In order for an antipsychotic medication to be effective in real-world clinical practice, it must not only be efficacious (i.e., reduce symptoms) but also tolerable and actually taken by the patient. There is no perfect antipsychotic, and the pragmatic goal is to find a medication that works “well enough,” is tolerated “well enough,” and is one that the patient is willing to adhere to at least most of the time.

Schizophrenia Case - Treatment Adherence in the Face of Side Effects

A 67-year-old patient with extrapyramidal symptoms who is treatment nonadherent
In the following excerpt, Dr. Stephen Stahl and Dr. Andrew Cutler discuss the recent approval of several long-acting injectable depot antipsychotic medications. Included is a question submitted by an NEI member regarding the use of long-acting depot olanzapine. The complete interview between Dr. Stahl and Dr. Cutler, “Contemporary Clinical Treatment of Schizophrenia,” was originally broadcast by NEI in October and November 2010, and is now available as an archived webinar at www.neiglobal.com (Search for “Archived Webinars/Webcasts”).

Dr. Cutler: Let’s review some of the new label changes relative to schizophrenia. For instance, we’ve had a couple of new long-acting injectable formulations approved.

Dr. Stahl: Certainly. We started out with Risperdal Consta, which is the risperidone long-acting injectable. It’s 2-week long-acting, but it needs a kick-start at the beginning. Then, paliperidone (Invega) has come out with a 4-week injectable. And there are a couple of others that are in development: The olanzapine version has been approved and there are others in process. I know that paliperidone is even talking about a 12-week injectable, and there are some other agents that are hoping to have long-acting injectables. You know what, Andy? These drugs don’t work unless you take them. I keep wanting these drug companies to make drugs that work whether you take them or not, but they don’t seem to be doing that! You can think of these long-acting injectables as a technology to enforce compliance; there is a subset of people who do very well if they are on the same drug for a long period of time with a very slow improvement over months and even years, and this is a technology for that, particularly for the chaotic and noncompliant patients.

Dr. Cutler: Well, we know compliance is a big issue. We know from the Clinical Antipsychotic Trials of Intervention Effectiveness CATIE study, there is a lot of “churn and burn.” And having participated in a number of those long-acting injectable studies, I can tell you, you really do see the power of the atypicals when they’re in the person’s body for a long period of time.

Question from NEI member: Have you seen evidence showing differences in metabolic properties between olanzapine (Zyprexa) and long-acting depot olanzapine?

Dr. Cutler: This is a fascinating question. I am not aware of the specific data looking at this over the long term, but I can certainly tell you that it is very possible that you are on to something, and I’ll tell you why. I was involved in the trials of the long-acting Zyprexa Relprevv, which is olanzapine depot, and we had patients who went 2 years long taking this, and none of them gained weight to any significant degree—it was shocking. And the issue there is you are smoothing out the pharmacokinetics so you have a smoother, lower blood level, and you don’t get the peaks. We know that weight gain is dose-related; it is blood level-related. And just like with depot haloperidol or depot fluphenazine (Prolixin), we don’t see much in the way of acute dystonias and extrapyramidal symptoms EPS because the blood level is smooth and low, and, theoretically, it’s in the effective range but just below the toxic range. So olanzapine depot may provide smoother pharmacokinetics, although I don’t know the details and can’t confidently say that for sure.
Treating Cognitive Symptoms of Schizophrenia

Cognitive deficits in schizophrenia are believed to be the greatest predictor of poor functional outcome. Cognitive deficits, including lack of illness insight, make treatment adherence difficult—if not impossible—for patients with schizophrenia. Although receptor binding profiles suggest that some of the newer atypical antipsychotics may potentially reduce cognitive symptoms, there are currently no approved pharmacological treatments for cognitive impairments in schizophrenia. There are, however, several nonpharmacological interventions that may help patients overcome and/or cope with cognitive deficits. One such therapy has even been shown to have neuroprotective effects with reduced gray matter loss in several brain areas relevant to schizophrenia.

Cognitive Adaptation Training (CAT)

- Compensatory approach
- Teaches patients to cope with cognitive impairments
- Most useful for patients whose illness-related memory deficits, apathy, easy distractibility, and/or lack of organization prevent them from being able to carry out activities of daily living, manage their physical and mental health care, and attain recovery in their illness
- Uses a host of reminders, alarms, and careful organization of belongings to help cue and sequence adaptive behavior
- Takes place in the patient’s home
- Tailored to the individual patient’s cognitive deficiencies
- Involves frequent home visits and monitoring by a CAT therapist
- Has been shown to lower relapse rates and improve functional outcomes

Cognitive Remediation Therapy (CRT)

- Restorative intervention
- Aims to improve cognitive functioning in patients with schizophrenia
- Involves pencil/paper tasks and computerized exercises aimed at improving cognitive skills, memory, and problem-solving skills
- Complexity of the training tasks increases as therapy progresses
- Uses both individualized programs and group therapy approaches
- Has been shown to improve cognition, skills acquisition, and functional outcomes
- Positive results are most robust when CRT is combined with other methods of psychiatric rehabilitation (including vocational support, social skills training, etc.)

References


- Dosing Tips and Prescribing Pearls -

Risperidone

Brands: Risperdal, Consta

Formulation: Tablet: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 6 mg
Oral disintegrating tablets: 0.5 mg, 1 mg, 2 mg
Liquid: 1 mg/mL
Two-week depot microspheres (IM): 25 mg vial/kit, 37.5 mg vial/kit, 50 mg vial/kit

Dosage Range: 2–8 mg/day

Approved For: Schizophrenia, bipolar maintenance, autism-related irritability

Side Effects

Weight Gain

Sedation

Dangerous side effects:
Dose-dependent extrapyramidal symptoms and hyperprolactinemia. Rare orthostatic hypotension; rare neuroleptic malignant syndrome; increased risk of death in elderly patients with dementia; rare seizures; hyperglycemia.

Drug interactions:
Metabolized by CYP450 2D6. Carbamazepine may decrease risperidone levels. Paroxetine and fluoxetine may decrease risperidone levels. Risperidone may increase effects of antihypertensive drugs and may antagonize dopamine agonists.

Pearls

Well-accepted for treatment of behavioral symptoms in children and adolescents, but may have more sedation and weight gain in pediatric populations than in adults.
Well-accepted for treatment of agitation and aggression in elderly demented patients. Many anecdotal reports of utility in treatment-refractory cases and for positive symptoms of psychosis in disorders other than schizophrenia. Hyperprolactinemia in women with low estrogen may accelerate osteoporosis. May cause more motor side effects than some other atypical antipsychotics, especially when administered to patients with Parkinson’s disease or Lewy body dementia.

Cardiac impairment:
Use caution due to orthostatic hypotension.

Renal impairment:
Use with caution. Slow titration recommended.

Hepatic impairment:
Use with caution. Slow titration recommended.

Children and adolescents:
Risperidone is the most frequently prescribed atypical antipsychotic in children and adolescents.

Pregnancy:
Risperidone is not recommended for use in pregnancy. Risperidone has not been shown to affect the breastmilk of women who are breastfeeding.

References


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Conventional vs. Atypical Antipsychotics

In order for an antipsychotic medication to be effective in real-world clinical practice, it must not only be efficacious (i.e., reduce symptoms) but also tolerable and actually taken by the patient. There is no perfect antipsychotic, and the pragmatic goal is to find a medication that works “well enough,” is tolerated “well enough,” and is one that the patient is willing to adhere to at least most of the time.

Much has been made about the dichotomy of conventional and atypical antipsychotics, but, in truth, there is extensive heterogeneity among first- and second-generation antipsychotics FGAs and SGAs as well as overlaps in their effects (Volavka and Citrome, 2009). This is entirely consistent with the understanding that each agent has its own unique receptor binding profile. Moreover, people with schizophrenia also form a heterogeneous group with different biological vulnerabilities.

Efficacy
The totality of the evidence supports the notion that there are tiers of atypical antipsychotics regarding comparative efficacy with conventional antipsychotics. As noted in a meta-analysis of 150 different studies that enrolled 21,533 participants, Leucht and colleagues (2009a) observed that clozapine produces the largest effect size difference from conventional antipsychotics, followed by amisulpride (not available in the U.S.), olanzapine, and risperidone. Other atypical antipsychotics included in the meta-analysis (aripiprazole, quetiapine, sertindole (not available in the U.S.), ziprasidone, and zotepine (not available in the U.S.)) were not more efficacious than the conventional antipsychotics, even for negative symptoms. When comparing the atypical antipsychotics against each other in another meta-analysis that included 78 studies and 13,558 participants, Leucht and colleagues (2009b) also found evidence for the superiority of clozapine, olanzapine, and risperidone over some of the other atypical antipsychotics. Although the results were robust with regard to the effects of industry sponsorship, study quality, dosages, and trial duration, the efficacy differences were small. Similar results were obtained in an earlier meta-analysis (Davis et al., 2003). Missing from these meta-analyses are the newer SGAs iloperidone, asenapine, and lurasidone, but best guess is that differences in efficacy compared to the conventional antipsychotics will also be marginal, if there is any difference at all. However, this information about antipsychotic efficacy is based on group data. In the real world, there are large variations in antipsychotic response. Clinicians routinely empirically prescribe one antipsychotic after another to find the medication that will optimally reduce symptoms for the individual person with schizophrenia. However, the group data and meta-analyses do inform us that the chances of obtaining adequate efficacy may be greater for some antipsychotics versus others. This may be more important depending on the progression of the disease. People early in their disease course may be more responsive to a variety of antipsychotics. As time proceeds, greater degrees of treatment resistance may be encountered, necessitating the use of other antipsychotics.

Tolerability
Tolerability is also an important driver of adherence, particularly when the person does not have any insight into the potential efficacy benefits of an intervention. The most obvious difference between conventional and atypical antipsychotics is the former’s greater propensity to be associated with extrapyramidal side effects and akathisia. Some conventional antipsychotics are more likely than others to be associated with these dose-related effects, but benzotropine use is common even among those agents less likely to be linked to extrapyramidal side effects. Unfortunately, use of benzotropine and other anticholinergic medication is not benign and can be associated with further impairment of cognition. Selecting an atypical antipsychotic would be preferable for patients who experience extrapyramidal side effects or akathisia, particularly when it impedes adherence. Among the atypical antipsychotics, there are some more likely than others to be associated with these issues, as evidenced in a meta-analysis (Rummel-Kluge et al., Epub ahead of print) in which risperidone was associated with more use of antiparkinson medication than clozapine, olanzapine, quetiapine, and ziprasidone. Ziprasidone showed more use of antiparkinson medication than olanzapine and quetiapine. Quetiapine showed significantly less use of antiparkinson medication than olanzapine, risperidone, and ziprasidone. Among the newer atypical antipsychotics, iloperidone also appears to have a favorable profile in this regard (Citrome, 2009) (Table 1).

Weight gain and adverse effects on metabolic variables are serious safety concerns for patients with schizophrenia. Although they can be observed with conventional antipsychotics, these effects have become more prominent with the increasing use of atypical antipsychotics. This may impact adherence, but not necessarily so if the person...
experiencing these effects is satisfied with the efficacy of the antipsychotic and otherwise unconcerned about the weight gain and additional “silent” alterations in lab values. Clinicians, however, are more consistently concerned about these safety issues. In a meta-analysis of the metabolic side effects of atypical antipsychotics (Rummel-Kluge et al., 2010), olanzapine produced more weight gain than all other atypical antipsychotics except for clozapine, where no difference was found. Clozapine produced more weight gain than risperidone. Olanzapine produced more cholesterol increase than aripiprazole, risperidone, and ziprasidone, but no differences were found with clozapine and quetiapine. Quetiapine produced more cholesterol increase than risperidone and ziprasidone. Olanzapine produced more increase in glucose than aripiprazole, quetiapine, risperidone, and ziprasidone, but no difference was found with clozapine (Table 1).

Sedation is the third adverse event that is both commonly encountered and often associated with adherence issues. This, too, is subject to an individual patient’s preferences and values. A person may actually desire a certain degree of sedation. Others may want to avoid that sensation entirely. Different antipsychotics—both conventional and atypical—have differing effects on the occurrence of sedation. In the past, we often categorized the conventional agents as either low-potency sedating agents or high-potency nonsedating agents, although the latter can still be quite sedating in a person vulnerable to this dose-related effect. The proportion of patients experiencing somnolence have been reported, with higher differences from placebo noted for olanzapine, quetiapine, and lurasidone (Citrome and Nasrallah, in review). However, mechanism of action for somnolence and sedation can differ among these agents as different receptors may be involved (Stahl, 2008) (Table 1).

### Enhancing Adherence
Adherence must be monitored. Asking nonjudgmental questions (such as, “Nobody is perfect. Over the past week, how many times have you missed a dose of your medication?”) will give the patient “permission” to admit to this. Targeting symptoms that the patient actually cares about will increase the “buy-in”—this may involve symptoms such as poor sleep or anxiety rather than the delusions and hallucinations for which they may have little or no insight. Specifically asking about adverse events and tolerability issues is crucial in fostering a therapeutic alliance. Shared decision-making will involve a discussion of the patient’s individual preferences in terms of efficacy and tolerability.

### Table 1. Side effect Profiles of Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Atypical Antipsychotic</th>
<th>Side Effects*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Sedating</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>common</td>
</tr>
<tr>
<td>Asenapine</td>
<td>common</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>common</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>common</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>common</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>problematic</td>
</tr>
<tr>
<td>Risperidone</td>
<td>common</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>not unusual</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>common</td>
</tr>
</tbody>
</table>

*Side effects scale: Unusual = reported in few patients; Not unusual = occurs in a significant minority; Common = many experience or can be in significant amount; Problematic = occurs frequently, can be in a significant amount, and may be a health problem in some patients.

References
Citrome L, Nasrallah HA. Expert Opin Pharmacother (in review).
Davis JM et al. Arch Gen Psychiatry 2003;60(6):553-64.
## Treatment Adherence in the Face of Side Effects

### Patient Intake and History:
- 67-year-old male
- Diagnosed with schizophrenia at age 21
- Seven hospitalizations over past 10 years
- Recurrent severe psychoses
- History of treatment nonadherence
- Trial of fluphenazine decanoate was effective at alleviating positive symptoms but resulted in development of extrapyramidal symptoms (EPS)
- Presents with visible tremor
- Currently incarcerated for assaulting a police officer with a baseball bat

### Chief Complaints
- Acting on persecutory delusions has led to the patient’s incarceration
- "Men in suits are trying to steal my brain"
- Refuses to take antipsychotic medication due to fear of side effects

### Current Medications
- None

### Previous Medications
- Olanzapine
- Aripiprazole
- Chlorpromazine
- Fluphenazine decanoate

### Clinician’s Notes
- This patient has a long history of undertreated schizophrenia, likely due to treatment nonadherence
- This particular patient’s nonadherence seems to stem, at least in part, from intolerable side effects
- To address the treatment nonadherence, a depot antipsychotic formulation seems to be a good choice. There are many long-acting depot formulations available, including both conventional and atypical antipsychotics
- Although conventional antipsychotics seem to be effective for this patient, they cause intolerable EPS
- An atypical depot antipsychotic agent will have reduced risk of EPS; however, there is increased risk for cardiometabolic side effects associated with atypical antipsychotics as a class
- The available options for long-acting depot formulations of atypical antipsychotics include paliperidone (4 week) and risperidone (2 week). There are also 2-week and 4-week depot formulations of olanzapine, but they are not currently available in the United States
- An antiparkinson agent may be useful for alleviating the patient’s current tremor

### Case Outcomes
- The patient was started on diphenhydramine 25 mg/twice daily, resulting in dramatic resolution of EPS
- To determine the patient’s tolerance for risperidone, the oral formulation of risperidone 2 mg/day was initiated (with gradual titration to 6 mg/day)
- There was no exacerbation of EPS on the oral risperidone dose
- Positive symptoms decreased but were still problematic
- Risperidone Consta (2-week depot formulation) was added to oral risperidone dose
- The patient was also recommended to cognitive behavioral therapy with emphasis on medication and illness management to learn how treatment adherence can prevent relapse and lead to greater quality of life

### Case Debrief
- Treatment nonadherence is a prevalent issue in schizophrenia and is thought to be one of the greatest contributors to relapse
- There are many reasons why patients with schizophrenia do not adhere to treatment. Intolerable side effects, lack of efficacy, cognitive deficits, and a poor therapeutic alliance have all been associated with treatment nonadherence
- There are many conventional and atypical antipsychotics available as long-acting depot formulations. These long-acting injections can greatly improve medication adherence, especially in the outpatient setting
- Conventional antipsychotics, as a class, have a higher risk of EPS, whereas atypical antipsychotics typically impart greater risk for cardiometabolic side effects. To increase medication adherence, it is important that treatment of schizophrenia is tailored to the individual patient so that treatment is optimal with minimal side effects
- Nonpharmacological interventions have also been shown to be useful for increasing treatment adherence in schizophrenia
Glossary of Schizophrenia and Psychosis Terms

**Affective blunting:** Restrictions in the range and intensity of emotional expression.

**Agonist:** A chemical agent that interacts with a cell receptor to trigger a response. Neurotransmitters are the natural agonists at their receptors.

**Akathisia:** A type of extrapyramidal side effect involving a feeling of inner restlessness and a constant urge to be moving.

**Alogia:** Dysfunction of communication with restrictions in the fluency and productivity of thought and speech.

**Anhedonia:** Reduced ability to experience pleasure.

**Antagonist:** A chemical agent that interacts with a cell receptor to stabilize the cell in a resting state.

**Asociality:** Reduced social drive and interaction.

**Atypical antipsychotic:** Often referred to as “second-generation” antipsychotics, atypical antipsychotics characteristically have a low risk for extrapyramidal symptoms (EPS) compared with conventional, “first-generation” antipsychotics. Pharmacologically, atypical antipsychotics demonstrate loose binding to dopamine (D2) receptors and often have actions at additional receptors (e.g. serotonin, 5HT receptors).

**Avolition:** Reduced desire, motivation, or persistence including restrictions in the initiation of goal-directed behavior.

**Cardiometabolic risk:** A collection of factors including high blood pressure, elevated triglycerides, and obesity that together increase the risk of developing type II diabetes and cardiovascular disease. Some antipsychotic agents are known to increase cardiometabolic risk.

**Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE):** A National Institute of Mental Health (NIMH)-funded clinical trial that compared the effectiveness of several conventional and atypical antipsychotics.

**Cognitive adaptation training (CAT):** A non-pharmacological treatment approach that is designed to improve medication adherence by compensating for the cognitive deficits often experienced by patients with schizophrenia. This support system involves various environmental cues such as signs, checklists, and alarms that remind patients to take their medication.

**Cognitive remediation therapy (CRT):** A type of psychotherapy that aims to improve memory and cognitive flexibility using a neurocognitive tasks.

**Cognitive symptoms of schizophrenia:** Symptoms of executive dysfunction including problems in representing and maintaining goals, allocating attentional resources, evaluating and monitoring performance, and utilizing these skills to solve problems.

**Conventional antipsychotic:** Often referred to as “first-generation” antipsychotics, conventional antipsychotics characteristically have strong antagonistic properties at dopamine (D2) receptors as well as actions at various other receptors.

**Cross titration:** A method for switching between two pharmacological agents that involves concomitant administration of both agents for a while as one goes up and the other goes down in dose.

**Delusions:** Misinterpretation of perceptions or experiences.

**Dystonia:** A type of extrapyramidal side effect involving sustained muscle contraction that causes repetitive movements or abnormal postures.

**Extrapyramidal side effects (EPS):** Physical symptoms including tremor, slurred speech, akathisia, and dystonia that often result from treatment with antipsychotics.

**Hallucinations:** Perceptions of a nonexistent object or event that may involve any sensory modality (auditory, visual, tactile, etc).

**Negative symptoms of schizophrenia:** Symptoms that are considered as a reduction in normal functioning and include alogia, affective blunting, asociality, anhedonia, and avolition.

**Polyparmacy:** Administration of two or more similar pharmacological agents at the same time.

**Positive symptoms of schizophrenia:** Symptoms that are considered as an excess in normal functioning and include delusions and hallucinations.

**Post-synaptic:** Occurring in the neuron located beyond or distal to the synaptic space between neurons.

**Pre-synaptic:** Occurring in the neuron located before or proximal to the synaptic space between neurons.

**Psychosis:** A mixture of positive symptoms including delusions, hallucinations, and disorganized speech and behavior.

**Psychotomimetics:** A drug-induced experience that mimics a state of psychosis.

**Tardive dyskinesia:** A hyperkinetic, choreiform movement disorder involving facial and tongue movements, and jerky limb movements. Tardive dyskinesia is often associated with long-term administration of conventional antipsychotics.