[25] Symptom resolution occurred for half of patients treated with clozapine at 8 weeks and at 12 weeks with chlorpromazine, and time in remission was longer for the clozapine group. A longer duration of untreated illness was associated with lower rates of remission; the odds of remission dropped by almost 15% for each extra year of untreated psychosis.

Another trial[26] examined patients with first-episode schizophrenia (N = 118) treated for 1 year according to an algorithm that allowed medication adjustments and switches until patients responded. Treatment response (not remission) was defined as a CGI-I rating of "much improved" or "very much improved" and a rating of mild or less on the Schedule for Affective Disorders and Schizophrenia—Change Version With Psychosis and Disorganization Items rating scale, which had to be sustained for 8 consecutive weeks. Eighty-seven percent of patients responded by 1 year.[26] Both studies demonstrate that high response and remission rates are possible in patients effectively treated early in the course of illness.

Early improvement also predicts subsequent remission and improved functional outcome in patients with schizophrenia. A post hoc analysis[27] of a randomized open-label trial of typical and atypical antipsychotic treatment for acute schizophrenia revealed that early response/nonresponse at 2 weeks reliably predicted response/nonresponse at 8 weeks. Early nonresponse was defined as less than a 20% reduction

in PANSS total score from baseline. Early responders were more likely to achieve symptom remission and improved functioning than early nonresponders. By linking the CGI-I rating with percent reduction of PANSS scores, this finding means that patients who are not even minimally better at 2 weeks are unlikely to respond later.[3]

After long-term follow-up. In long-term schizophrenia studies, remission rates are challenging to quantify due to varying definitions and outcome criteria.[28] Another problem in these studies is that many of them are cross-sectional, meaning that they assess patients at just one time point. Because patients could be between episodes when assessed, a better approach would be to assess patients over longer periods of time to see if patients are symptomatic. A review[29] found remission rates ranging from 17% and 88%, although the study lengths varied.

Application of Remission Criteria

A review[30] of over 50 studies that have used the RSWG remission criteria showed that a significant proportion of patients can achieve and sustain remission, which is associated with a good overall symptom status and functional outcome; a few examples follow. First, a naturalistic cohort study[31] evaluated the remission criteria in 341 patients with schizophrenia or schizoaffective disorder. Nearly 1 of 3 patients met full criteria for remission at endpoint, and those who achieved remission had better insight into their illness and higher global and daily living functioning compared with patients never meeting remission criteria and with patients meeting only the symptom severity criterion but not the time criterion. These results indicate that both the time and severity criteria should be clinical targets.

A reanalysis[24] of 7 antipsychotic trials examined how many patients (N = 1,708) with schizophrenia met the RSWG remission criteria.[20] At 4 weeks, 37% of acutely ill patients met the symptom severity criterion of "no worse than mild." To assess the applicability of the full remission criteria in the 2 long-term studies in which the 6-month time criterion could be applied, the noncompleters were presumed to have had no remission (worst case scenario). Among the intent-to-treat group, at 1 year, 27% met both the severity and time criteria. Among completers, 53% met both the time and severity criteria. Thus, the true expectation of remission, based on this analysis, lies between 27% and 53%.

Another study[32] that validated the RSWG remission criteria tracked 145 patients who met RSWG symptom remission criteria at baseline and 172 patients who did not; the median follow-up time was 1,132 days. Of the patients who met the symptom remission criterion at baseline, 35% moved out of remission during follow-up, while 31% of those who did not fulfill symptom remission criteria at baseline moved into remission. In both remission groups, remission status was associated with improved functioning compared with nonremission status.

The advantage of using remission criteria rather than percentage of reduction in rating scale scores to assess outcome is that the criteria specify how many patients are free of symptoms at the end of the study. In contrast, if a study uses a 50% reduction in PANSS scores as the primary outcome, some responders would still be considered severely ill. The disadvantage of remission criteria is that they do not indicate the amount of change. If study participants were not very ill at baseline, many patients will be in remission at the end. Responder rates, though, will indicate the amount of change, which is why studies should include results according to both remission criteria and reductions in rating scale scores. Presenting results in a simple table (see Table 2) would make research results more understandable and comparable than they are now.

RECOVERY

The final step and ultimate goal of treatment in schizophrenia is recovery. The recovery stage is focused on patients regaining functioning and participating in social and vocational opportunities. Although the second-generation antipsychotics are not the breakthrough treatment they were hoped to be, they still are an important advance to help patients achieve recovery.

Although no consensus exists on how recovery should be defined,[28] several criteria have been proposed. These criteria include some degree of symptom stabilization (such as being symptom free or having a BPRS/PANSS score ≤ 4 on all items) and functional improvement (eg, attending school or maintaining employment, socializing with peers) for a specified duration (for example, 2 or 5 years).[33] Jääskeläinen and colleagues[34] defined recovery in schizophrenia as having improvements in both clinical and social domains, with improvements in at least 1 of the domains persisting for at least 2 years, and current symptoms no worse than mild. Using these criteria, they conducted a meta-analysis of 37 studies in almost 9,000 patients and found a median recovery rate of 13.5%. The results from the Schizophrenia Outpatients Health Outcomes (SOHO) study,[35] which analyzed 6,642 patients with schizophrenia, showed that 33% achieved long-lasting remission and 13% achieved long-lasting functional remission during the 3-year follow up period. Although recovery rates are not high for patients with schizophrenia, recovery is achievable, and patients need hope to sustain them throughout treatment as well as the support of dedicated clinicians to encourage them along the way.[33] As pharmacologic and psychosocial treatments continue to improve, clinicians should have more options to create individualized treatment plans for their patients with schizophrenia.

CONCLUSION

The treatment goals of response, remission, and recovery have different meanings to schizophrenia researchers compared with clinicians. The rating scale cutoffs used to define response (typically at least a 20% reduction in PANSS/BPRS scores from baseline) vary from study to study and do not provide much clinical application. Linking rating scale results to CGI scores provides clinically meaningful terms. Because substantial improvement is associated with ≥ 50%

score reduction on symptom rating scales, studies should use a 50% cutoff for nonrefractory patients and a 25% cutoff for treatment-resistant patients rather than the typical 20% cutoff used in many trials. Cutoffs should be chosen a priori rather than post hoc to avoid manipulating results. Researchers may use a simple table to display PANSS/BPRS change rates from baseline to endpoint in 25% steps (unimproved or worse, up to 25% PANSS/BPRS reduction from baseline, up to 50%, up to 75%, up to 100%), as well as remission rates (see Table 2). A similar table should be used to show how many participants met the various degrees of improvement and severity of the CGI (see Table 3). Researchers must also remember to subtract 30 or 18 from PANSS or BPRS scores before calculating percentages of change.

The RSWG consensus definition of remission proposes measuring 8 symptoms based on *DSM-IV* criteria that are reflected on several rating scales (eg, PANSS, BPRS). Patients must have symptoms no worse than mild for at least 6 months to attain remission. These criteria are being applied in many studies and should make remission results easier to compare than before the consensus definition was created. Nevertheless, reducing the time criterion to 3 months might make the criteria more applicable. Symptom remission is possible for patients both early and late in the illness course.

Finally, recovery includes a return to social and occupational functioning. Although no consensus definition of recovery has been reached, recovery remains the ultimate goal of schizophrenia treatment. Using available pharmacologic and psychosocial treatments, clinicians can help patients work through the treatment steps while measuring improvement and offering encouragement.

Drug name: clozapine (Clozaril, FazaClo, and others).
Disclosure of off-label usage: Dr Leucht has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this activity.

REFERENCES

1. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13(2):261–276.
2. Guy W. *ECDEU Assessment Manual for Psychopharmacology.* Rockville, MD: National Institute of Mental Health; 1976.
3. Leucht S, Kane JM, Kissling W, et al. What does the PANSS mean? *Schizophr Res.* 2005;79(2–3):231–238.
4. Zimbroff DL, Kane JM, Tamminga CA, et al, for the Sertindole Study Group. Controlled, dose-response study of sertindole and haloperidol in the treatment of schizophrenia. *Am J Psychiatry.* 1997;154(6):782–791.
5. Leucht S, Kane JM, Kissling W, et al. Clinical implications of Brief Psychiatric Rating Scale scores. *Br J Psychiatry.* 2005;187(4):366–371.
6. Haro JM, Kamath SA, Ochoa S, et al, for the SOHO Study Group. The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. *Acta Psychiatr Scand Suppl.* 2003;107(416):16–23.
7. Spearing MK, Post RM, Leverich GS, et al. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res.* 1997;73(3):159–171.
8. Leucht S, Kane JM, Etschel E, et al. Linking the PANSS, BPRS, and CGI: clinical implications. *Neuropsychopharmacology.* 2006;31(10):2318–2325.
9. Leucht S, Fennema H, Engel R, et al. What does the HAMD mean? *J Affect Disord.* 2013;148(2–3):243–248.
10. Levine SZ, Rabinowitz J, Engel R, et al. Extrapolation between measures of symptom severity and change: an examination of the PANSS and CGI. *Schizophr Res.* 2008;98(1–3):318–322.
11. Leucht S, Engel RR, Davis JM, et al. Equipercentile linking of the Brief Psychiatric Rating Scale and the Clinical Global Impression Scale in a catchment area. *Eur Neuropsychopharmacol.* 2012;22(7):501–505.
12. Schennach-Wolff R, Obermeier M, Seemüller F, et al. Does clinical judgment of baseline severity and changes in psychopathology depend on the patient population? results of a CGI and PANSS linking analysis in a naturalistic study. *J Clin Psychopharmacol.* 2010;30(6):726–731.
13. Rabinowitz J, Levine S, Martinez G. Concordance between measures of functioning, symptoms, and change: examining the GAF, CGI-S, CGI-C, and PANSS. *J Clin Psychopharmacol.* 2010;30(4):478–480.
14. Ortiz BB, Pitta JC, Gadelha A, et al. Comparing PANSS scores and corresponding CGI scores between stable and acute schizophrenic patients. *Schizophr Res.* 2014;152(1):307–308.
15. Leucht S, Davis JM, Engel RR, et al. Defining 'response' in antipsychotic drug trials: recommendations for the use of scale-derived cutoffs. *Neuropsychopharmacology.* 2007;32(9):1903–1910.
16. Obermeier M, Mayr A, Schennach-Wolff R, et al. Should the PANSS be rescaled? *Schizophr Bull.* 2010;36(3):455–460.
17. Moncrieff J, Kirsch I. Efficacy of antidepressants in adults. *BMJ.* 2005;331(7509):155–157.
18. Kane JM, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry.* 1988;45(9):789–796.
19. Peuskens J, Kaufman L, Van Vleymen B. Analysis of resolution criteria in patients with schizophrenia treated with olanzapine for an acute psychotic episode. *Schizophr Res.* 2007;95(1–3):169–173.
20. Andreasen NC, Carpenter WT Jr, Kane JM, et al. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry.* 2005;162(3):441–449.
21. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
22. Levine SZ, Leucht S. Attaining and sustaining remission of predominant negative symptoms. *Schizophr Res.* 2013;143(1):60–64.
23. Doyle AC, Pollack MH. Establishment of remission criteria for anxiety disorders. *J Clin Psychiatry.* 2003;64(suppl 15):40–45.
24. Leucht S, Beitinger R, Kissling W. On the concept of remission in schizophrenia. *Psychopharmacology (Berl).* 2007;194(4):453–461.
25. Lieberman JA, Phillips M, Gu H, et al. Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. *Neuropsychopharmacology.* 2003;28(5):995–1003.
26. Robinson DG, Woerner MG, Alvir JM, et al. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry.* 1999;156(4):544–549.
27. Ascher-Svanum H, Nyhuis AW, Faries DE, et al. Clinical, functional, and economic ramifications of early nonresponse to antipsychotics in the naturalistic treatment of schizophrenia. *Schizophr Bull.* 2008;34(6):1163–1171.
28. Leucht S, Lasser R. The concepts of remission and recovery in schizophrenia. *Pharmacopsychiatry.* 2006;39(5):161–170.
29. Emsley R, Chiliza B, Asmal L, et al. The concepts of remission and recovery in schizophrenia. *Curr Opin Psychiatry.* 2011;24(2):114–121.
30. Lambert M, Karow A, Leucht S, et al. Remission in schizophrenia: validity, frequency, predictors, and patients' perspective 5 years later. *Dialogues Clin Neurosci.* 2010;12(3):393–407.
31. De Hert M, van Winkel R, Wampers M, et al. Remission criteria for schizophrenia: evaluation in a large naturalistic cohort. *Schizophr Res.* 2007;92(1-3):68–73.
32. van Os J, Drukker M, à Campo J, et al. Validation of remission criteria for schizophrenia. *Am J Psychiatry.* 2006;163(11):2000–2002.
33. Liberman RP, Kopelowicz A. Recovery from schizophrenia: a concept in search of research. *Psychiatr Serv.* 2005;56(6):735–742.
34. Jääskeläinen E, Juola P, Hirvonen N, et al. A systematic review and meta-analysis of recovery in schizophrenia. *Schizophr Bull.* 2013;39(6):1296–1306.
35. Novick D, Haro JM, Suarez D, et al. Recovery in the outpatient setting: 36-month results from the Schizophrenia Outpatients Health Outcomes (SOHO) study. *Schizophr Res.* 2009;108(1–3):223–230.