**Adherence to Antipsychotics: The Long (-Acting Depots) and Short of It**

### Causes and Consequences of Nonadherence in Schizophrenia

There are numerous pharmacological and nonpharmacological options for the treatment of schizophrenia. However, the effectiveness of a pharmacological agent is determined by treatment efficacy, tolerability, and adherence (Lindenmeyer et al., 2009). Although it is true that currently available antipsychotics are often neither as efficacious nor as tolerable as clinicians and patients would hope, improvement in treatment adherence is within the power of the patient and treatment team. Treatment nonadherence is a major issue and is considered to be one of the most important factors affecting relapse in schizophrenia (Ascher-Svanum et al., 2009). Assessing the prevalence of treatment nonadherence is somewhat difficult as the most accurate measures of adherence are less commonly used. For instance, whereas clinicians may estimate that less than 10% of their patients are nonadherent, medication bottle cap computer chip monitoring (a more accurate measure) indicates that more than 50% of patients are nonadherent (Byerly et al., 2007). Patients who are nonadherent with their treatment have a much poorer prognosis than those who are adherent. Each relapse is costly, and the financial burden from treatment received consequent to relapse is responsible for the largest portion of treatment costs in schizophrenia. Patients who relapse accrue annual mental health costs that are as much as 5 times greater than for nonrelapsed patients (Ascher-Svanum et al., 2010), and nonadherence increases external service costs by nearly 3-fold (Olivares et al., 2008).

Gaps of 1–10 days in medication adherence; one-half of nonadherent patients have a poor therapeutic alliance (compared to 29% of adherent individuals) (Olfson et al., 2009). Therefore, it is key that patients are provided with cognitive therapies that help them understand the importance of treatment adherence. One such means for improving adherence involves the use of long-acting injectable depot formulations of antipsychotics.

Comorbid substance abuse is strongly correlated with antipsychotic treatment nonadherence perhaps due to the impaired judgment and reduced motivation associated with intoxication (Llorca, 2008; Perkins et al., 2008). Disorder-related factors such as depressive symptoms, cognitive impairment, and lack of insight are perhaps some of the biggest risk factors for treatment nonadherence (Perkins et al., 2008; Patel et al., 2008). Individuals who are nonadherent or do not seek treatment often cite not believing they have a problem as the reason, reflecting a lack of insight that is unfortunately one of the core symptoms of schizophrenia (Kessler et al., 2001; Patel et al., 2008). Even when patients with schizophrenia do recognize the existence of a problem, many will cease treatment because they want to solve the problem on their own or have uncertainty about where and how to seek treatment (Kessler et al., 2001). A strong therapeutic alliance between the patient and treatment team has been found to be important for medication adherence; one-half of nonadherent patients have a poor therapeutic alliance (compared to 29% of adherent individuals) (Olffson et al., 2000). In fact, beliefs and attitudes toward antipsychotic medications are even more important than side effects in predicting nonadherence (Patel et al., 2008). Therefore, it is key that patients are provided with cognitive therapies that help them understand the importance of treatment adherence (Zygmont et al., 2002). Even adherent patients should be counseled about the consequences of nonadherence as it is not uncommon for previously adherent patients to cease taking their medication once they are feeling better (due to a misconception that treatment is no longer necessary) (Kane, 2006).

### Long-Acting Depot Formulations

While it is clear that nonadherence is a major issue in the treatment of schizophrenia, there are several interventions available for improving treatment adherence. One such means for improving adherence involves the use of long-acting injectable depot formulations of antipsychotics. Compared to oral antipsychotic formulations, depot formulations offer the following benefits: continued assurance that the patient is getting medication, no need to remember to take medication every day, immediate recognition if the patient misses a dose, more predictable pharmacokinetics, and avoidance of first-pass metabolism (Kane, 2006). It has also been predicted that long-acting depot antipsychotics should be associated with less adverse side effects due to bypassing the peak plasma levels that occur daily with oral formulations. There are several depot formulations of both conventional and atypical antipsychotics available, and several more are currently in development (Table 1). The advantage of long-acting formulations over oral antipsychotics has been investigated in depth. Many such studies indicate the superiority of long-acting depot formulations over oral formulations (Leucht et al., 2011; Adams et al., 2001; Bari et al., 2008; Emsley et al., 2008; Rosenheck et al., 2011); however, it is important to note that many of these studies are randomized controlled studies (rather than observational studies) that include patients who are cooperative and have enough illness insight to willingly participate in a study or involve inpatient settings. Such patients are likely more treatment adherent than the general population and may be receiving more intensive supervision (including monitoring of treatment adherence) than is available through usual outpatient care. It is not surprising that such patients may not show any additional benefits from the enhanced adherence (and consequent clinical and functional improvements) afforded by depot formulations (Tiitinen et al., 2011). In support of this idea, poor adherence is why oral antipsychotics often seem to work better in clinical trials than in real-world clinical practice (Patel et al., 2008).
Treatment with a long-acting depot formulation is not as widely used as the data recommend, especially for patients with lack of illness insight, poor adherence, and high recidivism. One possible reason for this underutilization of depot formulations is that they typically cost more than oral antipsychotics; however, this higher expense is offset by the reduction in relapses associated with long-acting injectable antipsychotics (Olivares et al., 2008). Not only is the reduction in relapses economical by reducing costly rehospitalization, relapse prevention also supports recovery efforts for patients living with schizophrenia, potentially allowing them more social integration, employment opportunities, and reduced need for government support. Another potential reason for the underuse of depot antipsychotics is the perception of clinicians that their patients may find long-acting injectable medications less acceptable than oral formulations; however, several studies have shown that patients—even first-episode patients—are accepting of injectable therapy and that depot formulations do not compromise the therapeutic alliance between patient and treatment team and do not negatively impact overall attitudes toward medication (Cañas and Möller, 2010; Weiden et al., 2009).

### Table 1: Long-Acting Depot Antipsychotics

<table>
<thead>
<tr>
<th>Available Long-Acting Depot</th>
<th>Long-Acting Depot in Development</th>
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<tbody>
<tr>
<td><strong>Atypical Antipsychotics</strong></td>
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<tr>
<td>Aripiprazole</td>
<td>4 week formulation in trials</td>
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<tr>
<td>Iloperidone</td>
<td>4 week formulation in trials</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2 weeks</td>
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<tr>
<td></td>
<td>4 weeks</td>
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<tr>
<td>Paliperidone</td>
<td>4 weeks</td>
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<td></td>
<td>12 week formulation in trials</td>
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<tr>
<td>Risperidone</td>
<td>2 weeks</td>
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<tr>
<td></td>
<td>4 week formulation in trials</td>
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<tr>
<td><strong>Conventional Antipsychotics</strong></td>
<td></td>
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<tr>
<td>Fluphenazine</td>
<td>2-3 weeks</td>
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<tr>
<td>Flupenthixol</td>
<td>1-4 weeks*</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>4 weeks</td>
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<tr>
<td>Pimozide</td>
<td>4 weeks</td>
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<tr>
<td>Zuclopenthixol</td>
<td>2-4 weeks*</td>
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</tbody>
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* Not available in the United States

**Adherence Is Only One Factor Affecting Functional Outcome**

The bottom line is that no antipsychotic medication will work to improve clinical and functional measures unless it is actually taken by the patient. The benefits of long-acting depot formulations over their oral counterparts are likely due primarily to their ensured delivery (Leucht et al., 2011). In fact, many of the studies comparing the effectiveness of depot versus oral formulations in clinically controlled settings, where adherence to either formulation is likely higher than for the general population, show improvements in time to rehospitalization, probability of hospitalization, and clinical outcomes (Olivares et al., 2009, Rosenheck et al., 2011) regardless of formulation. Similarly, in terms of atypical versus conventional antipsychotics, one long-term study suggests that although atypical antipsychotics may be more effective at shortening the time to negative-symptom remission and increasing the likelihood of functional recovery compared to conventional antipsychotics, long-term maintenance of either atypical or conventional oral antipsychotic resulted in some improvement in clinical and functional measures (Stahl et al., 2010). These data highlight the importance of adherence to antipsychotic medication, whether it be oral or depot, atypical or conventional. However, adherence is just one step in the road to recovery in schizophrenia. Some level of insight is needed not only for treatment adherence but also for optimal outcomes, especially since currently available antipsychotic treatments are not perfect for remitting the symptoms of schizophrenia or preventing relapse, even when treatment is adhered to. Recognition of having a problem, having the will and desire to cope with and overcome that problem, and setting achievable goals are essential for recovery in schizophrenia (Noiseux and Ricard, 2008; Corrigan, 2006). To this end, psychosocial
interventions, including cognitive behavioral therapies that help patients address and cope with symptoms of schizophrenia and cognitive adaptation therapies to help patients function despite the cognitive deficits associated with schizophrenia, may be essential for optimal recovery in schizophrenia (Velligan et al., 2008; Tarrier, 2010).

References


Kane JM. Utilization of long-acting antipsychotic medication in patient care. CNS Spectr 2006;11(12(suppl 14)):1-8.


