Guidelines for the Use of Long-Acting Injectable Atypical Antipsychotics

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the teleconference "Guidelines for the Use of Long-Acting Antipsychotics," held September 11, 2003.*

This teleconference was chaired by ***John M. Kane****, M.D., Albert Einstein College of Medicine, New York, and the Department of Psychiatry, The Zucker Hillside Hospital, North-Shore–Long Island Jewish Health System, Glen Oaks, N.Y. The faculty were* ***Robert R. Conley****, M.D., Maryland Psychiatric Research Center, Baltimore;* ***Samuel J. Keith****, M.D., Department of Psychiatry, University of New Mexico School of Medicine, Albuquerque;* ***Henry A. Nasrallah****, M.D., Department of Psychiatry, University of Cincinnati Medical Center, Ohio; and* ***Martin Turner****, M.B., B.S., MacKinnon House, Stobhill Hospital, Glasgow, Scotland.*

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John M. Kane, M.D., opened the meeting by addressing the need for guidelines on the use of long-acting injectable atypical antipsychotics. For about 40 years, some of the conventional antipsychotics, which include chlorpromazine, fluphenazine, and haloperidol, have been available in long-acting injectable formulations for the long-term treatment of schizophrenia. In 1989, clozapine became the first atypical antipsychotic to be approved by the U.S. Food and Drug Administration (FDA). However, until recently, none of the atypical antipsychotics—which also include aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone—have been available in injectable formulations. Since June 2002, ziprasidone has been available in the United States as a rapid-acting injectable formulation for the treatment of acute agitation in schizophrenia. In October 2003, risperidone became the first atypical antipsychotic to be approved by the FDA in a long-acting injectable formulation for the long-term treatment of schizophrenia.

The development of a long-acting injectable atypical antipsychotic has occurred so recently that many clinicians know little about the benefits and use of this type of antipsychotic. The guidelines presented at this meeting addressed the potential indications and methods for switching to a long-acting injectable atypical antipsychotic as well as strategies for monitoring and managing incomplete response, relapse, adverse effects, and comorbid conditions.

Medication Compliance in Schizophrenia

Samuel J. Keith, M.D., began by describing the extent of the problem with incomplete medication compliance and how switching to a long-acting injectable atypical antipsychotic may increase compliance.

Prevalence of Partial Compliance

Dr. Keith noted that although people in developed countries are used to taking a pill for most medical conditions, nearly everyone has difficulty completely adhering to a medication regimen. Partial compliance is a problem particularly for patients who must take medication over the long term. In studies of compliance with treatment for chronic medical illnesses, rates of compliance were only 25% for patients with diabetes,[1] 67% for those with rheumatoid arthritis,[2] and 53% for those with hypertension.[3]

Like these medical conditions, schizophrenia requires long-term medication treatment, and missing doses of an antipsychotic is common among patients with the illness. In a 1-year study[4] of prescription refill rates, only 50% to 55% of outpatients with schizophrenia or another psychotic disorder were refilling their prescriptions as directed.

Dr. Keith stated that both patients and physicians underestimate the degree of patients' partial compliance with antipsychotic treatment. Patients

might be unaware of how often they miss medication doses. In one study,[5] 67.5% of patients said that they had taken every dose, but only 10.3% had not missed a dose according to pill count.

Clinicians also tend to be overly optimistic when predicting compliance. In a study by Byerly et al.,[6] clinician ratings of patients' willingness to comply with therapy was compared with the number of times per day that patients opened their pill bottles, as measured by electronic Medication Event Monitoring System (MEMS) pill bottle caps. Clinically meaningful compliance was assessed at 3 monthly visits; patients who did not meet compliance criteria at any of the 3 visits were considered or predicted to be noncompliant. If, based on MEMS cap assessment, patients had opened their pill bottles at least 70% of the times that they were supposed to, they were considered compliant. Patients who clinicians thought were passively accepting of or participating in therapy (i.e., were not reluctant or did not refuse to take medication) were predicted to be compliant. By physician evaluation, 95% of patients were predicted to be compliant with treatment, but by MEMS cap measurement, only 38% were actually compliant.

Some physicians have erroneously assumed that compliance rates have greatly improved with the availability of atypical antipsychotics. However, evidence shows little difference among patients taking either conventional or atypical antipsychotics. An analysis[7] of prescription refill rates for oral antipsychotics showed that comparably low percentages of patients taking conventional antipsychotics (5%) and those taking an atypical antipsychotic (7%) had refilled all prescriptions on time for 1 year. During the year, the number of days that patients were without antipsychotic medication because of failure to refill the prescription was also similar: an average of 110 days for those taking an atypical antipsychotic and 125 days for those taking conventional antipsychotics.

Consequences of Partial Compliance

Dr. Keith noted that in the late 1970s and early 1980s, routine maintenance treatment of schizophrenia involved using extremely high doses of antipsychotics. Because high doses of antipsychotics are often associated with high rates of side effects, the optimal maintenance therapy has evolved in the past couple of decades to using the lowest effective yet tolerable antipsychotic dose.[8] A potential drawback to the newer approach is that patients who take lower doses might be less able to maintain an effective blood drug level when they miss several doses.

Being partially compliant with antipsychotic treatment and, therefore, receiving too little medication can be costly to the patient. Dr. Keith cited studies that detail the potential consequences of partial compliance, including relapse, hospitalization, and suicidal behavior. For example, in a study[9] of 104 first-episode patients with schizophrenia or schizoaffective disorder, not taking medication increased patients' risk for a first relapse nearly 5 times.

Dr. Keith noted that for prevention of relapse, continuous antipsychotic therapy has a higher success rate than vigorous targeted antipsychotic treatment. Carpenter and colleagues[10] compared the effectiveness of targeted versus continuous antipsychotic therapy in a 2-year trial in 116 patients with schizophrenia. The number of times that symptoms or functioning worsened was greater for patients receiving targeted therapy (4.2) than for patients receiving continuous therapy (2.6).

The severity of relapse can also increase when patients miss antipsychotic doses. Johnson et al.[11] evaluated the frequency and severity of relapse in 116 patients with schizophrenia who had been stable for 12 to 48 months. At the 12-month follow-up, more patients who discontinued treatment (65%) had experienced a relapse than controls who continued antipsychotic medication (16%). The patients who discontinued medication had more antisocial behavior, suicidal behavior, and hospitalizations. The long-term consequences of relapse were also greater for patients who had discontinued medication. For example, differences in work functioning were seen among the subgroup of patients who had relapsed but were stable at the 18-month follow-up: one third of the patients in this subgroup who had discontinued medication had poorer work functioning than those who had continued antipsychotic therapy.

Relapse associated with incomplete antipsychotic compliance can be so severe that patients require hospitalization. Grogg and coworkers[12] evaluated the effect of antipsychotic compliance on hospitalization rates in patients with schizophrenia or bipolar disorder who participated in a Medicaid program. The 2655 patients with a compliance rate less than 80% were 49% more likely to be hospitalized than the 5065 patients with a compliance rate between 80% and 125% (some patients had more medication available than they were prescribed, e.g., they refilled prescriptions early).

In another study of patients with schizophrenia in a Medicaid program, Kozma and Grogg[13] evaluated the effect of the number of days without medication on hospitalization rates in a 1-year period. Of the 4325 patients, 92.4% were without antipsychotic medication for at least 1 day. Analysis showed that about 6% of the patients who never missed a refill were hospitalized. However, the hospitalization rate was almost 2 times greater in the group of patients who had a maximum medication use gap of (i.e., were without medication for) 1 to 10 consecutive days during the 1-year period, and the rate steadily increased as the medication use gap increased.

When patients miss several doses of their antipsychotic medication, their risk for suicidal behavior increases. In a study[14] of 603 patients who were taking atypical antipsychotics, individuals who missed 30 or more days of treatment (based on prescription refill rates) were at 4 times greater risk for

attempting suicide than individuals who did not have interruptions in their treatment.

Role of Long-Acting Antipsychotics in Improving Compliance

Dr. Keith concluded that the high rates of relapse,[9,11] hospitalization,[12,13] and suicidal behavior[14] associated with untreated schizophrenia indicate that continuous antipsychotic treatment is the most likely contributor to successful outcome. Generally, patients with schizophrenia are willing to take an antipsychotic but have difficulty complying with their medication regimens because of human nature and the nature of the illness. Therefore, a long-acting injectable medication that patients do not have to take daily might increase compliance and substantially improve patients' symptoms. Dr. Keith pointed out that a long-acting injectable formulation will improve adherence and outcomes only if patients are willing to come to injection appointments and receive the medication.

For those patients who agree to take a long-acting injectable antipsychotic, the formulation has several benefits, which Dr. Keith highlighted. Patients will not have to take medication daily. They will be able to share the burden of compliance with clinic staff who can remind them in advance of injection appointments. Injections, unlike oral medication, allow the patient and physician to easily and immediately know whether the patient has received medication as scheduled. When the patient misses a dose, the clinician can intervene to remind the patient about the missed appointment and the importance of continued antipsychotic therapy for schizophrenia. If patients' compliance improves, they are likely to have fewer relapses and less suicidal behavior, which will result in a better quality of life.

Conclusion

Dr. Keith concluded by saying that long-acting injectable medications were created for long-term illnesses such as schizophrenia. The symptoms of schizophrenia, medication side effects, and inconsistent treatment can make the tasks of daily life difficult. If patients miss even a few doses of their antipsychotic, they may experience a return of symptoms and, therefore, an interruption in their education, jobs, and social lives.

The combination of the efficacy and favorable tolerability profile of an atypical, or newer-generation, antipsychotic and the benefits of a long-acting injectable formulation is an important step forward in the treatment of schizophrenia.

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For Whom and When a Long-Acting Injectable Atypical Antipsychotic Might Be Appropriate

Dr. Kane addressed which patients with schizophrenia should be considered for long-acting injectable atypical antipsychotic treatment and when the therapy should be initiated.

Psychiatrists' Perception of Long-Acting Injectable Medication

Dr. Kane pointed out that psychiatrists' view of long-acting injectable drugs greatly influences how often they will prescribe these medications for their patients.

The current view of long-acting injectable medication. Psychiatrists generally view long-acting injectable medications as a therapy that would benefit only a small subgroup of patients. Clinicians traditionally consider long-acting injectable medication only after an individual has repeatedly demonstrated difficulty with adhering to an

oral medication regimen and has, therefore, had several relapses.

A new approach to long-acting injectable medication. Dr. Kane said that clinicians' approach should be to consider any patient who is a candidate for long-term antipsychotic treatment as a candidate for long-acting injectable antipsychotic therapy. Clinicians should ask, "Why wouldn't this patient be a candidate for a long-acting antipsychotic?" rather than "Why would this patient be a candidate?" Although clinicians will not conclude that every patient should receive long-acting injectable medication, patients should not have to endure several relapses before being considered for long-acting medication. The goal of therapy should be to prevent a relapse from ever occurring.

A greater risk of relapse is found in patients who have poor compliance than in patients who regularly take their medication as prescribed.[1] Therefore, if long-acting injectable antipsychotic treatment helps patients improve their compliance, the therapy might also reduce patients' risk for relapse.

Dr. Kane cited the risk for relapse and other impairment in an illustration of why long-acting injectable medication should be considered for all patients with schizophrenia. Suppose that a group of physicians were invited to a consensus conference at which treatments for a nonpsychiatric illness were being evaluated. Available data suggest that the disease is associated with the following: increased mortality, including a suicide rate of about 10% and a higher rate of death from accidents than in the general population; a 1-year relapse rate of about 70% among first-episode and multiple-episode patients who are untreated; and nonadherence rates ranging from 20% to 60%. For this disease, would the experts recommend the use of a long-acting injectable medication if it were available and as safe and efficacious as oral treatment?

According to Dr. Kane, most clinicians would recommend a long-acting injectable treatment for such a nonpsychiatric disease with little hesitation. He said that in psychiatry, however, clinicians are often reluctant to recommend long-acting medication. They worry about individual autonomy and the uncertainty about how diseases that affect the brain influence behavior and decision-making. But psychiatrists must also remember that schizophrenia is associated with all of the risks mentioned above, including high mortality,[2,3] relapse,[4] and nonadherence rates.[5] Therefore, clinicians need to change the treatment paradigm for schizophrenia and evaluate the suitability of a long-acting injectable antipsychotic for every patient with the illness.

Patients Who Might Benefit From a Long-Acting Injectable Atypical Antipsychotic

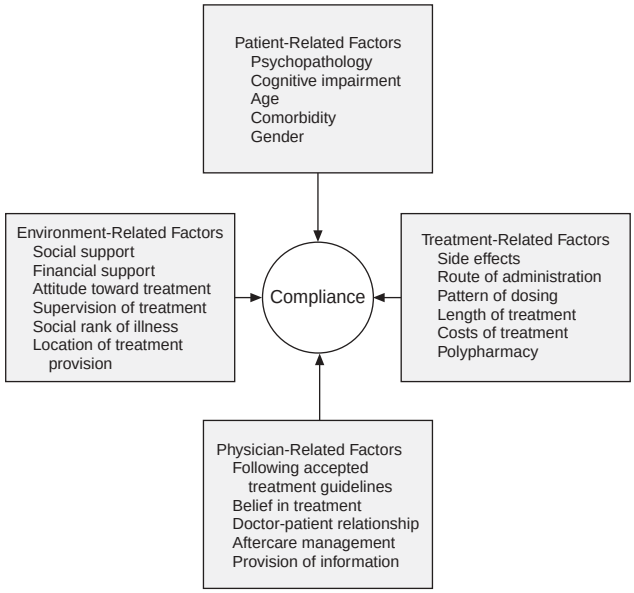
Dr. Kane stated that many stable patients with schizophrenia may benefit from long-acting injectable atypical antipsychotic treatment. However, long-acting injectable medication would be inappropriate monotherapy for patients suffering from acute symptoms because these drugs take weeks to reach therapeutic levels, about 3 weeks for long-acting risperidone.[6] Among stable patients with schizophrenia, those who are unable to tolerate the oral formulation of the drug should never be considered for the long-acting injectable formulation. For many other groups of stable patients, several of which Dr. Kane described specifically, a long-acting injectable atypical antipsychotic may be an optimal treatment.

Patients with a recent onset of schizophrenia who require long-term treatment. Long-acting antipsychotics are generally associated with better compliance rates than oral formulations, and the continuous therapeutic blood medication level attained with good compliance may prevent relapse. Unfortunately, patients who have been recently diagnosed with schizophrenia may have poor compliance rates,[7] which may lead to relapse. Preventing relapse is important for patients who have recently been diagnosed because with each relapse, patients are less and less likely to return to their prior level of functioning. Therefore, if patients begin taking a long-acting injectable atypical antipsychotic soon after the onset of schizophrenia, they may be able to prevent deterioration in their condition.

Partially compliant patients. Although clinicians should continue to consider using a long-acting injectable antipsychotic for individuals who have clearly demonstrated great difficulty adhering to a medication regimen, clinicians must also recognize that most patients with schizophrenia have some difficulty adhering to medication on a regular basis. Unfortunately, clinicians generally overestimate the ability of the average patient to adhere to medication. The result is that health care professionals in general and psychiatrists in particular invest more time and resources in treating acute relapses or symptom exacerbations, which can lead to rehospitalization, than in planning for community treatment or ambulatory care that could prevent relapses from happening. Relapse is more likely to be avoided if clinicians consider every patient to be at risk for noncompliance and take measures, such as prescribing long-acting medication, to encourage compliance in all patients.

Patients who are not completely adherent can be hard to identify because they generally do not actively refuse to take medication. To identify which patients are at greater risk for noncompliance, clinicians can look for any ambivalence about taking medication and a variety of other factors identified by researchers (Figure 1).[8] Nonadherence may be caused by patients' level of insight into their illness and understanding of the benefits of medication as well as their motivation to no longer experience the symptoms of schizophrenia. Other factors that may have a negative impact on patients' compliance include cognitive impairment, poor social support, insufficient psychoeducation, and adverse effects.

Figure 1. Factors Influencing Patients' Medication Compliance[a]



[a]Reprinted with permission from Fleischhacker et al.[8]

Because several factors may play a role in any individual's compliance, physicians can have difficulty identifying and addressing all the issues contributing to a particular patient's nonadherence. Although the use of a long-acting injectable antipsychotic will not completely eliminate partial compliance, the treatment regimen will help clinicians identify when noncompliance occurs so that they can work with patients to solve the problem.

Patients with substance use disorders. About 60% of patients with schizophrenia may also have substance abuse or dependence.[9] Because substance use disorders are associated with high rates of noncompliance[10] and relapse,[11] patients with these illnesses might be good candidates for long-acting injectable atypical antipsychotic treatment.

Aggressive or violent patients. About 10% of individuals with schizophrenia in developed countries exhibit aggressive or violent behavior toward other individuals.[12] Patients with schizophrenia may also inflict self-harm, as evidenced by a suicide rate of about 10%,[13] and the risk for suicidal behavior may increase when patients are not taking medication.[14] A long-acting injectable atypical antipsychotic may help these patients by providing continuous antipsychotic coverage and therefore reducing symptom exacerbations that lead to aggressive or violent behavior.

Patients who experience or are at risk for several or severe side effects with another antipsychotic. Switching to a long-acting injectable atypical antipsychotic may be beneficial for some patients who have had substantial side effects while taking another antipsychotic. For example, some patients have a good symptomatic response to oral risperidone but experience intolerable side effects. These patients may be able to stay on risperidone treatment and reduce their side effects by switching to the long-acting injectable formulation, which appears to be associated with a lower incidence of some side effects such as insomnia and extrapyramidal symptoms (EPS) than the oral formulation.[15,16]

Similarly, some patients prefer and respond well symptomatically to depot conventional antipsychotic therapy but experience intolerable adverse events such as EPS. These patients may be able to switch to long-acting injectable atypical antipsychotic treatment and maintain the benefits of long-acting injectable therapy while reducing their side effect burden.[17]

When Long-Acting Injectable Atypical Antipsychotic Therapy Should Be Initiated

Dr. Kane emphasized that long-acting injectable atypical antipsychotic therapy should be initiated once patients' schizophrenic symptoms are under control. Patients who are experiencing an acute exacerbation of symptoms will not benefit from starting long-acting injectable atypical antipsychotic therapy because a long-acting injectable drug will take weeks to reach therapeutic levels. Once patients are stable, clinicians can discuss long-acting injectable atypical antipsychotic therapy as part of a long-term treatment plan to prevent future relapse. Recognizing that schizophrenia is a chronic illness and understanding the therapeutic strategy may help patients accept treatment.

Patients who are being treated in an outpatient setting can begin treatment after their symptoms are stabilized. For patients who are hospitalized for an acute episode of schizophrenia, the first long-acting atypical antipsychotic injection can be given either in the hospital or in an outpatient facility.

In hospitalized patients, according to Dr. Kane, clinicians should consider initiating a long-term treatment plan with a long-acting atypical antipsychotic before the patient leaves the hospital. This approach allows the patient's response to the first injection of the drug to be closely monitored. Another advantage is that patients will have to adjust to only a new clinician when they leave the hospital, instead of a new clinician and a new treatment. Some patients may be reluctant when a physician who was not involved in their inpatient care wants to switch them from the oral formulation that helped them get better to a different medication.

Dr. Kane stressed that regardless of when the first long-acting atypical antipsychotic injection is given, the clinician should address both the acute and the long-term medication plans. To prevent treatment-related surprises, clinicians should tell hospitalized patients what will happen not only in the hospital but also in the outpatient setting. For example, the clinician can explain that he or she will use an oral antipsychotic for the first several weeks in the hospital and that staff at an outpatient clinic will administer an injectable form of medication over the long term, probably starting in the second or third month after the patient is discharged. If the first injection is given in the hospital, the clinician should tell the patient that the second injection will be administered 2 weeks later by a clinician at an outpatient clinic.

Conclusion

Dr. Kane ended his presentation by confronting misconceptions about who may benefit from long-acting injectable antipsychotic treatment. He said that the image of long-acting injectable treatment needs to be changed.

Physicians are correct in thinking that a primary benefit of these medications is identifying, and possibly improving, compliance. However, clinicians should not focus on only the small group of patients who have clearly and repeatedly demonstrated nonadherence. Clinicians should recognize that the average patient will have difficulty completely adhering to—although generally will not willfully refuse—a medication regimen. Adherence can be improved if physicians develop a strong therapeutic alliance and communicate well with patients, but these steps cannot eliminate adherence problems. Therefore, clinicians should also take advantage of the compliance benefits that long-acting injectable medication can provide.

Once clinicians realize the potential benefits of long-acting medication, they must convince their patients that the therapy should be used. According to Dr. Kane, the obstacle to long-acting injectable therapy is often not the patient but the doctor's assumption that the patient will resist treatment. Clinicians often assume that patients will be hesitant to receive an injection because of the pain involved. However, research suggests that long-acting risperidone injections are associated with only a low incidence of pain that decreases after the first injection.[6] Dr. Kane stressed that clinicians should give the average stable patient with schizophrenia the opportunity to decide whether he or she is willing to accept treatment with a long-acting injectable medication and to experience the associated benefits on compliance and symptom improvement.

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How to Switch Patients to Long-Acting Risperidone From Another Antipsychotic

In his presentation, Martin Turner, M.B., B.S., gave guidelines for switching patients from another antipsychotic to long-acting risperidone treatment.

Discussion With Patients

Dr. Turner said that the starting point for switching patients to long-acting risperidone is discussion with the patient and caregiver about why the patient might benefit from a change in medication and/or delivery system. Explaining long-term outcome, including the risk of relapse, to the patient and setting up a collaborative process for the switch will help patients see the

long-term advantages of taking a long-acting injectable antipsychotic. Clinicians should also detail for each individual patient what he or she might expect to experience during the transition period.

When appropriate, the discussion should be tailored on the basis of the individual's prior medication experience. For example, patients who are switching from another long-acting antipsychotic should know that an obvious reduction in some of the side effects they experienced with a depot conventional antipsychotic might take a while to appear.[1] Patients who have been taking an oral antipsychotic need to be informed that they will continue to take oral medication for the first 3 weeks after their first long-acting risperidone injection while a therapeutic level of the drug builds up in their system.[2]

All patients should be given a time frame for when they might expect to see benefits of long-acting risperidone treatment. Clinicians should stress that small improvements may occur after a few weeks but larger improvements may not appear until several months after the first injection.[3] If patients are prepared to wait, they will be less likely to discontinue the medication before it has had a chance to work.

Patients who are switching from an antipsychotic other than oral risperidone should be advised that they may experience a decrease in sedation because risperidone is associated with a lower incidence of somnolence than some other antipsychotics.[3–5] The reduction in sedation may sometimes result in agitation or insomnia.[3,6] These symptoms should be transient, are generally not indicative of relapse, and can be treated with concomitant medications.

Dr. Turner emphasized that if patients know when improvement in symptoms and reduction of previous side effects may occur as well as what new side effects they may experience, they should be more comfortable and willing to complete the switch to long-acting risperidone treatment.

Table 1. Steps in Switching Patients to Long-Acting Risperidone Treatment

1. If needed, administer a test dose of oral risperidone to rule out idiosyncratic hypersensitivity
2. Determine the best strategy for introducing long-acting risperidone on the basis of the patient's prior antipsychotic therapy (see Table 2)
3. Monitor for and, if needed, treat any residual psychotic symptoms
4. For patients on anticholinergic treatment for extrapyramidal symptoms (EPS) associated with prior antipsychotic therapy, discontinue the anticholinergic if EPS are no longer present
5. Evaluate symptom response after several months, and if needed, lower or raise the dose of long-acting risperidone

Table 2. Strategies for Initiating Long-Acting Risperidone Treatment on the Basis of Prior Antipsychotic Therapy

	Strategy for Patients Switching From	
Issue	Oral Antipsychotic Therapy	Depot Antipsychotic Therapy
Time to start	Immediately	At the time of the next scheduled injection
Initial dose		
For most patients	25 mg/2 wk	25 mg/2 wk
For patients who have demonstrated a clear need for high doses of an antipsychotic	37.5 or 50 mg/2 wk	37.5 or 50 mg/2 wk
Oral coverage	2–3 wk necessary	Generally not needed

Process for Switching to Long-Acting Risperidone

Dr. Turner outlined the steps for switching from another antipsychotic to long-acting risperidone (Table 1). He provided ways to tailor the process on the basis of the individual's symptoms and previous antipsychotic treatment (Table 2).

Test dose of oral risperidone. For patients who have never taken risperidone, a test dose of oral risperidone can be administered to rule out an immediate hypersensitivity to the drug. Dr. Turner pointed out, however, that a patient naive to oral risperidone treatment is highly unlikely to develop a hypersensitivity, especially one that would appear within 48 hours of being introduced to a small dose of the medication. Clinicians should remember that patients' symptomatic response to a test dose of oral risperidone will also not predict their response to long-acting risperidone. Administering a test dose can, however, provide physicians with the confidence that they have ruled out an idiosyncratic reaction to risperidone before giving a patient an injection of the long-acting form of the drug.

Switch from an oral antipsychotic. Patients who are switching from an oral conventional or atypical antipsychotic can begin taking long-acting risperidone immediately. Most individuals should begin with 25 mg/2 weeks of long-acting risperidone, which is the optimum dose for most patients in medication trials.[3,6] Exceptionally, a higher starting dose, 37.5 or 50 mg/2 weeks, may be indicated for individuals who have been taking high doses of another antipsychotic for a long period of time or have demonstrated great risk for relapse with low medication doses.

Regardless of the starting dose, patients switching from oral antipsychotics must receive continued oral coverage for 3 weeks after the first injection of long-acting risperidone, while the injectable medication reaches a therapeutic level.[2] Although patients can substitute oral risperidone if they have been taking another oral antipsychotic, this change is not necessary.[6,7] During the 3 to 6 weeks following the first long-acting risperidone injection, clinicians can gradually taper and discontinue the oral antipsychotic.

Switch from a long-acting injectable typical antipsychotic. Like pa-

tients who are switching from an oral antipsychotic, those who have been taking a long-acting injectable conventional antipsychotic should generally start with 25 mg/2 weeks of long-acting risperidone. Rarely, patients who have a history of requiring high doses of depot conventional antipsychotics (e.g., 200 mg/4 weeks of haloperidol decanoate) should begin with 37.5 or 50 mg/2 weeks of long-acting risperidone.

Data from a recent study[1] suggest that the first long-acting risperidone injection can be given in place of the next scheduled depot conventional antipsychotic injection. This is possibly because the prior long-acting injectable antipsychotic should maintain a therapeutic level in the body for months. Thus, providing oral coverage for the first 3 weeks after the first long-acting risperidone injection is generally not required unless the patient experiences breakthrough symptoms. Together, the patient and clinician can decide whether they think a brief period of oral coverage would be beneficial.

Residual psychotic symptoms and relapse. Dr. Turner stated that how psychotic symptoms should be treated depends on when and for how long they occur.

Psychotic symptoms that appear during the first 3 weeks after the first long-acting risperidone injection, as well as short-term relapse during continued therapy, should be treated with an oral antipsychotic. Raising the dose of long-acting risperidone would be impractical because of the 3-week delay between the adjustment of the injection and the change in the plasma medication level.

If an individual requires sustained oral coverage for residual symptoms after several weeks or months of long-acting risperidone treatment, the clinician may consider raising the dose of the long-acting medication. Doses of long-acting risperidone should be increased in increments of 12.5 mg/2 weeks. Once an increase has been made, clinicians must wait 3 weeks—while the higher dose of the medication is released throughout the body—before determining whether the adjustment has been successful. Therefore, patients should receive at least 2 consecutive injections of the same dose before another adjustment is considered.

Anticholinergic treatment. According to Dr. Turner, patients who switch to long-acting risperidone should discontinue any oral anticholinergic medication if they no longer experience EPS. Patients who have been taking an oral antipsychotic will probably be able to discontinue the anticholinergic within a few weeks. However, patients who have been taking a depot conventional antipsychotic may need to continue anticholinergic treatment for several months while the prior antipsychotic is cleared from the body.

Dose over time. After patients have been taking long-acting risperidone for at least 3 months, clinicians should reevaluate whether a higher or lower dose may be needed. According to clinical experience, Dr. Turner said that individuals who receive long-acting risperidone may be able to lower their dose after 1 or 2 years of treatment. However, there are currently no published results of flexible-dose studies.

Conclusion

Dr. Turner closed with the reminder that patients can be switched to long-acting risperidone from any other antipsychotic, but the previous treatment will determine the switching strategy for the individual patient.

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Monitoring Patients Who Take Long-Acting Risperidone

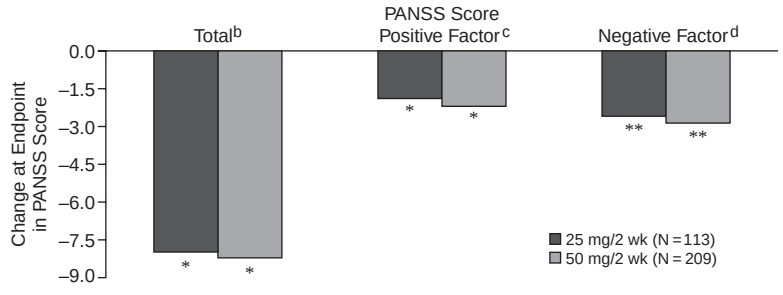
Robert R. Conley, M.D., presented recommendations for monitoring changes in symptoms, quality of life, and adverse events in patients switched to long-acting risperidone.

Schizophrenic Symptoms

Dr. Conley advised clinicians to routinely monitor patients receiving long-acting risperidone for changes in schizophrenic symptoms. He pointed out that standardized rating scales like the Brief Psychiatric Rating Scale,[1] the Positive and Negative Syndrome Scale,[2] and the Clinical Global Impressions-Improvement Scale[3] have been validated in clinical trials. However, he emphasized that clinicians should use the monitoring tools with which they are familiar and comfortable when evaluating symptoms in patients taking long-acting risperidone.

When monitoring patients, physicians should look for signs of potential relapse. Although hospitalizations are important, less impairing symptom

Figure 2. Change at Endpoint in Positive and Negative Syndrome Scale (PANSS) Total and Positive and Negative Factor Scores for Stable Patients Who Were Switched From Another Antipsychotic to Long-Acting Risperidone in a 12-Month Open-Label Trial (Last Observation Carried Forward)[a]



[a]Adapted, with permission, from Fleischhacker et al.[4]
[b]Mean baseline total scores were 61.9 for the 25-mg group and 67.3 for the 50-mg group.
[c]Mean baseline positive factor scores were 16.4 for the 25-mg group and 18.3 for the 50-mg group.
[d]Mean baseline negative factor scores were 17.7 for the 25-mg group and 19.2 for the 50-mg group.
*p < .01 vs. baseline.
**p < .001 vs. baseline.

Table 3. Treatment-Emergent Adverse Events Reported in 5% or More of Patients Treated With Placebo or With 25 or 50 mg/2 Weeks of Long-Acting Risperidone in a 12-Week, Double-Blind, Controlled Trial[a]

		Long-Acting Risperidone	
	Placebo (N = 98)	25 mg (N = 99)	50 mg (N = 103)
Adverse Event	%	%	%
Any adverse event	83	80	83
Agitation	25	15	11
Headache	12	15	22
Psychosis	23	15	10
Insomnia	14	16	13
Anxiety	15	7	6
Rhinitis	8	14	4
Dizziness	6	8	11
Hallucination	5	7	6
Pain	4	10	3
Dyspepsia	2	7	7
Extrapyramidal disorder	3	4	8
Hyperkinesia	4	2	9
Hypertonia	5	4	5
Somnolence	3	5	6
Constipation	1	5	7
Vomiting	6	4	3
Nausea	5	3	4
Coughing	4	5	2
Tachycardia	6	1	4
Weight increase	2	5	4
Fatigue	0	3	7
Diarrhea	3	5	1
Increased salivation	1	6	2
Nervousness	5	2	2
Dry mouth	1	0	7
Injury	6	0	2

[a]Adapted from Kane et al.[7]

worsening can also interfere with patients' lives. For example, people who are living in the community may have to visit the emergency room or contact a mental health provider because their symptoms have returned.

Clinicians should also monitor patients for symptom improvement after they have been taking long-acting risperidone for several weeks. According to Dr. Conley, patients who take long-acting antipsychotics can have a different medication experience than patients taking oral medication. That is, patients who are taking a long-acting medication will potentially maintain a therapeutic plasma drug level at all times. Therefore, patients who have been stable on oral antipsychotic therapy may experience further improvement in schizophrenic symptoms during long-acting risperidone treatment. Patients who switch from an older-generation antipsychotic to the newer-generation long-acting injectable agent may also see improvement.

Regardless of prior treatment, stable patients may experience substantial reductions in schizophrenic symptoms, including positive symptoms such as hallucinations and delusions and negative symptoms such as dysphoria as well as anxiety, disorganized thoughts, and hostility after they switch to long-acting risperidone (Figure 2).[4] Therefore, clinicians and patients should not give up hope that patients who are considered stable can continue to improve.

Adverse Events

Dr. Conley explained that stable patients who switch to a newer-generation long-acting injectable antipsychotic, like those who switch to a first-generation long-acting injectable antipsychotic, may have fewer side effects than they did while taking oral medication.[5] This reduction in side effects may be related to long-acting medications' lower peak plasma concentrations and smaller variations in plasma drug concentrations.[5] For example, data[6] show that long-acting risperidone is associated with lower peak plasma concentrations and smaller variations in peak and trough plasma concentrations than oral risperidone. Therefore, long-acting risperidone may have a more favorable side effect profile than the oral formulation.

However, although the incidence of many adverse effects may be low with long-acting risperidone, some adverse events will occur (Table 3), as they do with any antipsychotic.[4,7] Clinicians should monitor patients on long-acting risperidone therapy for the standard side effects of antipsychotics, including EPS, tardive dyskinesia, weight gain, and prolactin-related side effects. Dr. Conley also stated that physicians should inquire about pain related to injections.

EPS. A number of people who take an antipsychotic will have at least some EPS such as akathisia and parkinsonism.[8] However, EPS are often less common with newer-generation antipsychotics.[8] Furthermore, the incidence and severity of EPS may decrease among patients who switch to long-acting risperidone.[4] All patients taking long-acting risperidone should be monitored for EPS every time they see a clinician. If EPS have subsided, physicians should discontinue any medications used to treat EPS because many of these drugs are anticholin-

ergic medications, which can cause physical and cognitive side effects.[8]

Tardive dyskinesia. Like EPS, tardive dyskinesia is a concern with all antipsychotics but may occur less often with newer-generation drugs.[9,10] Some people who developed tardive dyskinesia while taking another antipsychotic may experience improvement in this condition when they switch to long-acting risperidone.[4] To evaluate any change in tardive dyskinesia, clinicians should monitor patients at least yearly.

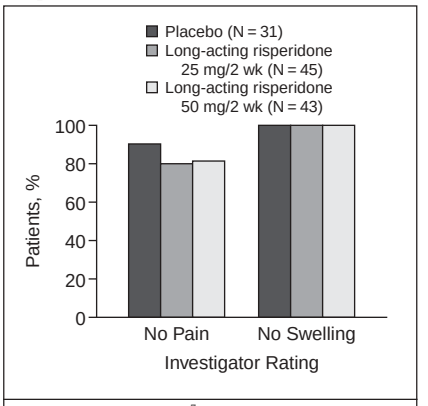
Weight gain. Many older-generation[11] and newer-generation[12] antipsychotics can increase body weight. Although weight gain may be uncommon with long-acting risperidone,[7] patients should be weighed at baseline and routinely thereafter for as long as they receive the drug.

Prolactin-related side effects. High prolactin levels can lead to side effects such as amenorrhea, galactorrhea, gynecomastia, and sexual dysfunction.[13] However, elevated prolactin levels are not always associated with clinically important adverse effects. Although oral risperidone is known to raise prolactin levels,[14] patients who switch from an oral antipsychotic to long-acting risperidone may experience a decrease in prolactin levels.[15] Prolactin-related side effects may be identified through questioning patients.

Pain and difficulty with injections. Some patients may be concerned about receiving injections because of the related pain. Pain has been associated with the older-generation depot preparations,[16] possibly because they are oil-based and generally have to be injected slowly. Injections of the older antipsychotics can also cause cysts or sore spots.[17] To reduce pain, clinicians must remember to rotate at which site they give the injection.

Injections of long-acting risperidone, which are water-based, appear to cause little pain and swelling (Figure 3).[7] In addition, patients in a 12-week trial[7] reported feeling less pain after the sixth injection than after the first injection. Clinicians may be able to reassure worried patients, particularly those who have experienced pain with depot injections, by informing them that they should expect to experience less pain over time.

Figure 3. Percentage of Patients Rated by an Investigator as Having No Pain or Swelling After Receiving Their Sixth Injection of Placebo or Long-Acting Risperidone in a 12-Week Trial[a]



[a]Data from Kane et al.[7]

Another possible effect of older-generation depot antipsychotic preparations is breakthrough EPS on the day of the injection, which is caused by a small amount of free drug released immediately into the patient's system.[18] However, free drug in the preparation and resulting breakthrough EPS may occur less often with long-acting risperidone.[19]

Clinicians should ensure that patients are aware of and monitored for the possible reactions associated with long-acting injectable antipsychotic medication. Patients who are given long-acting risperidone will also benefit from knowing that they are less likely to experience pain, an injection-site reaction, or breakthrough EPS than if they received an older-generation injectable antipsychotic.

Quality of Life

Dr. Conley explained that by reducing psychotic symptoms and adverse events, a change in antipsychotic treatment should lead to a better quality of life for patients. Individuals who receive long-acting risperidone should understand that they can expect to lead a more stable and independent life if their illness is controlled. In a 12-week placebo-controlled trial[20] in 369 patients with schizophrenia, the patients taking long-acting risperidone experienced clinically meaningful improvement in several areas, as measured by the patient-rated Medical Outcomes Study 36-Item Short Form Health Survey (SF-36). They had better general mental health, greater energy, better social functioning, and fewer limitations in their daily roles because of emotional or physical problems.

Monitoring for changes in quality of life should be individualized because each patient has different impairments and abilities. For some patients, simply being able to shop or cook for themselves would be a substantial improvement. Others may want to return to school or work. After identifying what quality-of-life improvements may be expected, the clinician and patient should work together to evaluate the patient's progress.

Conclusion

Dr. Conley emphasized that clinicians should monitor patients on long-acting injectable atypical antipsychotic therapy for changes in schizophrenic symptoms and for adverse events. Controlling these factors can help patients lead better lives.

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Use of Adjunctive Medication in Patients Taking Long-Acting Risperidone

Henry A. Nasrallah, M.D., described some of the situations that may require adjunctive medication in patients taking long-acting risperidone: breakthrough and residual schizophrenic symptoms, comorbid conditions, and side effects.

Breakthrough and Residual Symptoms

Dr. Nasrallah advised clinicians about strategies for managing breakthrough symptoms and residual stress-related psychotic symptoms such as agitation.

Breakthrough symptoms. To quickly control breakthrough symptoms, patients should begin adjunctive treatment with an oral antipsychotic. The temporary supplementation can generally be effective at a low dose. For example, 1 to 3 mg/day of oral risperidone for 2 to 3 weeks may be sufficient to stabilize the patient. If symptoms persist, increasing the dose of or changing the medication used for oral supplementation may be effective.

Because of the pharmacokinetics of long-acting risperidone, raising the dose from 25 mg/2 weeks to 37.5 mg/2 weeks or from 37.5 mg/2 weeks to 50 mg/2 weeks is not a practical strategy for immediate symptom relief. However, increasing the dose of long-acting risperidone in addition to reinstituting oral coverage may be considered. During the first 3 weeks after the first increased dose of long-acting risperidone, the patient will need to continue supplementation with an oral antipsychotic.[1]

Agitation and other stress-related symptoms. Emergence of agitation and other stress-related symptoms such as anger and hostility in otherwise stable patients may be treated with an oral antipsychotic.[2] Severe symptoms may require a clinician's intervention, but stable patients may be able to monitor and treat their transient stress-related symptoms with an oral antipsychotic.

Comorbid Conditions

Comorbid conditions may be the most common reason for adjunctive medication in patients on long-acting injectable atypical antipsychotic therapy, according to Dr. Nasrallah.

Depression, anxiety, and obsessive-compulsive disorder. Many patients with schizophrenia also have depression, anxiety, or obsessive-compulsive disorder (OCD).[3] Depressive and anxiety symptoms may substantially improve with long-acting risperidone.[4] However, some patients with severe forms of these illnesses might require adjunctive therapy. Depression may be treated with one of the many different types of available antidepressants, but anxiety and OCD generally respond best to selective serotonin reuptake inhibitors (SSRIs).[5]

Dr. Nasrallah stressed that the concomitant medication should be chosen carefully to avoid potentially adverse medication interactions. For example, the SSRIs fluoxetine and paroxetine inhibit the metabolism of cytochrome P450 2D6 (CYP2D6),[6] which is involved in the metabolism of risperidone.[7] High doses of fluoxetine or paroxetine may impair patients' ability to clear risperidone from their systems and result in an increased plasma drug level of risperidone and consequently more side effects. Therefore, other SSRIs that have a smaller effect on CYP2D6 such as sertraline, citalopram, and escitalopram may be preferable for patients taking long-acting risperidone.[6]

Manic symptoms. Although atypical antipsychotics including risperidone are generally effective for manic symptoms, bipolar disorder often requires combination therapy.[8] Some patients with schizophrenia and bipolar disorder or with schizoaffective dis-

order may have manic symptoms that require the combination of a mood stabilizer and the long-acting injectable antipsychotic.

At this time, 4 agents are approved by the FDA for mania: lithium, divalproex, olanzapine, and risperidone. Quetiapine has received approval for this indication in some European countries and Mexico and is expected to be approved by the FDA for bipolar mania at the beginning of 2004. The appropriate dose of the mood stabilizer should be chosen on the basis of the patient's symptom severity. For example, the dose for stable patients who experience breakthrough manic symptoms would probably not be as high as that for patients experiencing an acute manic episode.

Side Effects

Side effects may be another indication for the use of adjunctive medication in patients with schizophrenia.

EPS. Long-acting risperidone is associated with low rates of EPS.[9] Furthermore, some patients who have been taking another antipsychotic may have fewer EPS after they switch to long-acting risperidone.[9] However, some patients will experience EPS such as hypokinesia or akathisia for which the clinician should prescribe propranolol (for akathisia) or an anticholinergic (for hyperkinesia).[10]

Sexual dysfunction. The incidence of sexual dysfunction with long-acting risperidone is low.[11] If patients taking 37.5 or 50 mg/2 weeks of long-acting risperidone do experience sexual dysfunction, the dose may be lowered. If lowering the dose is impractical or ineffective, adding a dopamine agonist such as amantadine or bromocriptine may reduce patients' sexual side effects.[10,12,13]

Insomnia. In clinical trials,[9,14] insomnia occurred in about 13% to 22% of patients taking 25 or 50 mg/2 weeks of long-acting risperidone. Insomnia often occurs in the context of a stressor or an episode of anxiety, depression, or bipolar disorder. Therefore, clinicians should determine whether another untreated psychiatric disorder is causing patients' insomnia. If the underlying psychiatric disorder is being adequately treated or insomnia is caused by another factor, patients may be given an oral sedating agent p.r.n. such as zolpidem, 5 or 10 mg q.h.s., or zaleplon, 5 or 10 mg q.h.s.

Conclusion

Dr. Nasrallah concluded by saying that stable patients receiving long-acting injectable atypical antipsychotic treatment may require concomitant medication for residual schizophrenic symptoms, a comorbid condition, or side effects. If clinicians carefully assess the severity of the symptoms and consider potential medication interactions, adjunctive medication treatment can be safely administered.

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Drug names: *amantadine (Symmetrel and others), aripiprazole (Abilify), bromocriptine (Parlodel and others), chlorpromazine (Thorazine and others), citalopram (Celexa), clozapine (Clozaril and others), divalproex (Depakote), escitalopram (Lexapro), fluoxetine (Prozac and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), olanzapine (Zyprexa), paroxetine (Paxil and others), propranolol (Inderal and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), zaleplon (Sonata), ziprasidone (Geodon), zolpidem (Ambien).*

Disclosure of off-label usage: *The chair has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented that is outside U.S. Food and Drug Administration–approved labeling. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.*

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