An Evidence-Based Strategy for Remission in Schizophrenia

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Over the past 50 years, the therapeutic goal for schizophrenia has slowly but steadily increased, from one of modest improvement in self-care and control of aggression or self-injury in the 1950s, to effective control of both positive and negative symptoms in the 1990s. As physicians have become more equipped with a better tool kit of pharmacologic and psychosocial interventions, the pessimistic attitude toward long-term outcome has gradually given way to cautious and guarded optimism. Remission may even be considered a potentially realistic goal. This article briefly reviews the status of remission as a therapeutic goal in the treatment of schizophrenia and summarizes available treatment research reporting remission and recovery as clinical outcomes.

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DEFINITION OF REMISSION

The Remission in Schizophrenia Working Group has proposed to define remission as the following:

> . . . a state in which patients have experienced an improvement in core signs and symptoms to the extent that any remaining symptoms are of such low intensity that they no longer interfere significantly with behavior and are below the threshold typically utilized in justifying an initial diagnosis of schizophrenia.[1(p442)]

Two key aspects of this definition include the use of threshold symptom severity criteria rather than percent improvement from baseline and the fact that total absence of core symptoms is not required.[1] Six months of improvement is required in order to ensure that it is not transient. Furthermore, *remission* is distinguished from *recovery*, with the latter reserved for patients who achieve a stable and longer-term remission with a return to social and vocational functioning in the community.[1] As of yet, there are no consensus criteria for recovery or for what constitutes a "stable," long-term remission, though 2 years appears to be a reasonable choice. This is in line with the phases of treatment response delineated by the American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients With Schizophrenia,[2] which has identified 2 years postrelapse as the point at which the patient has achieved stability.

OPERATIONALIZING REMISSION

For conceptual and methodological reasons, a dimensional approach is more useful in operationalizing criteria for remission. This approach is not dependent on DSM-IV schizophrenia subtypes. Results of factor analyses have identified 3 core psychopathology dimensions that map onto DSM-IV diagnostic criteria for schizophrenia (Table 1[1]): psychoticism/reality distortion, disorganization, and negative symptoms.[3] Four widely used rating scales provide items that measure the severity of the core clinical dimensions of schizophrenia and that are relevant for defining remission: the Positive and Negative Syndrome Scale (PANSS),[4] the Brief Psychiatric Rating Scale (BPRS),[5] and the Scales for the Assessment of Positive and Negative Symptoms (SAPS[6] and SANS,[7] respectively). The Remission in Schizophrenia Working Group has proposed a definition of remission that requires patients to maintain a rating of mild or less on all core items for a minimum of 6 months.[1] The threshold for "mild" on the PANSS is an item score of ≤ 3, on the BPRS of ≤ 3 (based on a 1–7 range), and on the SAPS/SANS of ≤ 2.

A recent study evaluated the predictive validity of the proposed multidimensional consensus remission criteria.[8] The study compared clinical outcomes at 18 months in first-onset patients (N = 60) who met full remission criteria proposed by Andreasen and colleagues[1] versus first-onset patients (N = 65) who met unidimensional criteria that required only remission of positive symptoms. Pa-

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Table 1. Core DSM-IV Items Used as Operationalized Criteria for Remission[a]

DSM-IV Criteria	PANSS	BPRS	SAPS/SANS
Delusions	Delusions Unusual thought content	Grandiosity Suspiciousness	Delusions
Hallucinations	Hallucinatory behavior	Hallucinatory behavior	Hallucinations
Disorganized speech	Conceptual disorganization	Conceptual disorganization	Positive formal thought disorder
Grossly disorganized or catatonic behavior	Mannerisms/posturing	Mannerisms/posturing	Bizarre behavior
Negative symptoms	Blunted affect Social withdrawal	Blunted affect (no clearly related symptom)	Affective flattening Avolition-apathy/anhedonia-asociality

[a]Adapted with permission from Andreasen et al.[1]
Abbreviations: BPRS = Brief Psychiatric Rating Scale, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms.

tients in the stringent remission group showed significantly better 18-month outcomes on all PANSS subscale scores, as well as significantly superior functioning. The results are particularly impressive because the comparison group also met (less stringent) criteria for remission.[8]

STAGES OF TREATMENT RESPONSE

As outlined in the APA Practice Guideline for the Treatment of Patients With Schizophrenia, each stage of treatment has specific goals.[2] During the acute phase of treatment, when the patient is in the midst of an acute psychotic episode, the goals of treatment are to reduce the severity of psychotic symptoms and other problems (agitation, aggression) associated with acute psychosis, to identify and address any factors that might have contributed to the onset of the current episode, and to develop a therapeutic alliance with the patient and his or her family. The acute phase of treatment typically lasts for 2 to 4 weeks.[2] During the next stage of treatment, the stabilization phase (approximately the first 6 months), the goal is to optimize the treatment regimen (pharmacologic and psychosocial) in order to further reduce psychotic symptoms and to prevent relapse. A crucial secondary goal is to adjust the treatment to minimize adverse events.[2] Treatment acceptance and a strong therapeutic alliance are both essential to avoid treatment nonadherence, which is by far the single biggest cause of relapse.[9,10] As the patient enters the post–6-month stabilization phase of treatment, the goal of therapy is to sustain partial or full remission and to work toward recovery and normalization of functioning and quality of life.

STABILIZATION AND RELAPSE PREVENTION

A precondition for achieving sustainable remission and recovery is effective relapse prevention. It is well established that conventional antipsychotic drugs are effective in preventing relapse.[11] A review of published studies indicates that patients switched from conventional antipsychotics to placebo had significantly higher relapse rates than those remaining on conventional agents (70% vs. 30%).[11]

A more recent series of double-blind, 6- to 12-month trials[12–14] have also demonstrated significant efficacy in relapse prevention for the atypical antipsychotics (Table 2). The treatment samples in published relapse studies typically consist of patients with a history of chronic schizophrenia who are stable after responding to acute treatment.[12] Between-study differences in various demographic and clinical variables appear to account for the observed variability in relapse rates on placebo, although the drug versus placebo difference in risk of relapse is similar.[12] Treatment with olanzapine, ziprasidone, and aripiprazole yielded a 25% difference from placebo in the risk of relapse.[12–14] Published placebo-controlled maintenance trials were not found for clozapine, risperidone, or quetiapine.

Additional double-blind maintenance treatment studies have evaluated whether treatment with atypical antipsychotics offers any incremental relapse prevention benefit compared to conventional antipsychotics (Table 2).[12–18] The results of these trials suggest a substantial reduction in relapse risk in favor of atypicals over conventional antipsychotics, from a (unweighted) mean relapse rate of 23% to 15%.[12–18] The results of a meta-analysis suggest that the reduction in relapse risk for atypicals is not primarily attributable to better tolerability or lower attrition.[12]

Few of the available maintenance treatment studies provide operationalized definitions of nonadherence or systematically report its impact on relapse. This is unfortunate because nonadherence significantly increases the risk of relapse. In fact, it is likely that any between-drug difference in relapse prevention efficacy is smaller than the magnitude of the increase in relapse risk that occurs if patients are nonadherent and discontinue pharmacotherapy and psychosocial treatments. Nonadherence with pharmacotherapy is an enormous problem for people with schizophrenia, estimated to occur in ~50% of patients,[19] and it is associated with a 2- to 5-fold increase in the risk of relapse.[20] It is noteworthy that even partial nonadherence significantly increases the risk of relapse. In an outpatient study of a Medicaid population (N = 4325), a 1- to 10-day interval of nontreatment was associated with a 2-fold higher risk of hospitalization, while a gap of 30 days or longer was associated with a 4-fold increased risk.[21]

Table 2. Risk of Relapse in Placebo- and Active Comparator–Controlled Trials of Atypical Antipsychotics in Patients With Schizophrenia

Atypical Antipsychotic	Study	Population	Sample Size	Treatment Duration	Relapse Rate, %	Difference in Risk of Relapse, %
Placebo-controlled trials						
Olanzapine	Leucht et al 2003[12] (pooled data)	Chronic and stable schizophrenia	Olanzapine, N = 317 Placebo, N = 129	46–52 wk	8 31	23
Ziprasidone	Arato et al 2002[13]	Hospitalized patients with chronic schizophrenia	Ziprasidone, N = 206 Placebo, N = 71	12 mo	34 61	27
Aripiprazole	Pigott et al 2003[14]	Chronic and stable schizophrenia	Aripiprazole, N = 155 Placebo, N = 155	26 wk	34 57	23
Active comparator–controlled trials						
Clozapine	Leucht et al 2003[12] (pooled data)	Chronic and stable schizophrenia	Clozapine, N = 136 Conventional, N = 76	12 mo	18 25	7
Risperidone[a]	Csernansky et al 2002[15]	Chronic and stable schizophrenia	Risperidone, N = 177 Haloperidol, N = 188	12 mo	25 40	15
Risperidone[a]	Dossenbach et al 2005[16] (IC-SOHO)	Nonblinded, nonrandomized, naturalistic trial	Risperidone, N = 302 Haloperidol, N = 38	12 mo	5 16	11
Quetiapine[a]		Analysis sample was responder subset that continued monotherapy with acute drug	Quetiapine, N = 40 Haloperidol, N = 38		12 16	4
Olanzapine			Olanzapine, N = 1273 Haloperidol, N = 38		4 16	12
Olanzapine	Tran et al 1998[17]	Chronic and stable schizophrenia	Olanzapine, N = 627 Haloperidol, N = 180	12 mo	14 19	5
Aripiprazole	Kasper et al 2003[18]	Chronic and stable schizophrenia	Aripiprazole, N = 853 Haloperidol, N = 430	12 mo	23 27	4

[a]Placebo-controlled trial data are not available for clozapine, risperidone, or quetiapine.
Abbreviation: IC-SOHO = Intercontinental Schizophrenia Outpatient Health Outcomes.

Risk factors for nonadherence include poor insight, negative attitude and/or negative subjective response to medication, substance abuse, and shorter illness duration.[18] Effective discharge planning and a good therapeutic alliance are associated with increased adherence and may buffer the risk associated with negative predictors.[19] More randomized, prospective research is needed to delineate effective management strategies for patients at risk for nonadherence.[22]

Use of depot antipsychotics is one well-established approach to solving the problem of nonadherence to pharmacotherapy, since delivery of adequate plasma levels is assured.[23] Schooler[24] reports that the risk of relapse was lower on depot versus oral formulations of conventional antipsychotics (27% vs. 42%), although a summary of a Cochrane meta-analysis suggested that the advantage of the depot formulation may be more modest.[25] However, the review expressed a concern that the studies were not enrolling a representative sample with patients at risk for nonadherence.[25] In addition, studies of relatively short duration were included for which the potential advantages of depot formulations are not likely to be evident.

Currently, risperidone is the only atypical antipsychotic available in a long-acting injectable formulation. To date, no double-blind studies have been published that report the differential effect of long-acting risperidone compared to oral formulations of either atypical or conventional antipsychotics (although such studies are underway).

REMISSION AND RECOVERY

Relatively few double-blind, prospective clinical trials are available that report remission rates after acute treatment using specified criteria requiring amelioration of both positive and negative symptoms. Those that do exist differ in terms of the duration requirement. Perhaps the largest data set is a pooled analysis of patients treated in long-term, double-blind trials comparing olanzapine to haloperidol or other atypical antipsychotics (risperidone, ziprasidone, quetiapine)[26]; the Remission in Schizophrenia Working Group criteria[1] were used to define remission. These criteria required that a patient achieve PANNS item scores ≤ 3 (mild) on each of the following PANSS items: delusions, conceptual disorganization, hallucinatory behavior, blunted affect, passive/apathetic so-

cial withdrawal, lack of spontaneity and conversation flow, mannerisms and posturing, and unusual thought content. For the pooled treatment sample, visitwise remission rates were 38.2% at week 8 and 47.4% at week 16.[26]

A double-blind trial comparing people with first-episode schizophrenia who were treated with clozapine (N = 71) versus chlorpromazine (N = 72) used positive symptom criteria to define remission (the primary outcome).[27] Remission rates (based on symptom severity) at 8 weeks were significantly higher for clozapine (50%) compared to chlorpromazine (35%, p = .04, log-rank test).[27]

A small, double-blind trial by Merlo et al.[28] reported symptom remission rates, also based on positive symptom criteria, for 2 doses of risperidone, 2 mg (N = 23) and 4 mg (N = 26), in patients diagnosed with first-episode schizophrenia. Remission at week 8 was nonsignificantly higher on the 4-mg dose of risperidone (77%) compared to the 2-mg dose (70%, p = .20, log-rank test).[28]

Once remission is achieved, the goal is to sustain this level of improvement long enough for full recovery to occur, with associated normalization in quality of life and functioning. Sustained remission, using consensus criteria,[1] is not easy to achieve, as shown by post hoc analyses of 3 data sets. In the first data set, remission status at 1 year was analyzed in a sample of patients (N = 578) treated with long-acting risperidone injection, of whom 76% completed 1 year of treatment.[29] In this study, 85% of patients who achieved remission after acute treatment continued to meet remission criterion at 1 year.[29] It is uncertain if remission was sustained across all 12 months of follow-up. The second data set is a pooled analysis of patients treated in long-term, double-blind comparator trials with olanzapine, risperidone, ziprasidone, quetiapine, or haloperidol.[26] Remission at the 1-year endpoint occurred in 31% of patients who were in remission at week 8, 38% who were in remission at week 16, and 47% who were in remission at week 24.[26] Quality of life was significantly improved in patients with more sustained remission. It should be noted that attrition was high at both 6 months (44%) and at 12 months (80%) in this pooled data set.[26] The attrition in the risperidone trial was lower, but it is uncertain whether this can be attributed to use of a long-acting injectable formulation, or to differences in study designs (e.g., the risperidone trial was open label).[29]

In a third post hoc analysis of a double-blind, 6-month trial comparing olanzapine to oral risperidone,[30] the cumulative percent time spent in remission was significantly higher for olanzapine versus risperidone (40% vs. 31%, p = .03). Once again, attrition at 6 months was a significant confounding factor for both risperidone (53%) and olanzapine (48%).[30]

Recovery may be conceptualized as a stable remission with a return to social and vocational functioning in the community.[1] Prospective data on recovery come primarily from long-term (> 10 year) naturalistic outcome studies that lack rigorous assessment of symptomatic or functional outcome status.[31–34] Such studies, while providing only the most broad brush-stroke picture of recovery, still suggest that recovery occurs in a substantial minority of patients, sometimes after many years of illness.

More methodologically rigorous recovery data come from a prospective study that examined 5-year functional outcomes in a sample (N = 118) of patients with first-episode schizophrenia or schizoaffective disorder.[35] Treatment was open label and based on an algorithm in which patients first received fluphenazine, followed by haloperidol, haloperidol plus lithium, molindone or loxapine, and finally clozapine. Adjunctive sertraline or lithium and/or individual or group psychotherapy could be added to antipsychotic monotherapy as clinically indicated. To qualify as recovered, patients had to meet both remission and functional response criteria.[35] Remission criteria were similar to the new consensus criteria,[1] except that somewhat higher negative symptoms were permitted. Functional response criteria required patients to meet role functioning, daily living, and social functioning criteria on the Social Adjustment Scale. Full recovery was defined as meeting remission and functioning criteria concurrently for at least 2 years.[35]

Sustained remission (for 2 years or longer) occurred in 23% of patients at year 3 and in 41% of patients at year 5. Full recovery rates were low, occurring in only 10% of patients at year 3 and in 14% at year 5.[35] The proportion of patients meeting both symptomatic remission (66%) and normal functioning criteria (38%) during the course of the study was higher, but the majority of patients could not sustain this level of improvement.[35]

TIME COURSE OF ANTIPSYCHOTIC RESPONSE: WHAT CONSTITUTES AN ADEQUATE TRIAL?

Recent meta-analyses have convincingly refuted conventional wisdom that there is a 2- to 3-week lag time before the onset of clinically meaningful antipsychotic efficacy.[36,37] The concept of a lag in treatment response has resulted in practice guideline recommendations suggesting that a patient with schizophrenia be treated for at least 3 to 4 weeks before judging the patient to be a nonresponder and initiating alternative treatment.[38,39] Clinical issues relevant to the time course of antipsychotic response include the determination of what constitutes an adequate acute trial of an antipsychotic and whether there is a minimal initial level of early symptomatic improvement whose absence is predictive of ultimate nonresponse.[40]

In the first published study in the schizophrenia treatment literature to evaluate the predictive validity of early improvement, Correll et al.[40] evaluated the sensitivity, specificity, and positive predictive power of ≥ 20% improvement in the BPRS total or factor score at treatment day 7 for response at 28 days. Patients were treated with 20 mg/day of fluphenazine (unblinded). Improvement in the

BPRS total and thought disturbance scores had extremely high specificity (100% and 95%, respectively), indicating an almost perfect ability to predict nonresponders. The sensitivity was low for the BPRS total score (35%) and moderate for the thought disturbance score (53%), indicating a relatively high rate of false positives.[40]

More research is needed to empirically define predictive and clinically useful early improvement criteria. This is especially important because of a relatively consistent body of literature that finds delay in receiving effective treatment to be moderately correlated with less favorable clinical outcome, especially beyond the short term.[41] The negative impact of delay appears to be independent of the effect of other confounding variables.

PREDICTORS OF REMISSION AND RECOVERY

A regression analysis on a sample (N = 118) of first-episode patients diagnosed with schizophrenia or schizoaffective disorder identified 3 statistically significant predictors of remission: (1) shorter duration of untreated psychosis (DUP), (2) higher baseline levels of cognitive function, and (3) a diagnosis of schizoaffective disorder.[33] In a 12-month, double-blind, placebo-controlled trial,[27] DUP was also identified as a significant negative predictor of remission—for every 12-month increase in duration of untreated illness, the odds of achieving remission by 1 year were reduced by 15%.

The results of these 2 studies are consistent with a meta-analysis of 7 studies that found DUP to be a significant negative predictor of remission (Cohen's $d = 0.517$, $p = .01$).[41] Two other studies found longer DUP to predict a slower time to remission.[42,43] The negative effect of DUP was largely independent of premorbid levels of adjustment.[44]

A separate meta-analysis reported similar findings for DUP and treatment response (not remission).[45] This meta-analysis also examined recovery-related outcomes such as patient functioning and found that DUP was a modest but significant predictor of a reduced likelihood of return to normal functioning.[45] The study by Robinson et al.[35] also analyzed predictors of recovery. The results of the regression analysis identified higher baseline cognitive function as the strongest predictor of recovery ($p < .0001$), followed by higher levels of cortical asymmetry (based on a composite index on magnetic resonance imaging, $p < .01$) and DUP ($p < .05$).[35]

TREATMENT STRATEGIES TO CONVERT RESPONSE TO REMISSION

Typically, the use of switch, augmentation, or combination strategies is reserved for patients who fail to respond to an initial course of treatment, who have only a partial response, or who respond, but develop adverse effects that outweigh the benefit of the initially prescribed drug.[40] Adverse effects may include extrapyramidal side effects, weight gain, or adverse cardiac or metabolic effects. Approximately two thirds of patients may be categorized as partial or nonresponders, or as treatment responsive, but intolerant to the initially prescribed treatment.[40]

One potential clinical implication of establishing remission as the gold standard outcome in the treatment of schizophrenia is the use of more aggressive treatment strategies. At this point, however, almost no prospective data from controlled trials are available to guide clinicians as to when it is appropriate to introduce alternative treatments to optimize initial response and as to what are the most effective augmentation strategies. To answer the "when" question requires data that indicate the inflection point in remission-over-time curves, but only a few published studies report results of Kaplan-Meier analyses (censoring dropouts) that specifically use proposed remission[1] as an outcome. Data from a double-blind clozapine versus chlorpromazine comparator trial suggest that remission rates asymptote somewhere between 10 to 20 weeks.[27] It is important to note that this was a trial of drug-naive first-episode patients, and the time to response and time to remission are likely to occur later in more chronically ill patients.[27] Finally, remission of positive symptoms appears to reach an earlier asymptote at 6 to 9 weeks.[28,46]

Answering the "what" question requires large effectiveness trials of nonresponder samples that are randomly assigned to various dose escalation versus switch versus augmentation strategies. It should be emphasized that studying treatments for partial responders and/or nonresponders is a separate clinical issue requiring enrollment of a different patient sample. For remission to become a credible therapeutic goal, it must become part of the formal research agenda. None of the routinely used combination therapies have been evaluated for the efficacy in achieving remission based on adequately powered and designed controlled clinical trials. Furthermore, expert consensus panels rarely provide guidance on evidence-based treatment strategies to achieve remission.

CONCLUSIONS

Consensus criteria that operationally define remission have recently been proposed for patients with schizophrenia. The few controlled trials that are available and that do report remission as an outcome suggest that remission is a potentially realistic goal, but that it is difficult to maintain, and even more difficult to convert to recovery with normalization of function. Effectiveness trials, with designs similar to the one reported by Kinon and colleagues,[47] are needed to determine which treatment strategies will convert good clinical response to remission and recovery.

Drug names: aripiprazole (Abilify), chlorpromazine (Thorazine, Sonazine, and others), clozapine (FazaClo and others), haloperidol

(Haldol and others), lithium (Eskalith, Lithobid, and others), loxapine (Loxitane and others), molindone (Moban), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), sertraline (Zoloft and others), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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