Treatment Strategies to Prevent Relapse and Encourage Remission

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Remission is a realistic goal for patients with schizophrenia, and, if sustained remission without relapse can be achieved, then patients may attain functional recovery. With each relapse, recovery can be slowed and the course of illness worsened. The risk of self-harm and harm to others increases with each psychotic episode. The chance of relapse is decreased if pharmacotherapy continues uninterrupted, and one strategy to ensure continuous treatment is using long-acting injectable antipsychotic medications. Achieving remission of schizophrenia is clinically meaningful because, besides symptom control, remission allows for improved vocational and social functioning. Functional recovery without relapse allows patients to return to work, sustain interpersonal relationships, and lead more productive lives. Therefore, achieving the goals of remission and recovery is in the best interest not only of patients with schizophrenia but also of society.

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Clinicians should have 4 goals while treating patients with psychotic symptoms: (1) bring about response, (2) prevent relapse, (3) achieve remission, and (4) eventually attain functional recovery. In the past, symptomatic response and prevention of relapse were reasonable goals, but as treatment strategies have progressed, remission has become a realistic goal for patients with schizophrenia, and, if sustained remission can be achieved, patients may have a better chance of attaining functional recovery. When striving for each of these 4 goals, clinicians should consider how to define the goal, how to measure and assess patient progress toward the goal, what the success rates are, what the predictors of outcome are, and what ideal management strategies would help bring about the desired outcome.

PROVIDING RESPONSE

Generally, *response* to therapy is the clinically meaningful improvement of symptoms.[1] Responsive patients are often still symptomatic and in danger of relapse, and not all responsive patients achieve remission. A patient could have a meaningful response, but still be quite ill. Studies often assess response using a variety of cutoffs on different rating scales; the use of standard cutoffs would help clinicians translate research findings into clinical practice.[2] One suggested criterion[1] for response is a 50% decrease in scores on the Brief Psychiatric Rating Scale or the Positive and Negative Syndrome Scale.

PREVENTING RELAPSE

No consensus about what constitutes *relapse* in schizophrenia (e.g., symptom severity, hospitalization) exists.[1] However, despite various criteria used in studies, a meta-analysis[3] found that second-generation antipsychotic agents were more effective than first-generation antipsychotics for relapse prevention in patients with schizophrenia; the rate of relapse with these newer drugs (16%) was lower than with conventional antipsychotic agents (23%).

Relapse fuels the progression of schizophrenia in the following ways:

- Recovery can be slowed and less complete
- Admission to hospitals is more frequent and health care resources are utilized more
- Illness can become more resistant to treatment
- Risk of self-harm and homelessness is increased
- Regaining previous level of functioning is more difficult
- Self-esteem is lost
- Vocational and social disruptions occur
- Burden on families and caregivers is increased

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Only by receiving treatment strategies that prevent relapse will patients achieve remission and eventually attain functional recovery.

Adherence to Antipsychotic Medications Aids Relapse Prevention

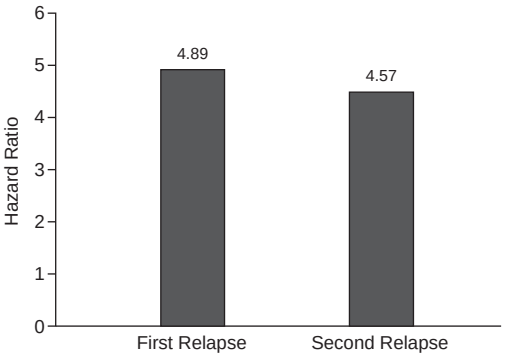
Measures can be taken to prevent relapse. The rate of relapse is decreased if pharmacotherapy continues uninterrupted, even while a patient is asymptomatic. For example, one study[4] in first-episode individuals showed that patients who discontinued pharmacotherapy were almost 5 times more likely to experience relapse than adherent patients (Figure 1). Even partial nonadherence to medication is a barrier to preventing relapse.[5] Nonadherence to medications in patients with psychiatric disorders has been estimated to be as high as 80%.[6] The lifelong nature of schizophrenia necessitates ongoing medication to prevent relapse.[7–9]

Long-acting injectable formulations of antipsychotics provide reliable delivery of medication and help the clinician to accurately assess treatment adherence.[10] Identifying nonadherence or partial adherence after a relapse has occurred does not fully aid the patient because the damage from relapse is already done. One meta-analysis[10] of depot antipsychotics found a significantly lower rate of relapse compared with placebo but not compared with oral antipsychotics. However, the investigators pointed out that patient participants in studies may be more likely to comply with oral medication than typical patients. The depot antipsychotics did show a benefit over oral agents on global outcome. In terms of outcomes, a meta-analysis[11] spanning 2 decades showed that patients treated with depot antipsychotics spent less time in the hospital than patients treated with oral formulations of the same medication. A review by Janicak et al.[12] showed that patients given depot formulation were more likely to avoid relapse than patients given oral formulations. Thus, long-acting injectable atypical antipsychotic medication may aid in the prevention of relapse by assuring adherence as well as tolerability and can also aid clinicians in measuring response by eliminating any uncertainty regarding adherence.

Misconceptions About Depot Antipsychotic Medications

Misconceptions associated with long-acting injectable antipsychotic formulations include the belief that they are not a standard treatment, that they are too invasive, or that they give patients the sense of being controlled. These medications are often viewed by clinicians as only to be used if a patient has repeatedly demonstrated nonadherence to oral medications. Also, many clinicians and patients alike hold the misconception that the conversion from an oral formulation to a depot formulation is complicated and difficult to manage.

Figure 1. Stopping Medication as a Predictor of a Relapse in Patients With a First Episode of Schizophrenia or Schizoaffective Disorder[a]



[a]Data from Robinson et al.[4]

However, research[13] has shown that many patients prefer long-acting injectable antipsychotics to oral formulations of the same pharmacotherapies. Receiving an occasional injection can be more convenient than taking oral medications on a daily basis. Because the injections are given in a clinical environment, the clinician is immediately aware of patient nonadherence and can differentiate lack of efficacy from problems owing to nonadherence. First-pass metabolism complications can be avoided because the medicine is given by injection. Clinicians are better able to identify the lowest effective dose for each individual patient because plasma drug levels are more predictable and stable owing to the route of administration.[10] In addition, because these formulations are long-acting, no abrupt loss of efficacy occurs if a dose is missed.

ACHIEVING REMISSION

Achieving sustained remission is a critical step toward attaining recovery and wellness. Remission provides lasting control of symptoms and decreases the risk of self-harm and harm to others. Long-term outcome will be facilitated by remission rather than by response. The goal is for patients to reach the point at which they have few, if any, symptoms. *Stability* and *remission* are not synonymous because a stable patient may still be very symptomatic and may still have room for further response to pharmacologic interventions.[14] Remission and functional recovery are in the best interest not only of patients with schizophrenia but of families, communities, and society as a whole.

In the past, remission was not considered a realistic goal for many patients with schizophrenia and was not well defined. Treatment advances led to increasing the possibility of remission, and criteria to define remission were needed. Ideal criteria for remission should be attainable and relatively easy to measure, relate to diagnostic

criteria, be applicable throughout the patient's life, employ a time component, and support an alignment of views among the patient, caregiver, and clinician. Having a clinically viable definition of remission will improve research design and interpretation, allow for accurate comparison across clinical trials, and result in more effective psychotherapeutic and pharmacologic interventions.

In 2005, the Remission in Schizophrenia Working Group[15] developed criteria for symptomatic remission in schizophrenia. The criteria proposed a score of mild or less on selected target symptoms on the Scale for the Assessment of Negative Symptoms, the Scale for the Assessment of Positive Symptoms, the Positive and Negative Syndrome Scale, or the Brief Psychiatric Rating Scale to determine remission, quantified as lasting for at least 6 months. Leucht et al.[16] suggested that remission according to these criteria is an achievable goal. Among completers of 7 antipsychotic trials, 41% of subjects met the severity component of the remission criteria at 4 weeks, and 52% met both the time and severity components at 1 year.

ATTAINING RECOVERY

If relapse is prevented, remission can be achieved and remission can facilitate recovery. *Recovery*, in general, refers to sustained asymptomatic functioning without relapse. Patients who have recovered can return to work, school, or homemaking and maintain meaningful interpersonal relationships.[17] Investigators at the University of California at Los Angeles (UCLA) developed criteria for recovery from schizophrenia.[18] The UCLA recovery criteria comprise the following 4 domains: symptom remission, appropriate role functioning, ability to perform day-to-day living tasks without supervision, and engagement in social interaction. Improvement in each domain must be sustained concurrently for at least 2 years. Because the criteria include the time component of 2 years, any patient who relapses must essentially begin again. Therefore, minimizing relapse is a critical step in facilitating recovery.

Robinson et al.[17] used the UCLA criteria to measure recovery among first-episode patients with schizophrenia or schizoaffective disorder. After 5 years, 13.7% of patients had met the criteria for recovery for 2 years or more. In a reanalysis[19] of an influential older study, about 12% to 15% of patients with schizophrenia recovered. Therefore, although much improvement in recovery rates is needed, recovery should be viewed as an attainable goal.

CONCLUSION

Remission and recovery are realistic goals for patients with schizophrenia. To help patients achieve and sustain remission, clinicians must be sure that their patients are receiving effective medications and are adhering to those medications. One strategy to facilitate adherence is the use of long-acting injectable antipsychotic medications. Clinicians may benefit from the development of practical criteria to define remission and recovery. If sustained remission can be achieved, then clinicians should be able to guide more patients to recovery.

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