Functional Outcomes in Schizophrenia

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A recent expert panel has proposed consensus criteria for remission in schizophrenia. They distinguished remission from recovery, noting that the latter outcome was likely to require not only remission of symptoms, but also improvement in cognitive and psychosocial functioning. The panel deferred the task of establishing operational criteria for recovery since there was insufficient research on the topic. This article provides a summary of this still "uncharted" aspect of treatment.

(J Clin Psychiatry 2008;69[suppl 3]:20–24)

For persons suffering from schizophrenia, remission of psychotic symptoms is only the first step on the road to recovery. Recent consensus criteria[1] define remission as "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."(p442) However, recovery requires symptomatic remission that is sufficiently sustained so that the individual experiences improvement in their psychosocial functioning and is able to return to competitive employment. However, various disruptive factors impair the ability to achieve stability, including persistent cognitive deficits that interfere with vocational learning and the development of normal routines; high rates of substance abuse; and often unsupportive family and community environments. It is perhaps not surprising that pharmacotherapy alone is rarely sufficient to achieve remission, not to mention recovery.

IMPEDIMENTS TO RECOVERY: COGNITIVE DEFICITS IN SCHIZOPHRENIA

Schizophrenia is associated with a wide range of cognitive deficits that are most notable for impairment in working and explicit (declarative) memory, executive function, and problem solving.[2,3] In a meta-analysis of cognitive function in schizophrenia,[4] impairment was moderate across a range of 22 neuropsychological tests, with scores averaging from 0.46 to 1.41 standard deviations below the control mean. Cognitive deficits in schizophrenia occur early, preceding the onset of treatment,[5] and usually persist in persons who are otherwise in remission.[6]

A recent National Institute of Mental Health conference[7] identified 7 cognitive domains as key targets for research and treatment in schizophrenia: (1) speed of processing, (2) attention/vigilance, (3) working memory, (4) verbal learning and explicit memory, (5) visual learning and memory, (6) reasoning and problem solving, and (7) social cognition.

Recent baseline data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study measured 5 of these 7 cognitive domains.[8] The CATIE study found diffuse levels of impairment across the range of cognitive tests that were similar in magnitude to what was reported in a previous meta-analysis.[7] In tests for which appropriately matched normative data were available, participants in the CATIE trial had cognitive scores ranging from 0.84 to 2.47 standard deviations below normative data. On the composite cognitive measure, cognitive impairment was significantly correlated with higher illness chronicity (0.317), older age (0.305), less education (0.286), and a higher Positive and Negative Syndrome Scale (PANSS) negative score (0.271).[8] Interestingly, the PANSS positive symptom score was not correlated with cognitive impairment. Cognitive function was significantly higher among patients who were drug free or currently taking atypical antipsychotics than among patients taking typical antipsychotics.[8] Cognitive deficits have been shown to have a range of negative consequences in schizophrenia, including poorer functional outcomes,[9,10] poorer treatment compliance,[11] and higher risk of relapse.[12]

Another consequence of illness-related cognitive deficits is the impact on psychosocial interventions. The type

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This article is derived from an expert consensus roundtable meeting, which was held March 29, 2006, in New York, N.Y., and supported by an educational grant from Bristol-Myers Squibb and Otsuka Pharmaceutical.

The author acknowledges Edward Schweizer, M.D., for his editorial assistance in the preparation of the draft manuscript under a freelance contract to CME Outfitters (Rockville, Md.). Dr. Schweizer has also received consulting fees from Pfizer, Eli Lilly, Bristol-Myers Squibb, Wyeth, Neurocrine, and Solvay.

Dr. McEvoy is a consultant for GlaxoSmithKline and Acadia and has received honoraria from Eli Lilly and Pfizer.

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of learning that takes place within the safe harbor of a therapist's office is largely ineffective for an individual suffering from schizophrenia. Optimal therapy-based learning relies on intact explicit memory. Schizophrenia significantly impairs explicit or declarative memory, although implicit or procedural memory tends to be normal.[13] Psychosocial interventions are much more likely to be successful if they focus on "learning by doing." Taking patients out to do specific activities is much more instructive than sitting in a circle and talking about how to do the activity. Successful psychosocial approaches must take advantage of the relative preservation of procedural memory to establish routines that will enhance treatment compliance and participation in important social and occupational activities. Programs that facilitate procedural learning are more labor intensive and costly than programs that rely on explicit/declarative memory. Unfortunately, we know very little about the dose-response curves for procedural learning in persons with schizophrenia.[13]

IMPEDIMENTS TO RECOVERY: SUBSTANCE USE DISORDERS IN SCHIZOPHRENIA

Substance use disorder (SUD) is pervasive among persons suffering from schizophrenia, with prevalence estimates ranging up to 50% or higher.[14,15] In the CATIE trial,[16] 37% of patients met DSM-IV criteria for an SUD, while an additional 23% used substances but did not meet criteria.

The presence of a comorbid SUD is associated with a range of negative consequences, including treatment nonadherence, increased risk of relapse and frequency of hospitalization, homelessness, impulsivity and violence, and overall poor outcome.[17–19] Results from CATIE[16] are consistent with previous data and confirm that persons with schizophrenia and comorbid SUD are younger (mean age of 38.6 vs. 42.4 years), more likely to be male (85% vs. 65%), and more likely to have suffered a clinical exacerbation in the previous 3 months (36% vs. 22%).

Insufficient treatment data are available from randomized, double-blind trials to make a recommendation as to what combination of pharmacotherapy and psychosocial treatments is best for treating comorbid substance abuse. Preliminary studies suggest that treatment with clozapine may reduce SUDs.[20]

PSYCHOSOCIAL THERAPIES OF SCHIZOPHRENIA

One of the most durable and best-studied psychosocial interventions in the treatment of people with schizophrenia is family therapy. While there are many variants, each emphasizing different techniques, all have several components in common: forming a therapeutic alliance with family members; working with family members to enhance problem solving, to set reasonable expectations and limits, and to decrease the negative expressed-emotion family environment; psychoeducation about family members' behaviors and beliefs; crisis management; and family support. The greatest benefit of family therapy appears to be a reduction in the risk of relapse.[21] Using stringent methodological criteria for study inclusion, a Cochrane group meta-analysis concluded that risk of relapse was reduced by 28% when family therapy was used.[22] The meta-analysis also suggested that therapy may reduce medication noncompliance. The authors noted that there was a fair degree of heterogeneity in study outcomes.[22] For example, several randomized trials of family therapy found no relapse prevention advantage for family therapy compared to individual treatment,[23,24] biweekly supportive therapy,[25,26] and crisis management combined with assertive community treatment.[27] Nonetheless, since the overall empirical evidence appears to support the effectiveness of family therapy, the Patient Outcomes Research Team has recommended that family therapy be a standard component of schizophrenia treatment regimens.[28]

CASE MANAGEMENT: THE ASSERTIVE COMMUNITY TREATMENT MODEL

Case management has long been standard practice in the treatment of patients with schizophrenia. However, the patients who most need the assistance of case managers to help them negotiate the complexities of community services are the very patients who are least able to avail themselves of case management. The assertive community treatment (ACT) model addresses this service need with a comprehensive, integrated, 1-stop, 1-point of contact, 24/7 "assertive" form of case management. The high staff-to-patient ratio and the active ownership of a case by a single member of the multidisciplinary team are key features of this approach. The goals of ACT are to reduce relapse and hospital readmissions and to improve quality of life and social and occupational functioning in the community.[29]

The meta-analytic report card on ACT is among the most favorable of all psychosocial interventions.[29] A Cochrane group meta-analysis found that patients treated with ACT were 41% less likely to be rehospitalized compared to patients receiving standard community care (odds ratio = 0.59, 99% CI = 0.41 to 0.85). If hospitalized, they spent less time in the hospital. Treatment with ACT appeared to significantly facilitate the ability of patients to live independently. However, a critical review[30] has noted that the efficacy of ACT for improving secondary outcomes (e.g., social adjustment, employment) was more limited and inconsistent.

The ACT model has been successfully used in clinical settings in patients who are high utilizers of inpatient services.[31] Future research is needed to determine the pre-

cise, active ingredients in the ACT package that contribute most to its efficacy and the most appropriate, cost-effective target populations for ACT (i.e., should its use be limited to high utilizers of inpatient services?).

SOCIAL SKILLS TRAINING

The persistence of deficits in social skills and continued unemployment among successfully treated patients suggests that the majority of individuals with schizophrenia might benefit from psychosocial treatments specifically designed to enhance social skills. Deficits in social skills are significantly correlated with low quality of life and satisfaction,[32] while improvement in social skills and overall social competence may serve to buffer the individual from the toxic effects of life stressors.

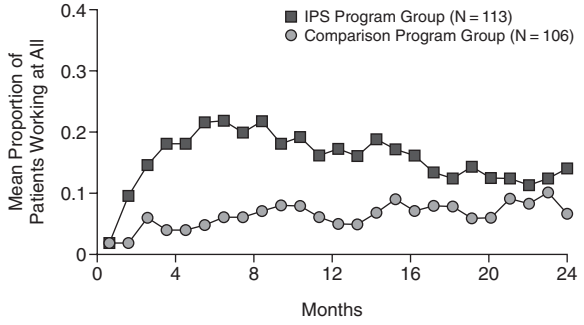
Several types of social skills training have been studied. For example, the social problem-solving approach focuses on optimizing skills in practical domains, including the ability to carry on a conversation and make friends, take care of one's own daily needs, reliably take one's medication, and participate in routine social interactions.[33] Several studies of this social problem-solving approach have demonstrated modest but significant enhancement of social skills with a concomitant improvement in long-term social adjustment.[33] The problem-solving approach has been codified in manuals and has been successfully exported to clinical settings.

Since deficits in social skills may be secondary to underlying cognitive deficits in executive function, planning, and attention, social skills training might be more effective if focused on cognitive remediation. The results from this approach have been mixed, though 1 study found cognitive remediation to enhance problem solving and social competence.[34] These results are not surprising because specific cognitive deficits account for only some of the variance in observed social skills.[35] Furthermore, enhancing social skills may have a reciprocal effect in improving cognitive function.[36]

SUPPORTED EMPLOYMENT

Individual placement and support (IPS, supported employment) is another approach to vocational rehabilitation that is combined with skills training. Supported employment bypasses the traditional incremental approach in favor of rapid job placement accompanied by active and ongoing supportive interventions. The supportive interventions are designed to enhance practical, job-related social skills and might include training individuals how to anticipate job stressors, how to effectively use stress management techniques, how to obtain feedback and help from a supervisor, and how to perform routine social amenities with coworkers.[37] Several studies suggest that the supported employment approach is effective in helping patients to retain jobs and in improving job satisfaction, especially in the early stages of schizophrenia.[38]

Figure 1. Mean Proportion of Patients Working at All During 24 Months of Treatment With an IPS Program Versus a Psychosocial Rehabilitation Program[a]



[a]Reprinted with permission from Lehman et al.[39]
Abbreviation: IPS = individual placement and support.

Lehman and colleagues[39] have reported the results of a study in which outpatients with severe mental illness (N = 219, 64% with schizophrenia or other DSM-IV 295.xx disorder) were randomly assigned to IPS or a standard psychosocial rehabilitation program. In the IPS treatment model, an employment specialist was an integral part of a comprehensive, multidisciplinary treatment team using a 1-stop, 24-hour approach. Assessment performed over 24 months of prospective follow-up found that patients in the IPS treatment condition were significantly more likely to have worked at all (Figure 1) and to have worked competitively (data not shown).[39] Rates of competitive employment were 27% for IPS versus 7% for the standard program ($p < .001$, OR = 5.58). Individual placement and support did not improve job retention (duration of time on a job). The results of this study may be difficult to generalize to the full range of patients with schizophrenia because the treatment sample was a chronically ill, inner-city sample (25% white), with high rates of disability (89% on disability, 51% with no job in the past 5 years) and current substance abuse (40%). Although IPS appeared to have benefit, the treatment effect was not as large as anticipated.

Interventions such as IPS and social skills training are typically combined with drug therapy, usually with first- or second-generation antipsychotics. Some studies suggest that monotherapy with antipsychotics improves both social skills and work outcomes. In 1 randomized, double-blind, 52-week comparison of olanzapine and haloperidol, Hamilton et al.[40] reported that the proportion of patients engaged in part-time or full-time employment significantly increased when taking olanzapine but not when taking haloperidol. Unfortunately, very few antipsychotic clinical trials evaluate social skills or real-world work outcomes.

MEDICATION EFFECTS ON COGNITIVE FUNCTION

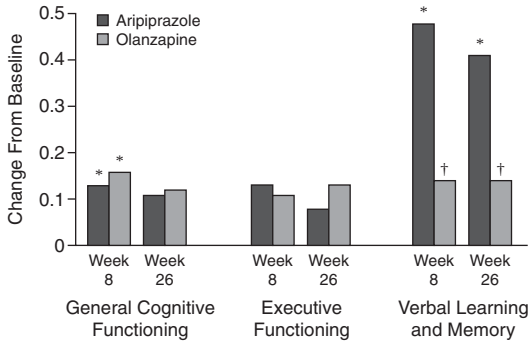
Although first-generation antipsychotics have not proven consistently effective in improving cognitive function in patients with schizophrenia, studies suggest that atypical antipsychotics may be beneficial in improving neurocognitive deficits.

A randomized, double-blind, 14-week trial compared the efficacy of clozapine, olanzapine, risperidone, and haloperidol in patients with treatment-resistant schizophrenia or schizoaffective disorder.[41] Treatment with all 3 atypical antipsychotics resulted in significantly greater improvement in psychotic symptoms than haloperidol. In a second study,[42] patients completed an extensive cognitive battery that assessed 4 domains (memory, attention, psychomotor function, and executive function and perceptual organization). Significant clinical improvement in cognitive function was defined as a change from baseline of at least one half of a standard deviation (change in z score ≥ 0.5) on the global composite cognitive test score. Treatment with olanzapine resulted in significantly greater improvement in cognitive function than clozapine or haloperidol, and treatment with risperidone resulted in significantly greater improvement than clozapine.[42] Clozapine showed only numerical superiority to haloperidol. Improvement in overall cognitive function was significantly correlated with improvement in negative symptoms ($p = .016$), with the exception of verbal learning and memory. Interestingly, however, clozapine improved negative symptoms significantly more than risperidone, but risperidone was associated with greater improvement in cognitive function. Also of note is that improvement in positive symptoms was not correlated at all with improvement in cognitive function.[42] This latter finding is consistent with baseline data from CATIE.[8]

A randomized, open-label, 26-week trial compared the effects of aripiprazole and olanzapine on executive function, verbal learning and memory, and general cognitive function.[43] Treatment with aripiprazole was associated with significantly greater improvement in verbal learning and memory compared with olanzapine (Figure 2); improvement from baseline was modest and comparable in the 2 other cognitive domains.[43]

In another long-term (6-month), double-blind, comparator trial,[44] treatment with ziprasidone and olanzapine both resulted in significant improvement in cognitive function, with 10% to 40% of patients achieving full normalization of cognitive function, depending on the cognitive domain tested. These results illustrate that treatment-related improvement in neurocognitive function is often gradual and progressive, with clinically meaningful improvement continuing to occur at 6 months and possibly longer. More research is needed to determine which atypical antipsychotics have the most procognitive effects and to identify other (drug or nondrug) treatments that can normalize cognitive function. Research also is needed to customize psychosocial interventions to adapt to the types of deficits common among persons suffering from schizophrenia. Data from a small, open-label, 1-year study with clozapine ($N = 29$)[45] suggest that improvement in cognitive function is significantly correlated with improvement in quality of life ($r = 0.40$, $p = .03$). Future research will delineate whether improvement in particular cognitive domains translates in improvements in function, vocational performance, and/or quality of life.

Figure 2. Mean Change in Cognitive Measures: Results at Week 8 and Week 26 for Aripiprazole Versus Olanzapine[a]



[a]Reprinted with permission from Kern et al.[43]
*Significant improvement from baseline.
†Significant difference between groups.

CONCLUSION

The arsenal of effective tools available to treat persons with schizophrenia continues to grow. Options now include both typical and atypical antipsychotics, family therapy, various forms of social skills training, active case management, and individual placement and support. Much additional research is needed to identify optimal target populations for various psychosocial treatments and to test which strategies are the most cost-effective.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

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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