Medication Adherence and Relapse in Recent-Onset Psychosis

Psychotic exacerbation is undesirable for any patient, but it is particularly important to prevent psychotic exacerbations for recent-onset patients. Early relapse may disrupt important life tasks typically accomplished during adolescence or early adulthood, such as completing schooling, starting a career, and establishing social relationships outside one's family of origin. In this issue of the *Journal*, Subotnik et al. (1) present the results of their analyses of the association of medication nonadherence and symptom exacerbation among patients with recent-onset schizophrenia spectrum disorders. Of particular note, even mild nonadherence, defined as compliance with only 50%–75% of a prescribed oral antipsychotic for 2 consecutive weeks or longer, was associated with a clinically meaningful increased risk of psychotic exacerbation.

Strengths of the study include careful longitudinal assessment of symptoms and adherence (using multiple measures, including blood levels) over an 18-month follow-up period. As with all studies, this study has limitations. Reflecting the difficulty of recruiting recent-onset patients, only 49 subjects were included. Further, there remains the possibility that nonadherence is an early stage of relapse in some patients. For such patients, nonadherence may not be a cause but a consequence of relapse. Finally, subjects who were judged to have substance abuse that would be a prominent factor in the course of illness were excluded from study participation. Nonetheless, including substance use during the follow-up period in the analyses would have strengthened the findings, given the potential of substance misuse to precipitate psychotic relapse.

"First-episode patients are susceptible to relapse from even partial nonadherence to medication treatment."

Considered as a whole, the data provided by Subotnik et al. further the evolution of our understanding of the antipsychotic maintenance treatment needs of patients with recent-onset schizophrenia spectrum disorders. Data (summarized in Table 1) from placebo-controlled, maintenance treatment trials for first-episode schizophrenia have been available since the 1980s. All trials showed a substantial advantage for active medication compared with placebo for prevention of relapse, despite differences in key aspects of study design (e.g., stability of response before randomization, definition of relapse) that contributed to substantial variability in the reported rates of relapse across studies. Maintenance studies with different methodologies (2–4) have also demonstrated the advantages of maintenance medication. Despite these data, clinicians have often been wary of strong recommendations for maintenance treatment, possibly because of an understandable reluctance to tell young patients that they have a persistent illness, much less one that might require indefinite treatment. The data from Subotnik et al. move us beyond our previous evidence base—that episode patients are susceptible to relapse if maintenance medication is totally withdrawn—to an understanding that first-episode patients are susceptible to relapse from even partial nonadherence to medication treatment. From a treatment perspective, first-episode schizophrenia has gone from being considered a disorder that may not need maintenance treatment to a disorder requiring high degrees of adherence to maintenance treatment in order to prevent relapse.

TABLE 1. Placebo-Controlled Maintenance Trials With First-Episode Schizophrenia Patients

Study	Follow-Up Period	Relapse Rate	
		Placebo (%)	Maintenance Medication (%)
Kane et al. (7)	1 year	41	0
Crow et al. (8)	2 years	62	46
Scottish Schizophrenia Research Group (9)	1 year	57	0
Hogarty and Ulrich (10)	2 years	64	43
Chen et al. (11)	1 year	79	41

The challenge to the field is how to help our recent-onset patients obtain this needed level of adherence. Many of the factors (e.g., lack of insight, severe positive symptoms) associated with nonadherence by multiepisode patients are applicable in early-phase patients. However, several factors may make enhancing adherence by recent-onset patients more challenging. Recent-onset patients are young, and young people as a group generally have difficulty with the concept that they could have a serious illness or potential substantial limitation to their lives. Further, continuance of a maintenance treatment involves acceptance of current side effects for potential avoidance of future return of symptoms. Recent-onset patients and their family members lack experience with the adverse consequences of repeated psychotic relapses. Direct experience of side effects but lack of direct experience of the benefits of preventive treatment may skew patients' and their families' assessment of the relative benefits of maintenance antipsychotic treatment.

We currently lack a strong evidence base for strategies to overcome these obstacles. Clinicians who treat recent-onset patients have long known that families can be enlisted to assist with medication adherence. This family-provided version of supervised medication administration is often effective but may exacerbate tension within some families and is often not sustainable by families for long periods. Embedding medication treatment within a comprehensive treatment program providing a variety of services may assist engagement in treatment and adherence, and such approaches are now being tested in the NIMH research project RAISE (Recovery After an Initial Schizophrenia Episode). Although a logical approach to enhancing adherence, data from the Subotnik et al. study suggest that comprehensive treatment programs probably will not solve the nonadherence problem. All subjects examined by Subotnik et al. were participants in a research study and received individual case management and therapy in addition to medication treatment. Despite subjects being cooperative enough to participate in a research study and being treated in the enriched environment available through research participation, only 32% were fully adherent to antipsychotic medication during the follow-up period.

Another potential intervention to maintain adherence is the use of long-acting formulations of antipsychotics with recent-onset patients early in the course of treatment before nonadherence becomes established. Long-acting formulations eliminate the covert nonadherence that can occur with oral formulations. Knowing that patients are nonadherent allows for discussions between patients and their families and clinicians about the patient's choice to suspend medication treatment and about making appropriate plans. Long-acting formulations have advantages that may be especially relevant with recent-onset patients. Young patients frequently do not wish to have their peers know that they are receiving medication and may live in situations, such as dormitories, that limit the ability to comply with oral medications without detection. Injectable medications can enhance confidentiality, since they only have to be taken within a health facility. Because recent-onset patients tend to be responsive to monotherapy with antipsychotics, they are more likely than multiepisode patients to only require injections, without supplementation with oral medications. Of specific interest in light of the data from the Subotnik et al. study, patients who accept injections are fully adher-

ent in contrast with the partial adherence common with oral formulations. Preliminary data for long-acting formulations of newer antipsychotics suggest promise with these strategies. Two studies (5, 6) have demonstrated that agreement to injections can be obtained with a substantial percent of recent-onset patients. Weiden et al. (6) found that medication adherence, measured by time to a 2-week medication gap, was significantly longer in subjects who were randomly assigned to receive and also accepted long-acting risperidone treatment compared with subjects receiving oral maintenance medication. However, the number of recent-onset subjects studied with long-acting antipsychotic strategies remains relatively small, and further study is clearly indicated.

Enhancing long-term medication adherence is a difficult challenge in all branches of medicine. Nonadherence is often caused by multiple factors, and no one intervention can be effective for all patients. The data from Subotnik et al. remind us of the adverse effects of even partial nonadherence and the importance of efforts to develop and test new interventions to enhance adherence by recent-onset patients.

References

1. Subotnik KL, Nuechterlein KH, Ventura J, Gitlin MJ, Marder S, Mintz J, Hellemann GS, Thornton LA, Singh IR: Risperidone nonadherence and return of positive symptoms in the early course of schizophrenia. Am J Psychiatry 2011; 168:286–292
2. Robinson D, Woerner MG, Alvir JMJ, Bilder R, Goldman R, Geisler S, Koreen A, Sheitman B, Chakos M, Mayerhoff D, Lieberman JA: Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry 1999; 56:241–247
3. Gitlin M, Nuechterlein K, Subotnik KL, Ventura J, Mintz J, Fogelson DL, Bartzokis G, Aravagiri M: Clinical outcome following neuroleptic discontinuation in patients with remitted recent-onset schizophrenia. Am J Psychiatry 2001; 158:1835–1842
4. Wunderink L, Nienhuis FJ, Sytema S, Slooff CJ, Knegtering R, Wiersma D: Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. J Clin Psychiatry 2007; 68:654–661
5. Emsley R, Medori R, Koen L, Oosthuizen PP, Niehaus DJ, Rabinowitz J: Long-acting injectable risperidone in the treatment of subjects with recent-onset psychosis: a preliminary study. J Clin Psychopharmacol 2008; 28:210–213
6. Weiden PJ, Schooler NR, Weedon JC, Elmouchtari A, Sunakawa A, Goldfinger SM: Long-acting injectable risperidone vs continuation on oral atypical antipsychotics for first-episode schizophrenia patients: initial RCT adherence outcomes. J Clin Psychiatry 2009; 79:1397–1406
7. Kane JM, Rifkin A, Quitkin F, Nayak D, Ramos-Lorenzi J: Fluphenazine vs placebo in patients with remitted, acute first-episode schizophrenia. Arch Gen Psychiatry 1982; 39:70–73
8. Crow TJ, MacMillan JF, Johnson AL, Johnstone EC: A randomized controlled trial of prophylactic neuroleptic treatment. Br J Psychiatry 1986; 148:120–127
9. Scottish Schizophrenia Research Group: The Scottish First Episode Schizophrenia Study, VII: two-year follow-up. Acta Psychiatr Scand 1989; 80:597–602
10. Hogarty GE, Ulrich RF: The limitations of antipsychotic medication on schizophrenia relapse and adjustment and the contributions of psychosocial treatment. J Psychiatr Res 1998; 32:243–250
11. Chen EY, Hui CL, Lam MM, Chiu CP, Law CW, Chung DW, Tso S, Pang EP, Chan KT, Wong YC, Mo FY, Chan KP, Yao TJ, Hung SF, Honer WG: Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomized controlled trial. BMJ 2010; 341:c4024

DELBERT G. ROBINSON, M.D.

Address correspondence and reprint requests to Dr. Robinson, The Zucker Hillside Hospital, Glen Oaks, NY 11004; drobinso@nshs.edu (e-mail). *Editorial accepted for publication December 2010 (doi: 10.1176/appi.ajp.2010.10121736).*

Dr. Robinson has received grant support from Bristol-Myers Squibb and Janssen. Dr. Freedman has reviewed this editorial and found no evidence of influence from these relationships.