Relapse prevention is a primary goal in the treatment of schizophrenia. Relapse can cause significant personal distress, interfere with rehabilitation efforts, and result in psychiatric hospitalization. The emergence of psychotic symptoms and disruptive behaviors can also lead to arrest and incarceration, particularly among patients who are not engaged in treatment. This article focuses on the process of relapse in schizophrenia and theoretical foundations of relapse prevention. The Program for Relapse Prevention is presented, along with the results of a recently completed controlled prospective evaluation. Based upon this study and the current literature, the author presents a series of seven clinical strategies for optimal relapse prevention.

KEY WORDS: schizophrenia, relapse prevention, prodromal symptoms, early intervention, nonadherence.

AN OVERVIEW OF RELAPSE IN SCHIZOPHRENIA

Although operational definitions exist,4 relapse in schizophrenia may be clinically defined as the emergence of psychotic symptoms to the point that crisis intervention or hospitalization is required. Understanding the relapsing and remitting course of schizophrenia is central to relapse prevention. Figure 1 illustrates the longitudinal course of illness and how the pattern of relapse can vary significantly between groups of patients.5 It is noteworthy that DSM-IV has introduced a useful classification of the course of schizophrenia, including categories of single episode, episodic with interepisode symptoms, episodic without interepisode symptoms, and continuous.6

Relapse in schizophrenia should not be viewed as occurring “spontaneously.” According to the vulnerability-stress model, individuals with schizophrenia have a biologically mediated vulnerability to stressful events that can result in acute psychosis.7, 8 Whether a full-blown relapse occurs depends upon a complex interaction between an individual's degree of vulnerability, the nature of the stressful event, and the presence or absence of protective factors.9 Protective factors include an individual's coping skills, family and social supports, and therapeutic interventions. The role of protective factors was emphasized in the development of the Program for Relapse Prevention described in the next section.10

A PROGRAM FOR RELAPSE PREVENTION IN SCHIZOPHRENIA

The Program for Relapse Prevention (PRP) was developed as a state-of-the-art approach incorporating a number of interventions shown to be effective in preventing relapse in schizophrenia.10, 11 In addition to maintenance pharmacotherapy, PRP includes four primary components:

1. Monitoring for prodromal symptoms of relapse by treatment providers, patients, family members, and others in frequent contact with the patient
2. Prompt clinical intervention whenever prodromal symptoms of relapse are detected
3. Weekly supportive group therapy meetings, with individual sessions as needed
4. Multifamily psychoeducation group meetings, bi-weekly for 6 months and monthly thereafter.

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To assess the effectiveness of the program, it was compared to treatment as usual (TAU) consisting of biweekly individual supportive therapy and family contact on an “as needed” basis. Eighty-two outpatients with schizophrenia or schizoaffective disorder were randomly assigned to receive PRP or TAU, and were followed in an 18-month prospective study. Subjects in both groups received standard doses of antipsychotic medications. Over 18 months, 17% of patients relapsed and 22% were hospitalized in the PRP group compared to 34% of patients relapsing and 39% being hospitalized in the TAU group ($P = 0.01$ and $0.03$, respectively). A preliminary analysis of total direct costs of care showed that PRP actually cost less than TAU, although the difference was not statistically significant. Based on experience with the PRP model and a review of the current literature on relapse prevention, a list of seven strategies for relapse prevention has been developed. Although they were derived from intensive treatment programs including PRP and assertive community treatment (ACT), these strategies can be used successfully in a variety of treatment settings.

**RELAPSE PREVENTION STRATEGIES**

**Strategy 1: Be Available and Flexible**

Availability and flexibility are the cornerstones of relapse prevention. Patients and their support persons should be able to reach clinicians easily, particularly during evenings and weekends. Patients and family members in the PRP study group were given a pager number for their treatment team, with instructions to call whenever they were concerned about the possibility of relapse. Although clinicians may be reluctant to provide this level of access for several reasons, including the possibility of receiving multiple calls after hours, the experience of the PRP team suggests that such calls are infrequent, especially with ongoing instruction and practice. While an answering service or other system of reaching treatment providers after hours may be adequate, arrangements that require patients to work with unfamiliar clinicians are not optimal.

Whenever possible, patients with schizophrenia who may be relapsing should be evaluated within 24 to 48 hours. Many relapses have resulted from the common practice of assigning such patients the “next available appointment”—even when the appointment is several days or weeks away. Clinicians can achieve flexibility in their daily work schedules by maintaining regular time slots for crisis appointments or by overbooking crisis appointments when needed.

Along with personal qualities such as warmth and genuineness, availability and flexibility can promote a strong therapeutic alliance. Since a positive therapeutic relationship is associated with improved adherence to treatment, it is likely that being available and flexible will have therapeutic benefits that extend beyond enabling prompt clinical intervention.

**Strategy 2: Watch for Prodromal Symptoms**

Prodromal symptoms—often called early warning signs—are the earliest noticeable signs of relapse. The regular occurrence of prodromal symptoms before relapse in schizophrenia has been established by several investigators. Common examples of prodromal symptoms are insomnia, tension and nervousness, eating less, difficulty concentrating, social withdrawal, auditory hallucinations, depressed mood, loss of interest, decreased personal hygiene, and irritability. Prodromal symptoms vary considerably among patients, but tend to remain relatively consistent within a given individual from relapse to relapse.

Effective monitoring for prodromal symptoms requires frequent contact and careful evaluation. Open-ended questions such as “How are things going?” or “Are there any problems?” are not adequate for detecting prodromal symptoms. A shortened version of the Early Signs Questionnaire (see Appendix) was administered to patients in the PRP study at the start of each weekly
group therapy meeting. This tool can be administered to patients in any treatment setting where regular contact is maintained. It is important to note that patients may report various symptoms on the questionnaire even during a stable phase of illness. Since many patients experience interepisode symptoms such as insomnia, anxiety, and auditory hallucinations, a thorough knowledge of each patient is necessary to distinguish these “baseline” symptoms from prodromal symptoms.

**Strategy 3: Intervene Early**

The process of relapse in schizophrenia is usually a gradual one that presents a window of opportunity for early intervention (Figure 2). Although prodromal symptoms typically precede full relapse by at least a week, intervention often does not occur until late in the course of relapse when an emergency room visit or hospitalization is necessary. In the PRP study, 40% of patients in the TAU group required hospitalization by the time that the treatment providers became aware that the patients were relapsing.

The relapse process in schizophrenia is reversible if intervention occurs early enough in its course. When prodromal symptoms are detected, intervention should consist of supportive therapy visits, increased medication as needed, and crisis problem solving. The likely precipitating cause of the prodromal episode should be identified and addressed through appropriate measures. For instance, a patient who begins to relapse due to anxiety about moving into a group home could be given transitional visits in order to get acquainted with the facility. Pharmacological intervention usually consists of increasing a patient’s standing dose of antipsychotic medication or of adding an extra dose on an as-needed basis. The additional medication should be continued until the precipitating factors have been addressed and the prodromal symptoms have fully resolved. Adjunctive benzodiazepines may also be considered for the treatment of prodromal symptoms.

**Strategy 4: Work Closely With Families and Other Supports**

Some patients are unable to detect or report the onset of relapse, despite education about prodromal symptoms and considerable personal experience. For such individuals, it is critical to enlist the help of family members and supportive others, including friends, employers, group home counselors, and day treatment program staff. These individuals, who have frequent contact with the patient, can become the “eyes and ears” of the treatment team in detecting the onset of relapse. They can also have a protective effect by helping patients manage stressful situations and by supporting adherence to treatment.

In recent years, family psychoeducational approaches have been developed to assist families and others in providing support for persons with schizophrenia. As a group, these approaches emphasize providing education about schizophrenia, teaching problem solving and communication skills, and developing social networks. Several research studies have demonstrated the effectiveness of family psychoeducation in reducing relapse rates in schizophrenia. The strength of the evidence for the effectiveness of family psychoeducation in preventing relapse is perhaps second only to that for antipsychotic medications. Despite the evidence, the Patient Outcomes Research Team (PORT) study and a recent review of the literature have suggested that family psychoeducation interventions are highly underutilized.

The multifamily group format was chosen for the PRP intervention because it lends itself to teaching about
SEVEN KEYS TO RELAPSE PREVENTION IN SCHIZOPHRENIA

Relapse prevention, it promotes formation of family networks, and it may be more cost effective than single family models. Although only 29% of PRP patients’ families participated in the multifamily groups, only one patient from these families relapsed and was hospitalized during the study period. Interested clinicians are referred to the excellent practical overview of multifamily group psychoeducation by McFarlane and Cunningham.

**Family members and supportive others can become the “eyes and ears” of the treatment team in detecting the onset of relapse. They can also have a protective effect by helping patients manage stressful situations and by supporting adherence to treatment.**

**Strategy 5: Use Assertive Outreach When Necessary**

When they are relapsing, patients often withdraw from their usual activities, including attending outpatient appointments. Assertive outreach to such patients, carried out in a positive, confident, and persistent way, can promote engagement in treatment. Forms of outreach may include letters, phone calls, and home visits. In the PRP study, all patients in the experimental group who missed an appointment received a follow-up phone call, and home visits were conducted if clinically indicated.

The assertive community treatment (ACT) model has been developed for patients who consistently require outreach in order to engage in treatment. It consists of mobile multidisciplinary treatment teams with a high staff-to-patient ratio and around the clock availability. ACT places a strong emphasis on delivering comprehensive services in community settings, outside the walls of outpatient clinics.

**Strategy 6: Address Nonadherence**

It has been estimated that nonadherence to treatment with antipsychotic medications accounts for approximately 40% of all relapses in schizophrenia. Medication nonadherence was also the single strongest predictor of relapse in the PRP study. Causes of medication nonadherence include denial of illness, perceived lack of benefit from treatment, financial and environmental obstacles, and motivational factors. The self-determination theory of human motivation suggests that medication adherence is most likely to occur and persist if the patient experiences the behavior as autonomous—as emanating from within him- or herself. Recent studies of adherence to weight loss regimens, diabetes diets, and medications in outpatient medical settings have highlighted the impact of clinicians’ behaviors on patient motivation. The following clinical strategies, which are based on the self-determination model, should be considered for patients who are nonadherent with antipsychotic medications:

1. **Listen**: elicit the patient's experiences and concerns.
2. **Empathize**: acknowledge the patient's perspective.
3. **Educate**: provide a clear rationale for the recommended treatment.
4. **Provide choices**: promote choice whenever possible.
5. **Minimize control**: minimize controlling behaviors.

Despite this approach, some patients with schizophrenia will continue to refuse medications. These patients are at risk for entering a “revolving door” cycle of repeated relapse and hospitalization. For patients whose refusal of medication consistently results in behaviors that pose a risk of harm to themselves or others, involuntary outpatient commitment should be considered.

Outpatient commitment has been shown to reduce hospital readmission rates and medication nonadherence among patients with psychotic disorders, although its effectiveness may depend upon the ability of outpatient programs to engage such individuals.

Patients with schizophrenia who are not engaged by existing treatment programs present difficult challenges for relapse prevention. These patients often have co-occurring substance use disorders, and many experience homelessness, arrest, and incarceration. New models of outpatient service delivery are being developed to prevent relapse and recidivism among such individuals. An example is Project Link, an integrated approach that spans healthcare, social service, and criminal justice systems. The program incorporates elements of the ACT model and features a mobile treatment team with a forensic psychiatrist, a dual diagnosis residence, and culturally diverse staff. It also involves active collaboration between treatment team members and criminal justice system representatives, including jail staff, judges, and probation and parole officers. While preliminary program evaluations have suggested that this model may be effective, controlled studies are needed to further examine the impact of this approach on relapse and recidivism.

**Strategy 7: Optimize Pharmacotherapy**

Pharmacotherapy can be optimized by simplifying drug regimens, by considering the use of atypical and decanoate antipsychotic medications, and by minimizing drug side effects. Although side effects are a major cause of medication nonadherence among patients with...
schizophrenia, patients may not report side effects unless asked about them directly. Clinicians should therefore carefully assess all patients for side effects on a regular basis. While most medication side effects have the potential to affect adherence, extrapyramidal side effects (EPS) such as akathisia and akinesia may be especially problematic. Since novel “atypical” antipsychotic medications produce noticeably fewer EPS than standard antipsychotic medications, they have the potential to improve adherence and help prevent relapse.

Recent studies have suggested that atypical antipsychotic medications are superior to standard medications in preventing psychotic relapse. In a review of three large international studies of olanzapine versus haloperidol, the Kaplan-Meier estimated 1-year risk of relapse was 28% with haloperidol compared to 19.7% with olanzapine ($p < 0.05$). In a study comparing risperidone and haloperidol in a group of 365 patients, 34.6% of patients on haloperidol and 23.2% of patients on risperidone relapsed after 1 year ($p < 0.01$). In addition to studies that have examined relapse rates, a number of pharmaco-economic studies have shown decreased rates of hospitalization associated with atypical antipsychotic drugs compared to standard drugs. Although these pharmaco-economic studies have methodological limitations, the results to date are encouraging.

Long-acting decanoate medications should also be considered for reducing the risk of relapse in schizophrenia. Decanoate medications have been found to lower relapse rates by approximately 15% compared to standard oral antipsychotic medications. These injectable medications have the additional advantage of allowing clinicians to detect nonadherence, thus providing an opportunity for early intervention. No randomized controlled studies have been published comparing the effectiveness of decanoate and atypical antipsychotic medications in preventing relapse and hospitalization in schizophrenia.

**SUMMARY AND CONCLUSIONS**

Although effective approaches to relapse prevention in schizophrenia have been developed, they remain largely underutilized. This paper has presented seven fundamental principles for relapse prevention that are based upon existing approaches and can be flexibly applied in outpatient treatment settings. A consideration of these principles calls to mind the expression “simple but not easy”—the principles are simple to understand, but their application requires persistence and practice for optimal effectiveness. However, these efforts are worthwhile investments, because effective relapse prevention can provide a foundation for rehabilitation and recovery among those who suffer from schizophrenia.

**REFERENCES**

## Appendix. Early Signs Questionnaire, Short Form

**NAME___________________________________________ DATE___________________**

Compared to last week, has there been an increase in any of the following symptoms?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
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<tr>
<td>1. Problems with sleep</td>
<td></td>
<td></td>
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<td>2. Problems with appetite</td>
<td></td>
<td></td>
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<td>3. Depression</td>
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<td></td>
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<td>4. Problems with concentration</td>
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<tr>
<td>5. Restlessness</td>
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<td></td>
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<td>6. Tension or nervousness</td>
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<tr>
<td>7. Use of alcohol</td>
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<td></td>
</tr>
<tr>
<td>8. Use of street drugs (includes marijuana)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Hearing voices or seeing things that others can’t hear or see</td>
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<td>10. Less pleasure gained from things you usually enjoy</td>
<td></td>
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<tr>
<td>11. Feeling people were watching you, were against you, or were talking about you</td>
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<tr>
<td>12. Preference for being alone and/or been spending less time with other people</td>
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<td>13. Arguments with others</td>
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<tr>
<td>14. Inability to get your mind off of one or two things</td>
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Have any other symptoms appeared or increased?  
If so, what were they?

__________________________________________________________________
__________________________________________________________________

Did anything specific happen last week which upset you?  
If so, what was it?

__________________________________________________________________
__________________________________________________________________

Have you been taking your medication as it is prescribed for you?  
__________________________________________________________________

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