Relapse Prevention and Recovery in the Treatment of Schizophrenia

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Nonadherence to medication is a predictor of relapse in patients diagnosed with schizophrenia, and preventing relapse is crucial to achieving the goal of recovery. Long-term treatment with antipsychotics can be effective, although long-term patient response to medication may be difficult to predict from trials that measure response, remission, and relapse rates because they are often too short. Longer trials are needed to fully understand the implications of adherence and symptom remission in patient outcome. Recovery, however, is contingent on the stabilization of the symptoms of schizophrenia and the acquisition of the skills necessary to function in society. Psychosocial interventions, such as family psychoeducation, social skills training, and cognitive-behavioral therapy, used in conjunction with pharmacotherapy are effective in helping to prevent symptom relapse and promote functional recovery in patients with schizophrenia. *(J Clin Psychiatry 2006;67[suppl 5]:19–23)*

Because schizophrenia is a chronic disorder, the treatment strategy must have long-term goals. After acute treatment has been successful, the clinician should help the patient adhere to pharmacotherapy and psychosocial interventions in order to meet the goals of long-term treatment, which include preventing symptom relapse and rehospitalization, maintaining symptom stability, and achieving overall remission of symptoms. Finally, attaining functional recovery is the ultimate goal.

RELAPSE PREVENTION IN SCHIZOPHRENIA

Maintenance of drug therapy is key to preventing relapse. According to a meta-analysis[1] conducted by the American Psychiatric Association Task Force of 30 controlled studies, 17% of patients diagnosed with chronic schizophrenia who received antipsychotic medication from 3 months to more than 1 year relapsed as opposed to 56% of patients treated with placebo. Similarly, another study[2] reported that placebo-treated patients had almost twice the relapse rate of drug-treated patients after 2 years of treatment. In this case, 374 patients diagnosed with schizophrenia were treated with the older generation atypical antipsychotic chlorpromazine or placebo. The cumulative relapse rates, usually indicating hospitalization, at 1 year were 67% for placebo and 31% for chlorpromazine, and at 2 years were 80% for placebo and 48% for chlorpromazine. The mean survival time over 2 years for the drug-treated group (17.4 months) was substantially longer than for the placebo-treated group (10.3 months). The results of these studies graphically demonstrate the importance of antipsychotic treatment over the long-term.

A 1-year study of patients with schizophrenia treated with either fluphenazine hydrochloride (oral) or fluphenazine decanoate (depot) revealed a consistent relapse rate in both treatment groups over the first year (Figure 1).[3] Of 214 patients, 28% relapsed by the end of 1 year. However, a 2-year study[4] of 105 patients with schizophrenia that compared the same oral and depot medications found a difference between the 2 treatments that emerged only in the second year (Figure 2). Important predictors of relapse in this study were personal discomfort and intrafamilial stress. These studies indicate that trial duration may be an important factor in understanding relapse risk. Because 2-year studies are rare, analyses concerning relapse rates of 1-year trials may not be reliable and can underestimate the long-term benefits of injectable medications.

A recent study[5] of 365 patients with schizophrenia or schizoaffective disorder compared relapse rates between the older generation antipsychotic haloperidol and the newer generation antipsychotic risperidone over 2.3 years. A differentiation favoring risperidone occurred as early as the first year, with the gap widening considerably over the second year. By the end of the study, 40% of the haloperidol-treated patients relapsed while 25% of the risperidone-treated patients relapsed. The risk of relapse, according to the Kaplan-Meier estimate, was 60% with haloperidol and 34% with risperidone. The difference in mean time to

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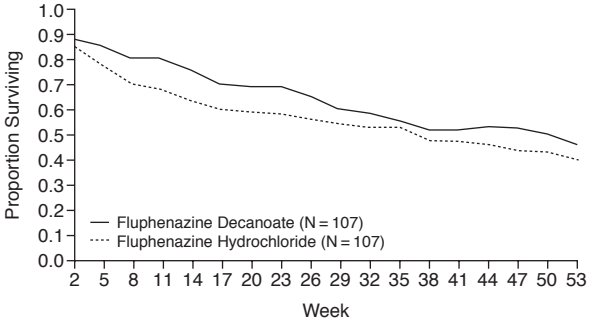
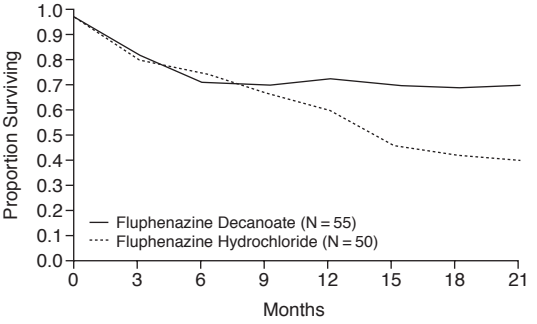
Figure 1. One-Year Relapse Rates of Oral and Long-Acting Depot Medications[a]



[a]Reprinted with permission from Schooler et al.[3]

Figure 2. Two-Year Relapse Rates of Oral and Long-Acting Depot Medications[a]



[a]Adapted with permission from Hogarty et al.[4] The study also included a psychosocial treatment comparison within each of the medication arms. Data are collapsed across psychosocial treatments in this figure.

relapse between the 2 drugs was almost 50 days on average, a clinically relevant difference.

SYMPTOM STABILITY AND REMISSION IN SCHIZOPHRENIA

Symptom stability must be maintained for patients with schizophrenia so that they are in the position to develop the skills and abilities required to reach functional recovery. A 1-year study[6] of 1294 patients with acute relapse of chronic schizophrenia compared the second-generation medication aripiprazole to haloperidol to assess maintenance of symptom stability. At each assessment point (8, 26, and 52 weeks), a greater proportion of patients randomized to aripiprazole showed response and treatment adherance. At 52 weeks, 40% of the aripiprazole group were still in treatment compared with 27% of the haloperidol group, indicating better treatment adherance, safety, and tolerability.

A 28-week comparison between the newer generation antipsychotics olanzapine and risperidone showed greater maintenance of symptom stability with olanzapine than with risperidone.[7] Although psychopathology was reduced and symptoms improved with both medications from baseline to endpoint, olanzapine was found to be more effective in treating negative symptoms, such as blunted affect, avolition, and anhedonia. Furthermore, the olanzapine-treated patients achieved greater response rates and improvement as measured with the Positive and Negative Syndrome Scale.

The absence of relapse does not necessarily indicate a patient's improved social adjustment within the community. In fact, symptom stability does not ensure that patients will progress to a position of recovery. For example, a study[3] of fluphenazine cited earlier measured the social adjustment of nonrelapsed patients in work, household chores, social leisure, external family interactions, and general adjustment. This analysis did not define remission, but, instead, included only those patients who had not met the criteria for relapse by the end of the 1-year trial. According to the global ratings on the Social Adjustment Scale II, these nonrelapsed patients' social adjustment was rated as "poor" to "fair," even after a year of treatment. Therefore, a lack of relapse does not mean that patients are functioning well.

Recently, Andreasen et al.[8] proposed symptom remission criteria that exceed improvement in symptoms of the psychopathology of schizophrenia (Table 1). These criteria are valuable for several reasons. First, they define a range of symptoms, e.g., psychotic symptoms of delusions and hallucinations, symptoms of disorganization, and negative symptoms that include blunted affect, poverty of speech, lack of social engagement, and withdrawal, that should be considered in making a judgment of remission. Second, they set a standard for rating these criteria for remission; all symptom levels must be mild or less. Finally, they define a duration of remission: at least 6 months. Acceptance of these criteria will be a useful step toward the study of recovery because determining whether a treatment, medication or psychosocial, affects remission will require trials that last more than 6 months. Most typical clinical trials, which usually last from 4 to 6 weeks, cannot assess remission as defined here. Six months is also a clinically important period of time during which the patient may become acclimated back into the community, achieving adequate functional status. A limitation of these criteria is that the goal of remission refers only to the symptoms of psychopathology and does not address the broader issue of recovery.

RECOVERY IN SCHIZOPHRENIA

Robinson et al.[9] have developed an operational definition of recovery for patients with first-episode schizophrenia that incorporates both symptom remission and social/

Table 1. Proposed Items for Remission Criteria With Cross-Scale Correspondence and Relationship to Historical Constructs of Psychopathology Dimensions and DSM-IV Criteria for Schizophrenia[a,b]

		Proposed Remission Criteria Items					
		Scale for Assessment of Positive Symptoms (SAPS) and Scale for Assessment of Negative Symptoms (SANS) Items		Positive and Negative Syndrome Scale Items		Brief Psychiatric Rating Scale (BPRS) Items	
Dimension of Psychopathology	DSM-IV Criteria	Criterion	Global Rating Item Number	Criterion	Item Number	Criterion[c]	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 (SANS)	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.[8]
[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 use of the SANS criteria for evaluating overall remission.

Figure 3. Cumulative Recovery Rates in First-Episode Schizophrenia[a]

[a]Data from Robinson et al.[9]
[b]No patients met the criteria for social functioning; therefore, none achieved full recovery.

vocational functioning and specifies a duration of at least 2 years. Their symptom remission criteria differ somewhat from those of Andreasen et al.[8]; Robinson and colleagues distinguish between symptom levels required for positive and negative symptoms. Symptom remission is defined as no more than mild levels of positive symptoms, such as delusions, hallucinations, impairment of understandability, derailment, illogical thinking, and bizarre behavior, and no more than moderate levels of negative symptoms, such as affective flattening, avolition/apathy, and anhedonia/asociality. Social/vocational functioning requires appropriate role functioning as a worker, homemaker, or student; the ability to perform day-to-day living tasks such as managing one's clothing and doing chores; and social interaction with peers, in which peers are defined as nonfamily members. The 2-year duration criterion can be met only if the patient has continuously met the criteria for symptom remission and social/vocational functioning. And finally, recovery can be met if a patient is receiving antipsychotic medication.

From this long-term, observational study[9] of 118 patients diagnosed with first-episode schizophrenia or schizoaffective disorder, over 50% of the patients met the criteria for symptom remission by year 6 (Figure 3). The rate of social functioning climaxed at 25% by year 5, and the overall recovery rate, requiring both symptom remission and social functioning, peaked at only 14% by year 5. By year 6, none of the patients met the criteria for social functioning; thus, none achieved full recovery. This study suggests that there is a potential for recovery in patients with schizophrenia and that the ability to maintain symptom remission is far greater than the ability to maintain social functioning. Furthermore, the ability to achieve both at the same time is limited. Finally, all patients who met recovery criteria were taking antipsychotic medication, the strongest predictor of recovery.

PSYCHOSOCIAL TREATMENTS

Medication alone may be inadequate to allow patients to achieve functional recovery. The U.S. Department of Veterans Affairs (VA), a major health care provider in the United States, has made recovery for patients with schizophrenia a formal goal by widely implementing recovery-oriented programs. In order for patients to achieve full recovery, the VA recommended the following evidence-based psychosocial treatments: family psychoeducation, social skills training, and cognitive-behavioral therapy (CBT).[10]

Family Psychoeducation

Family psychoeducation is based on principles regarding the nature of a schizophrenic illness and the role of the family in dealing with that illness and on the use of specific techniques. Treatment can be provided either individually or in groups. One advantage of group-based family interactions is that mutual social support strengthens families in dealing with members that have been diagnosed with schizophrenia. Providing information about schizophrenia is an important principle and is the foundation to understanding and coping with the disorder. Finally, the last principle is the development of problem-solving and coping strategies that families can use to deal with both day-to-day problems and crises. Information is provided in a supportive setting and a range of problem-solving techniques, coping strategies, and stress management may be included. Although psychoeducation programs for families vary, they are mainly based on the assumption that schizophrenia is an illness that is exacerbated by stress and that stress management and coping skills are necessary techniques needed to reach recovery. Families who have participated in psychoeducational approaches have commented that these programs are beneficial and that, in addition to the knowledge and skills gained, the recognition that they are not alone is very helpful.

According to a meta-analysis conducted by Pharoah et al.,[11] the relative risk of relapse and rehospitalization is substantially reduced for patients with schizophrenia if the families have experienced psychoeducation. This psychosocial treatment also encouraged patient's adherence to medication, reduced general social impairment, and improved the levels of expressed emotion within the family unit. Even though family psychoeducation is helpful to patients and their families, it is not widely available and some families may not wish to participate even when family psychoeducation is available.

Social Skills Training

Social skills training is based on the principle that social behavior is a skill (like driving a car or playing the piano) that can be taught and learned. The acquisition of these skills is incremental, happening in steps during which complex behaviors can be deconstructed, learned as separate elements, and then fused together to achieve the more complicated behavior. Techniques of this method of psychosocial treatment include repetition, reinforcement, modeling, behavioral rehearsal, and feedback. Social skills training is a very specific psychosocial treatment that can be implemented by skilled practitioners in either a group or individual format. The group format is attractive because group members can assist one another as well as receive aid from the instructor, and it is more economical with regard to clinician time than individual treatment.

Medication may provide a foundation on which social skills training can be developed, but medication alone cannot improve social functioning or problem-solving. In a study[12] of clozapine versus risperidone, the results showed a general stability for both medications over the duration of 29 weeks. However, despite clinical improvement, the medications had almost no effect on either social competence or problem-solving. A 2-year study[13] compared social skills training to supportive group therapy for patients who were all receiving low doses of antipsychotic medication and supplementation of either medication or placebo at early or prodromal signs of relapse. Although social skills training did not reduce the chance that patients would develop prodromal signs of relapse, it did reduce the likelihood that prodromal signs would progress to full exacerbation and frank relapse. Further, those randomized to social skills training showed better social adjustment over the course of the 2 years.

Cognitive-Behavioral Therapy

A major assumption of CBT is that misinterpretations of both sensory inputs and other experiences underlie schizophrenic symptoms—especially delusions and hallucinations. This is key because one of the most important principles of CBT is to normalize the patient's experiences, so that hallucinations, for example, can be conceived as falling along a continuum of normal perception. Delusions can be interpreted as disturbances in appraisal and judgment. Turkington et al.[14] describe 4 key stages of CBT. The first is establishing a therapeutic alliance as in other psychosocial treatments. The alliance is based on understanding the patient's perspective on his or her experiences. The second stage is the development of alternative explanations for the experiences that are usually labeled as symptoms. The third stage focuses on reducing the impact of symptoms on daily life, and the fourth stage attempts to develop alternatives to a medical model to enhance medication adherence. These methods are explicitly not diagnosis-based. For this reason, CBT becomes an extremely helpful approach when dealing with patients who refuse to accept the diagnostic label of schizophrenia.

A study[15] of patients diagnosed with chronic schizophrenia measured the effects of different types of therapy

on positive symptoms (e.g., delusions and hallucinations) that continued despite the administration of antipsychotic medication. The results showed that CBT was more effective in ameliorating psychotic symptoms than supportive therapy and routine therapy. In another study,[16] patients who received CBT demonstrated improved insight (which indicates that patients receiving CBT may be more inclined to adhere to pharmacotherapy), used coping strategies more effectively, and had shorter hospital stays than patients who received pharmacotherapy alone.

CONCLUSION

With recovery as the ultimate goal, prevention of relapse is a cornerstone in the treatment of schizophrenia. The low recovery rates reported in the literature illustrate the need to develop better treatments. The treatment plan that will promote recovery in patients with schizophrenia is going to have to be a multipronged one that does not involve just a single prescriber, even one who is in the position to provide optimal pharmacotherapy. Ensuring adherence to medication is crucial. Injectable medications can enhance adherence, although additional interventions may be required to motivate patients to accept and continue to receive medications.

Although there are improved medications and enhanced medication delivery strategies, an understanding of the psychosocial treatment needs of patients with schizophrenia is key to attaining recovery. The prospects for developing strategies that will lead patients to recovery are becoming increasingly bright, but that goal has not been realized for many of the patients with schizophrenia.

Drug names: aripiprazole (Abilify), chlorpromazine (Sonazine, Thorazine, and others), clozapine (Clozaril, Fazaclo, and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

Disclosure of off-label usage: The author has determined that, to the best of her 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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