

EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists will be able to:

- Discuss how schizophrenia's propensity to cause internal conflict and subjective distress often leads to nonadherence and use patient centered approaches to improve care
- Implement pharmacologic approaches to address suboptimal outcomes for persons with schizophrenia
- Identify situations in which oral, long-acting injectable (LAI) antipsychotics, or a combination of both are reasonable choices
- Compare available long-acting injectable antipsychotic agents' indications, risks and benefits, pharmacokinetic profiles, dosing, and administration techniques in the pharmacy
- Discuss emerging opportunities for pharmacists administer and monitor LAI antipsychotic medication

After participating in this activity pharmacy technicians will be able to:

- Discuss the association between schizophrenia diagnosis and medication adherence
- List long-acting injectable drugs used in schizophrenia, and address inventory management issues
- Recognize when to refer patients to the pharmacist for help with their schizophrenia
- Determine the best way to help patients engage in a patient assistance program



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Pharmacists and pharmacy technicians are eligible to participate in this application-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

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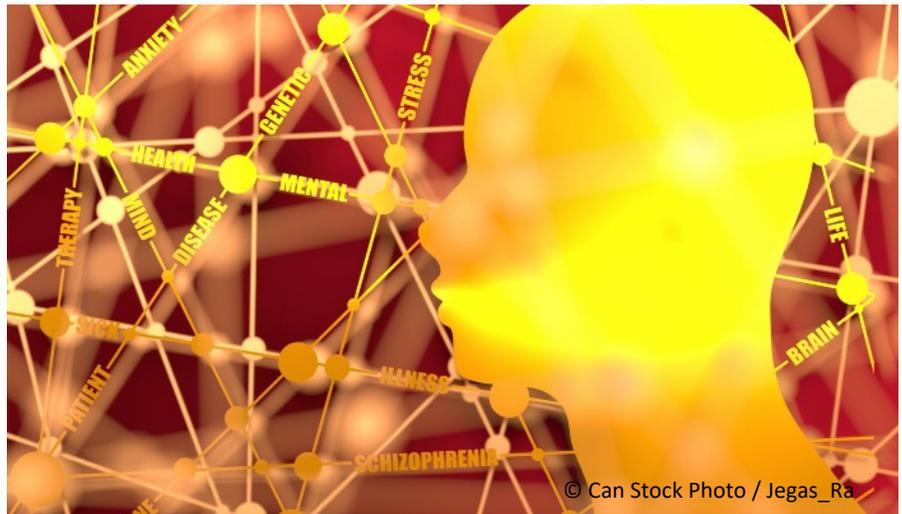
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Injecting Pharmaceutical Skill into Schizophrenia Care

ABSTRACT: Schizophrenia is a severe, persistent mental illness that affects 0.3% to 0.7% of the U.S. population. Individuals with schizophrenia often lack insight into their illness and struggle with periods of adequate and inadequate symptom control. Individuals are often stigmatized by a community that is uncomfortable with schizophrenia's symptoms due to fear and misunderstanding. The antipsychotics that have been developed over the last 60 or more years have numerous side effects and require close monitoring. Lack of insight, stigma, and side effects put individuals with schizophrenia at high risk for medication nonadherence, poor clinical outcomes, and costly hospitalizations. More antipsychotics are available in long-acting injectable formulations. These delayed-release formulations allow patients to maintain therapeutic levels of antipsychotics for weeks to months after an injection. Such properties can help improve medication adherence. In some states, pharmacists can administer LAIAs in community pharmacies and improve patient access to these valuable medications.

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INTRODUCTION

Schizophrenia is a chronic, debilitating, serious mental illness (SMI) that affects approximately 0.3 to 0.7% of the global population. Patients with schizophrenia have a significant decline in life expectancy. In a comparison of 220 unique disease conditions, acute schizophrenia was shown to impose the highest degree of disability.¹ Schizophrenia's economic burden is high, with an approximated cost of \$155.7 billion in the United States in 2013.²

Pharmacists and pharmacy technicians may hold attitudes or beliefs about schizophrenia that are more negative than their beliefs about other SMIs such as major depression and bipolar disorder. Although these beliefs may not necessarily be stigmatizing, they may impact the pharmacy staff member's ability to

provide optimal care. Because patients with schizophrenia have altered or disorganized thought processes, pharmacy staff must employ strong communication skills, sensitivity, and empathy when providing care to these patients.

Medication adherence and continuity of care continue to be major issues for patients with schizophrenia. Access to medication may be a barrier that contributes to nonadherence. Pharmacy staff is well-placed to recommend different approaches based on medications' mechanisms of action or adverse effect profiles.

This continuing education activity will improve pharmacy staff's ability to optimize treatment for patients with schizophrenia while addressing negative beliefs about this patient population. It will explore factors that contribute to nonadherence. It will also identify pharmacologic approaches for schizophrenia, including oral and long-acting injectable antipsychotics (LAIAs). After comparing the different LAIAs currently available, it will discuss the pharmacist's role in administering LAIAs and monitoring for adverse effects.

Community Pharmacy Staff's Role

Community pharmacy staff may hold a combination of stigmatizing and non-stigmatizing attitudes and beliefs about mental illnesses that vary by SMI. In general, community pharmacy staffs' beliefs and attitudes about depression and anxiety disorders are more positive than their beliefs and attitudes about schizophrenia.³

Studies have found that pharmacists were significantly less willing to provide pharmacy services to consumers with mental illnesses than to consumers with cardiovascular diseases and asthma.^{4,5} Pharmacists may feel uncomfortable discussing psychotropic medication use and mental illness symptoms with patients.⁶ The disparity in willingness to provide services seems to emanate from pharmacists' lack of knowledge of schizophrenia; discomfort with awkward or challenging behaviors; or lack of privacy in some community pharmacies.^{6,7}

The concept of establishing pharmacist-managed clinics for LAIA administration is gaining momentum. However, patients and providers may associate LAIAs with coercion or consider them old-fashioned. Pharmacists can help reduce that stigma.⁸ LAIAs generally improve adherence by preventing missed doses and minimizing adverse effects associated with peak drug levels. Clinicians can identify medication nonadherence earlier when patients miss a scheduled injection. Many patients begin LAIA therapy during hospitalization to prevent immediate nonadherence at discharge. However, the drugs are costly (average wholesale price, \$296–\$1779 per dose in 2009 dollars), and hospitals must absorb these costs in the per diem reimbursement cost.⁹ Healthcare systems may



therefore be more receptive to the idea of community-based injection services.

Studies have shown that pharmacists can manage referred outpatients with services including adjusting the doses of and administering LAIAs while monitoring for adverse events including metabolic disturbances and extrapyramidal symptoms (EPS). These services are cost-effective.⁹ In addition, support programs have used convenient locations, often community pharmacies, where patients can receive monthly injections to improve adherence. These programs also increase patient engagement with other supportive activities.¹⁰

PAUSE AND PONDER: A patient with schizophrenia was recently hospitalized and the psychiatrist started treatment with a LAIA. The patient has arrived to pick up a dose of the LAIA to be administered at his next outpatient appointment, and you tell him it will cost \$300. The patient is visibly upset and states that he cannot afford the medication. What do you say to the patient and what actions do you take?

SCHIZOPHRENIA: BACKGROUND

As mentioned previously, schizophrenia is relatively rare. Schizophrenia's cause is unknown, although several suspected causes have been noted. These include perinatal insults, infectious or autoimmune causes, substance use during pregnancy (especially cannabis or methamphetamine), and genetics.¹¹

Schizophrenia is a thought disorder characterized by symptoms that fall into three primary domains: positive, negative, and cognitive symptoms (see [Table 1](#)).¹ These symptoms typically begin during the late teens to mid-30s and tend to occur later in women than men (median age late-20s vs. early to mid-20s).¹² Unfortunately, symptoms in all three domains may contribute to medication nonadherence.

Table 1. Schizophrenia's Symptoms

Positive Symptoms	Negative Symptoms	Cognitive Symptoms
<ul style="list-style-type: none"> ● Delusions ● Hallucinations ● Disorganized thoughts or speech 	<ul style="list-style-type: none"> ● Blunted affect ● Alogia (reduced fluency of speech) ● Anhedonia (inability to experience pleasure in normally pleasurable acts) ● Amotivation ● Avolition (a lack of interest or engagement in goal-directed behavior) 	<ul style="list-style-type: none"> ● Memory impairment ● Decreased concentration ● Impaired executive functioning

All patients with schizophrenia present with different symptom combinations. During an acute exacerbation, patients are more likely to display predominantly positive symptoms. However, they often suffer with enduring negative symptoms and cognitive dysfunction between exacerbations. The result is overall functional impairment that decreases the likelihood of successful occupational and academic functioning, interpersonal relationships, and functioning in other areas of life.¹

Schizophrenia: Shared Decision Making

National guidelines and mental health advocacy organizations underscore the need for shared decision-making (SDM) in antipsychotic prescribing. SDM is defined as “the conversation that happens between patients and their healthcare professionals to reach a healthcare choice together.” It is especially important that patients with schizophrenia be involved in the decision-making behind their care.

A recent interview-based study examined mental health pharmacists’ views of and experiences with SDM.¹³ Pharmacists indicated that SDM often contributed to positive clinical outcomes (e.g. better adherence, service user satisfaction, and improved therapeutic relations). Collectively, they believed that SDM was essential to stigma-free clinical care. They also indicated, however, that clinicians do not use SDM as often as they could. Barriers included a lack of knowledge about how to employ SDM and time pressures on clinical staff. They expressed a desire for improved teamwork, greater patient engagement, and more interdisciplinary collaboration.¹³ Good continuing education can galvanize SDM.

Patients with first-break schizophrenia may present and respond to treatment quite differently than those with long-standing schizophrenia. All patients require a range of treatments (e.g. cognitive behavioral therapy, vocational help, family support, substance use intervention, and antipsychotic medications). The treatment team, working closely with the patient to determine the patient’s history and preferences, must individualize the exact mix of services. Without support, people with schizophrenia experience many treatment-preventable outcomes. These may include relapse, multiple or chronic hospitalization(s), comorbid substance use disorders, homelessness, adverse experiences with the legal system, estrangement from loved ones and society as a whole, and suicide.

Pause and Ponder: You work at a busy community pharmacy. A patient you do not know has dropped off a prescription for an antipsychotic. While she waits for the prescription to be filled, you notice that she appears to be talking to herself and paces back and forth in the waiting area. Other customers appear uncomfortable. What would you do in this situation?

Schizophrenia and Medication Adherence

Numerous studies have documented that medication adherence among patients with schizophrenia is usually poor, and the professional literature is replete with studies and opinion pieces. Systematic review indicates that approximately 40% of patients with schizophrenia (and most likely more) are partially adherent or nonadherent with antipsychotic medications.¹⁴ The U.S. Department of Veterans Affairs, which provides care for a large population of patients who have schizophrenia, documents that 40% of patients fill less than 80% of their prescriptions.^{15,16}

Despite decades of study, adherence remains a major treatment impediment in schizophrenia. People with schizophrenia have several problems that healthcare providers may fail to appreciate¹⁷⁻¹⁹:

- Impaired insight into illness
- Co-occurring substance use disorders
- Abnormal biopsychosocial-cultural filters that distort perception and cause internal conflict
- Withdrawal and diminished interactions with others
- Altered observation of others’ behavior, and internalization of fewer functional behavioral models than those without schizophrenia
- Pervasive stigma around treatment with antipsychotic medications
- Complex medication regimens
- Significant adverse effect profiles of antipsychotics

Impaired insight is a primary reasons for nonadherence.²⁰ Poor or absent insight can have many implications. Patients may not be aware that they have a mental illness, and therefore may be unaware of the need for treatment or the consequences of not accepting treatment.²¹ Patients who lack insight may minimize or deny the need for treatment and develop negative attitudes towards medication. This increases the likelihood that the patient

Table 2. Results from CATIE

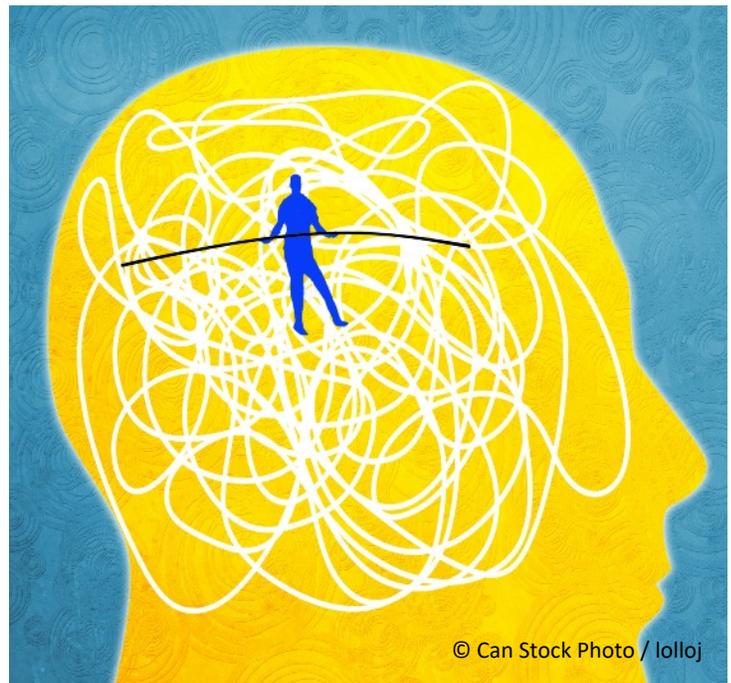
Time After Study Initiation	% Nonadherent to Prescribed Antipsychotic			p-value
	No impairment	Minimal impairment	Moderate-to-severe impairment	
6 months	17	20	25	0.012
12 months	19	24	29	0.05
18 months	31	37	43	0.0007

will self-discontinue medications.²² Non-pharmacologic methods such as cognitive behavioral therapy may have some benefit in improving the patient's insight into his or her psychiatric condition.²³

A large, prospective study (the CATIE trial, published in 2005) provided data regarding the effectiveness of first- and second-generation antipsychotics to treat schizophrenia. A recent analysis of the CATIE trial's data was conducted to estimate the time to medication nonadherence (taking less than 80% of monthly medication) between patients with differing degrees of insight impairment.²² The researchers classified patients as having no impairment, minimal impairment, or moderate-to-severe impairment based on the insight item of the Positive and Negative Syndrome Scale (PANSS) score. **Table 2** presents the results of this analysis.

At both six months and 18 months after treatment initiation, adherence to the prescribed antipsychotic differed significantly depending on the patients' degree of insight. Time to medication nonadherence was also shorter (13.5 months) for patients with moderate-to-severe impairment compared to those with minimal (14.4 months) and no impairment (15.1 months). Associations between insight and adherence remained significant after adjusting for illness severity, substance use, attitudes about medication, cognition, level of hostility, and depression.

Substance use is another factor that may have a major effect on adherence in patients with schizophrenia. A systematic review and meta-analysis published in 2018 suggests that 42% of patients with schizophrenia have comorbid substance use disorders.²⁴ Tobacco, alcohol, and cannabis use disorders are among the most common in this patient population.^{24,25} Comorbid substance use disorders may contribute to more symptom exacerbations including clinical relapse and need for hospitalization, treatment nonadherence, and suicide. Pharmacists are in a position to reduce or eliminate these risks by identifying and recommending treatment for patients with concomitant schizophrenia and substance use disorders.



TREATMENT OF SCHIZOPHRENIA

The unique problems experienced by patients with schizophrenia mean that the clinical implications are complex¹⁷:

- Treatment to reduce and eliminate deficits requires more than just medication. Patients with schizophrenia need time-intensive therapy and support for optimal treatment.
- Simply eliminating psychotic symptoms may, from the patient's point of view, move him from a more favorable psychotic condition back to a troublesome reality. Some people with schizophrenia prefer a psychotic state to a relative drug-induced normality. This is known as subjective distress.
- Many patients report feeling worse while taking medications. This may be caused by the medications' adverse effects, but subjective distress seems to be a greater factor.
- Patients are more receptive to medication if clinicians offer different medications or a medication with fewer, different, or more tolerable adverse effects.

Pharmacologic Approaches

Antipsychotics remain the mainstay of pharmacologic treatment of schizophrenia. However, approximately one-third of patients respond incompletely to these medications.³ Before diagnosing a patient as treatment-resistant, clinicians must rule out¹:

- Medication nonadherence. As discussed previously, adherence poses a significant problem in the treatment of this SMI. Treatment with a LAIA may be a strategy to ensure patients receive adequate medication trials.
- Confusion regarding lack of efficacy versus intolerability
- Unclear diagnosis (substance use, psychiatric comorbidities, and somatic comorbidities may confound diagnosis)
- Pharmacokinetic anomalies due to rapid metabolism, drug–drug interactions, and drug–food interactions

Antipsychotic medications are categorized into two classes: first generation (typical) antipsychotics (FGA) and second generation (atypical) antipsychotics (SGA; see [Table 3](#)).

Treatment Guidelines

There are no specific, comprehensive treatment guidelines for acute agitation in schizophrenia. For general treatment, clinical guidelines recommend the following²⁶⁻²⁸:

- First-line: Some guidelines recommend SGA monotherapy as first-line, while others include both SGAs or FGAs
- Second-line: SGA or FGA (different from initial antipsychotic)
- Third-line: Clozapine
- Fourth-line: Augmentation with another antipsychotic

Prescribers must take patient-specific factors into account when selecting a medication for each patient. They must consider previous medication trials, actual or potential adverse effects, and response to treatment. Consideration of patients' previous responses to medication trials is critical. For example, if a patient has responded poorly to a particular antipsychotic, either in terms of efficacy or adverse effects, it would be prudent to select an antipsychotic that is dissimilar to the first antipsychotic. On the other hand, if a patient has responded well to an antipsychotic in the past, it would make sense to re-try that medication.

Evidence to support the use of multiple antipsychotics is lacking and contributes to significant risk of adverse effects. Three clinical situations may justify use of more than one antipsychotic²⁶:

1. Three or more failed trials of antipsychotic monotherapy
2. Cross-titration of antipsychotic medications
3. Augmentation of clozapine

Despite these recommendations, up to 90% of patients who have schizophrenia are treated with polypharmacy.²⁹ No new medications with clearly novel mechanisms of action are expected imminently. Consequently, the best approach to managing schizophrenia is to employ current therapies in innovative and evidence-based ways including the use of LAIAs.¹⁰

Table 3. Oral Antipsychotics

First-Generation Antipsychotics (FGAs)		Second-Generation Antipsychotics (SGAs)	
Generic Name	Brand Name	Generic Name	Brand Name
Chlorpromazine	Thorazine	Aripiprazole	Abilify
Fluphenazine	Prolixin	Asenapine	Saphis
Haloperidol	Haldol	Brexpiprazole	Rexulti
Loxapine	Loxitane	Cariprazine	Vraylar
Perphenazine	Trilafon	Clozapine	Clozapine, Fazacllo (ODT)
Thioridazine	Mellaril	lloperidone	Fanapt
Thiothixene	Navane	Lurasidone	Latuda
		Olanzapine	Zyprexa
		Paliperidone	Invega
		Quetiapine	Seroquel
		Risperidone	Risperdal
		Ziprasidone	Geodon

Medication Initiation, Onset, Titration, Discontinuation

Prescribers should initiate both FGAs and SGAs at low doses and titrate up to make the medication more tolerable. Acute symptoms such as agitation, aggression, and increased motor activity will typically respond to antipsychotic treatment within a few days. Psychotic symptoms such as hallucinations, delusions, and disorganized thoughts usually will respond within two weeks although it may take up to four to six weeks for a full response.³⁰ Patients with an early nonresponse (less than a 20% reduction in PANSS score at week 2) may be less likely to respond to the prescribed medication and may benefit from a switch to a different antipsychotic medication.³⁰ However, if it is the first psychotic episode, longer trials of the initial medication are appropriate even with an early nonresponse.

The antipsychotic dose is generally increased until improvement in behavior is noted or intolerance occurs. For some patients, it is beneficial to split doses (from two times to four times per day) when first initiating treatment to decrease the potential for side effects. In many cases, the doses can eventually be consolidated into one nightly dose for ease of administration.³¹

When discontinuing an antipsychotic, the prescriber should taper the dose down over several weeks to months to prevent withdrawal symptoms and symptom reemergence.³¹ Withdrawal symptoms, including nausea, vomiting, malaise, and headache, typically begin two to three days after an abrupt discontinuation and may last for up to two weeks.³¹

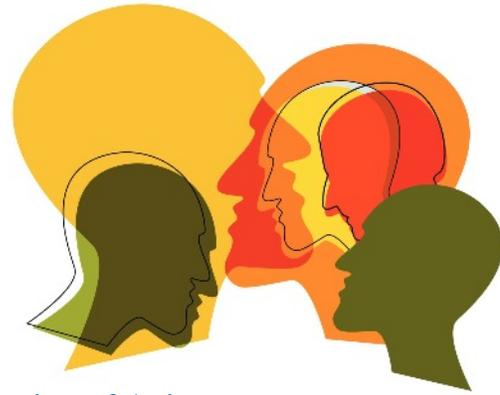
When switching between antipsychotics, a cross-taper approach is common. The new antipsychotic is started at a low dose while concurrently decreasing the dose of the original antipsychotic to prevent rebound psychosis or withdrawal.³¹

Treatment Goals and Duration

Treatment of schizophrenia can be divided into three phases:

1. Acute stabilization: Reduce threat to self or others and reduce acute symptoms
2. Stabilization: Reduce positive, negative, and cognitive symptoms; improve social deficits
3. Maintenance/relapse prevention: Symptom remission or control and improvement in psychosocial functioning

It may be difficult to determine the optimal treatment duration for some patients. Experts recommend continuing treatment for at least one year after adequate symptom control in patients experiencing their first episode to prevent relapse. For patients with previous episodes, duration should be based on each patient's continued symptoms and previous response to dose decreases or treatment discontinuation. The American Psychiatric Association suggests prescribers should consider lifelong treatment for patients with multiple prior episodes or two episodes within five years. Continuous treatment with antipsychotics remains the gold standard to lower the relapse rate and to prolong the time to relapse for patients with schizophrenia.^{1,10}



Mechanism of Action

FGAs block dopamine (D₂) receptors within four areas of the brain. Dopamine blockade in these areas contributes to these medications' effectiveness and adverse effect profiles:

1. Mesocortical pathway in the prefrontal cortex → may worsen negative symptoms
2. Mesolimbic pathway in the basal ganglia → decrease positive symptoms
3. Nigrostriatal pathway in the substantia nigra → EPS
4. Tuberoinfundibular pathway in the hypothalamus → increased prolactin release (hyperprolactinemia)

SGAs block D₂ receptors in these four pathways, but also block serotonin receptors (5HT_{2A}). Some SGAs (aripiprazole, brexpiprazole, cariprazine) are also D₂ partial agonists which may help to reduce EPS symptoms.

Antipsychotics may additionally block histaminergic, muscarinic, and adrenergic receptors which contribute to potential adverse effect profiles.

Adverse Effect Profiles

FGAs and SGAs both have extensive adverse effect profiles.

Many of these potential adverse effects are risks for both drug classes:

- EPS (more frequent with FGAs than SGAs)
- Metabolic adverse effects (more frequent with SGAs than FGAs)
- Worsening of negative symptoms of schizophrenia
- Anticholinergic symptoms (dry mouth/eyes, mydriasis, tachycardia, constipation, urinary retention, cognitive problems in elderly patients)
- Hypotension, QTc prolongation, venous thromboembolism
- Hyperprolactinemia
- Neuroleptic malignant syndrome
- Sexual dysfunction, priapism (abnormal, often painful, persistent erection)
- Seizure
- Increased risk of mortality in elderly patients treated for dementia (boxed warning for all antipsychotics)

One key difference between the two classes of antipsychotics is that the FGAs have a higher incidence of movement disorders or EPS (especially the high-potency FGAs such as haloperidol and fluphenazine) compared to the SGAs. However, the SGAs have a much higher risk of metabolic abnormalities which cannot be overlooked during antipsychotic selection.

Table 4. Extrapyramidal Symptoms³¹⁻³³

EPS Type	Description
Dyskinesia	Repetitive, involuntary, purposeless body or facial movements Lip smacking, tongue movements, finger movements
Tardive dyskinesia	Involuntary uncontrollable movements especially of the mouth, tongue, trunk, and limbs. Occurs after longer duration of use (months to years) and may be permanent.
Akathisia	Extreme form of internal or external restlessness, inability to sit still, urge to move constantly
Dystonia	Muscle tension disorder → strong muscle contractions, unusual twisting of parts of body especially neck
Pseudoparkinsonism	Mask-like facies (an appearance and expression of the face characteristic of a particular condition especially when abnormal), resting tremor, cogwheel rigidity, shuffling gait, bradykinesia

Mild to moderate EPS can be treated with anticholinergic medications, such as diphenhydramine or benztropine. It may also be reasonable to consider dosing patients prophylactically with an anticholinergic if selecting an antipsychotic with a high likelihood of EPS or if the patient has a previous history of EPS. Anticholinergics should be used with caution in elderly patients, and it should be noted that they may worsen pseudoparkinsonian symptoms or tardive dyskinesia.³² Divided doses of propranolol may also be used to treat akathisia.³³

Tardive dyskinesia, a neurologic disorder characterized by hyperkinetic movements, will usually occur after prolonged blockade of dopamine receptors and may be irreversible.^{34,35}

Although the muscle movements (i.e. face, tongue, lips, trunk) may be disturbing to the patients' caregivers or loved ones, they may not bother the patient. Treatment of tardive dyskinesia is beyond the scope of this activity, but the Food and Drug Administration (FDA) approved two new agents, valbenazine and deutetrabenazine, in 2017 for the treatment of this adverse effect.³⁴ Another treatment strategy is to switch to an antipsychotic with a low incidence of tardive dyskinesia (quetiapine, clozapine).³⁵

Metabolic abnormalities associated with antipsychotics include weight gain, glucose intolerance, and lipid abnormalities. Patients with schizophrenia have been found to have increased visceral adiposity compared to controls even if they are drug-naive SGAs may contribute to weight gain by a variety of mechanisms including increased appetite and food intake, a reduction in resting energy expenditure, and changes in insulin homeostasis.^{37,38} Although some SGAs are less like to cause weight gain (aripiprazole, ziprasidone, lurasidone) compared to others (clozapine, olanzapine, quetiapine), all SGAs can cause this adverse effect. Prescribers typically treat metabolic adverse effects using non-pharmacologic lifestyle intervention. However, some evidence supports treatment or prophylaxis with metformin.^{39,40}

Treatment-Resistant Schizophrenia

Patients with schizophrenia that does not respond to two or more adequate antipsychotic trials are deemed treatment-

resistant. Once treatment resistance is diagnosed, clozapine is most likely to be effective, but requires careful monitoring.^{1,5} Pharmacy staff members are in a position to confirm treatment resistance and may help identify treatment nonadherence. Clozapine is labeled with a boxed warning that describes five possible adverse events:

1. Neutropenia
2. Myocarditis
3. Orthostatic hypotension
4. Seizures
5. Increased risk of death in elderly patients with dementia-related psychosis

Clozapine is only available through a restricted program under a Risk Evaluation Mitigation Strategy (REMS) called the Clozapine REMS Program which addresses the risk of neutropenia. To meet REMS requirements and ensure patient safety, the patient, provider, and pharmacy must all enroll in the program. The treatment team must monitor absolute neutrophil count (ANC) on a pre-designated basis to initiate and continue treatment safely. Pharmacists must also report required lab data to the Clozapine REMS program.

Frequent lab draws (ranging from weekly to monthly) can be a significant burden for patients but they are an absolute requirement. Pharmacists can educate and encourage patients treated with clozapine. A patient may attempt to fill a prescription for clozapine at a community pharmacy. If the pharmacy staff is unable to dispense it due to a missing ANC, a staff member can coordinate with the patient and provider to ensure that the patient is able to fill the prescription as quickly as possible so as to not interrupt therapy.

Preventing treatment interruption is imperative for continuity of care; if a patient misses more than two days of clozapine, the dose must be reduced to 12.5-25 mg daily and re-titrated back up to the previous dose. Pharmacy staff members can also help with this aspect of clozapine treatment. For example, if a patient had been prescribed clozapine 400 mg daily but had not picked it up for several months and then came into the pharmacy to fill the prescription, the pharmacy staff member should contact the patient's provider to identify a safe plan for reinitiating treatment.

Zeroing In: Long-Acting Injectable Antipsychotics

A major cause for nonadherence to antipsychotics is this: individuals with cognitive difficulties may forget and/or lack motivation to take oral antipsychotic medications regularly and refill medications consistently. Prescribing a LAIA (see [Table 5](#)) is one approach to preventing nonadherence and gaps in treatment. More than 20 years ago, drug manufacturers developed a limited number of LAIA formulations; haloperidol decanoate and fluphenazine decanoate could be injected intramuscularly once every month. LAIAs avoided the need for daily doses and circumvented administration-related challenges. LAIA formulations release the drug slowly over time (creating long half-lives). Despite the older LAIAs' value on improving medication adherence, the older medications' oral and injectable forms were associated with tardive dyskinesia and other potentially irreversible neuromuscular side effects. Such side effects significantly limited their widespread use.

In the past five years, the FDA approved five new LAIA with lower incidences of neuromuscular side effects and generally better side effect profiles than the older LAIA. Subsequently, newer LAIAs hold great promise for expanding LAIA use and improving medication adherence among patients with FDA-approved indications such as schizophrenia and bipolar illnesses. Several meta-analyses show LAIAs are superior to oral antipsychotics in terms of efficacy and relapse prevention.⁴¹⁻⁴³

PAUSE AND PONDER: I work in a community pharmacy setting. How could I possibly help promote greater use of the LAIAs? How can I encourage more doctors to use these effective medications to improve medication adherence? How can I get more patients interested in using LAIAs?



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Indications for Use

All LAIAs have an FDA indication for use in the initial and maintenance treatment of schizophrenia. A few have additional indications. Aripiprazole extended-release and risperidone microspheres have additional indications for use in bipolar I disorder.^{46,52} However, risperidone microspheres is only indicated for adjunctive treatment with lithium/valproic acid therapy in the maintenance treatment of bipolar I disorder. Paliperidone palmitate (Invega Sustenna) has an additional indication of monotherapy or combined use with mood stabilizers in adults with schizoaffective disorder.⁴⁹ The FDA requires pharmacies to dispense Medication Guides for aripiprazole products and olanzapine palmitate (See <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=medguide.page>)

Dosing Considerations

It is important to note that most patients should receive a trial of the oral formulation (to ensure patient tolerability and no allergic reaction to medication) before receiving the LAIA. If the patient tolerates the oral form, then the prescriber can transition the patient to the LAIA formulation. Knowing that a patient might be a candidate for an LAIA is a valuable consideration when first starting medication; the healthcare team might like to start the patient on an atypical antipsychotic that is also available as an LAIA for later conversion.

Dosing of several of the LAIAs depends on the patient's oral antipsychotic dose. For example, the starting dose of haloperidol decanoate is usually 10-20 times the oral dose (with 100 mg maximum per dose, with the remainder above 100 mg administered 3- to 7 days later).⁴⁵ The starting dose of olanzapine palmitate also depends on the oral dose with higher oral doses associated with higher olanzapine palmitate doses.⁴⁸ Although not an oral formulation, the concept of dosing based on prior exposure to the drug also holds for the Invega Trinza paliperidone palmitate, as this every 3-month LAIA is dosed based on LAIA Invega Sustenna paliperidone palmitate monthly dosing.⁵⁰

The time it takes to convert from the oral to LAIA forms varies somewhat based on the drug and involves overlap between oral and LAIA forms. For example

- Conversion from fluphenazine oral to deconate form may take up to 10 weeks depending on the oral dose before conversion.⁴⁴ Prescribers must decrease the oral fluphenazine dose while simultaneously increasing the deconate dose every two weeks until target deconate dosing is achieved.
- Converting haloperidol oral to deconate is typically based on clinical stabilization with target goal to discontinue oral dosing within one month of starting the deconate.⁴⁵

Table 5. Currently Available Long Acting Injectable Antipsychotics (LAIAs)

Medication	Initial Dose	Target Dose	Dosing Interval	Loading Dose
First Generation LAIAs				
fluphenazine deconate ⁴⁴	12.5 mg per every 10 mg fluphenazine (or use conversion schedule)	12.5 mg-50 mg (Max 100 mg)	Q 2-4 weeks	N/A
haloperidol deconate ⁴⁵	10-20 mg x daily oral dose (Max 100 mg per injection, separated by 3-7 days)	10-15 x daily oral dose (may administer > 100 mg per injection)	Q 4 weeks	Yes
Second Generation LAIAs				
aripiprazole extended-release (Abilify Maintena) ⁴⁶	400 mg	Same as initial dose	Q 4 weeks	No
aripiprazole lauroxil (Aristada) ^{47*}	441 mg, 662 mg, 882 mg, 1064 mg	Same as initial dose	Q 4 weeks; Q 6 weeks for 882 mg only	No
aripiprazole lauroxil (Aristada Initio) ^{47*}	675 mg on Day 1			
olanzapine palmoate (Zyprexa Relprevv) ⁴⁸	150-300 mg Q 2 weeks 405 mg Q 4weeks	Same as initial dose; Max 305 mg Q 2 weeks, 405 mg Q 4 weeks	Q 2 weeks or Q 4 weeks	Yes
paliperidone palmitate (Invega Sustenna) ⁴⁹	234 mg day 1, 156 mg day 8	Same as initial dose	Q 4 weeks	Yes
paliperidone palmitate (Invega Trinza) ⁵⁰	273 mg, 410 mg, 546 mg, 810 mg	Same as initial dose	Q 3 months	Yes
risperidone (Perseris) ⁵¹	90 mg or 120 mg	90 mg or 120 mg	Q 4 weeks	No
risperidone microspheres (Risperdal Consta) ⁵²	25 mg	25-50 mg (Max 50 mg)	Q 2 weeks	No

*ARISTADA INITIO is part of a 1-day initiation regimen (along with a single 30mg aripiprazole dose) given in conjunction with the first dose of ARISTADA. The 1-day initiation regimen is an alternative to 21 days of oral aripiprazole prescribed with the first dose of ARISTADA.⁴⁷

** INVEGA TRINZA may only be used in patients after they have been adequately treated with INVEGA SUSTENNA for at least four months.⁵⁰

For the newer atypical antipsychotics, most can be converted from oral to deconate more quickly.

- Oral risperidone should be given for three weeks after the first risperidone microspheres injection and then discontinued. In 2019, the FDA approved subcutaneous risperidone (Perseris).⁵¹ Subcutaneous risperidone dosing of 90 or 120 mg corresponds to oral risperidone 3 mg/day or 4 mg/day respectively. The product labeling recommends against oral risperidone supplementation.
- Oral olanzapine and paliperidone can be tapered immediately after first injection of olanzapine palmoate and paliperidone palmitate (Invega Sustenna) respectively.^{48,49}
- Aripiprazole requires the oral form to be continued for 14 days prior to starting aripiprazole extended-release and 21 days before starting aripiprazole lauroxil (Aristida) (except if the patient ALSO RECEIVES aripiprazole lauroxil [Aristada Initio] upon initiation).^{46,47}

The LAIAs have a few differences in approaches to initial and target dosing. **Table 5** compares dosing. For many of the LAIAs, maintenance dosing will be based on patient response to the initial doses and the maintenance/target dose is similar to the initial dose. There are a few exceptions. Paliperidone palmitate (Invega Sustenna) has a recommended maintenance dose of 117 mg (maximum of 234 mg) which is lower than the combined first and eighth day loading doses.⁴⁹ When reviewing Table 5, note that prescribers can give some LAIAs in lower but more frequent doses (every 2 weeks or 4 weeks) or administer higher, less frequent doses (every 4 or 6 weeks).

Prescribers may need to make initial and maintenance dosing adjustments in some patients with hepatic and/or renal impairment. For example, the labeling recommends starting risperidone microspheres at 12.5-25 mg⁵¹; both paliperidone palmitates are not recommended if creatine clearance is less than 50^{49,50}; and paliperidone palmitate (Invega Sustenna) dosing is lower for days 1 (156 mg) and 8 (117 mg).⁴⁹ Maintenance dosing for paliperidone

palmitate (Invega Sustenna), therefore, is lower with a target of 78 mg in these patients with hepatic/renal impairment.⁴⁹ We also see the need for dosing adjustments with several LAIAs when patients are taking cytochrome P-450 2D6 or 3A4 inhibitors or 3A4 inducers for more than two weeks. Pharmacists should review the patient's current medications for potential interactions with the LAIA being used.

For a variety of reasons, patients may need to receive their LAIAs earlier or later than their scheduled dose. Risperidone microspheres, both paliperidone palmitates, and both aripiprazole formulations have specific recommendations about administering them before or after the regularly scheduled dose without having to start again with initial dosing or titrations.⁴⁶⁻⁵⁰ Please consult the manufacturer's labeling for specific information.

Administration Considerations

Except for risperidone microspheres, all LAIAs can be stored at room temperature and do not require refrigeration.⁴⁴⁻⁵² Most of the LAIAs can be injected as intramuscular (IM) injections into either the gluteal or deltoid muscles with the exception of aripiprazole extended-release, aripiprazole lauroxil (the 441 mg dose could be given in the deltoid), and olanzapine palmoate.⁴⁴⁻⁵² Subcutaneous risperidone (Perseris) is the only subcutaneous LAIA available.⁵¹ The newer LAIAs come with all of the items needed for injection such as diluents, needles, and/or adapters; haloperidol deconate and fluphenazine deconate require purchase of syringes and needles. The pharmacy would need to have alcohol wipes available for wiping the vial tops before injecting and the patient's skin before injection.

Prepare syringes according to manufacturer's recommendations. For example, some specify removing the package from the refrigerator at least 15 minutes prior to injection (risperidone microspheres and subcutaneous risperidone) to facilitate reconstitution.^{51,52} A few LAIAs specify shaking the vial vigorously for 10 to 20 seconds. Also, it is necessary to follow the manufacturer's administration recommendations. Aripiprazole lauroxil's manufacturer recommends rapid, continuous injection,⁴⁷ but the manufacturers of aripiprazole extended-release, paliperidone palmitate, and risperidone microspheres recommend injecting slowly.^{46,49,50,52} Pharmacists need to note the needle size and volume to be administered at one time (many of these products are viscous solutions that are hard to push quickly). As with administering any injection, always follow best practices for safe needle handling and disposal, and sterile cleaning of medication and diluent vials before puncture. Pharmacists new to preparing and administering LAIAs should receive training. Some pharmacist LAIA training programs may be available locally or nationally through pharmacy associations and universities/colleges of pharmacy.

LAIAs Adverse Effects

Experts indicate that LAIAs should have fewer adverse effects than their oral counterparts since serum drug concentrations fluctuate less and receptor occupancy is more stable. Also, the LAIAs' high bioavailability lowers the effective dose and reduces dose-related side effects. However, a 2017 meta-analysis found LAIAs and their oral counterpart produced similar adverse effects.⁵³ This analysis found that the LAIA formulation of risperidone was slightly less likely to elevate prolactin blood levels than the oral form. However, another analysis found that LAI risperidone was associated with more prolactin-related adverse events than oral medications.⁴³

A meta-analysis reported a higher incidence of more than one adverse event and tremor with LAIAs over oral antipsychotics.⁴³ Yet another meta-analysis also found higher rates of EPS and prolactin-related side effects with LAIAs over oral SGAs.⁴² Based on these findings, clinicians can expect to see LAIA side effects that are fairly similar to those noted earlier in this CE activity (**Table 4**; see page 7). In addition to the common and severe side effects associated with the oral antipsychotics, pharmacists should counsel patients about the possibility of injection site reactions including injection site pain, swelling, erythema, rash, and induration (localized hardening).

The LAIAs carry the same warnings as the oral antipsychotics, such as that older adults with dementia-related psychosis are at risk of death when treated with antipsychotics. Olanzapine palmoate is labeled with a boxed warning; patients are at risk for severe sedation (including coma) or delirium after injection and must be observed for at least three hours in a registered facility with ready access to emergency response services. Due to this risk, olanzapine palmoate is only available through a restricted distribution program and requires prescriber, healthcare facility, pharmacy, and patient enrollment.⁵⁴

PAUSE AND PONDER: How would you respond if an agitated, upset patient with schizophrenia came into the pharmacy? What protocol does your pharmacy have in place to manage these situations? How would you manage these symptoms in a patient with no history of mental illness?

LAIA Cost Considerations

Pharmacists and technicians should consult the patient's insurance formulary to confirm coverage of specific LAIAs. In general, LAIAs are more expensive than the oral antipsychotics, and the newer LAIAs are more expensive than the older LAIAs. A retrospective analysis of healthcare costs showed that discontinuation rates and inpatient costs were significantly lower with LAIAs compared to oral antipsychotics.⁵⁵ However, this same analysis reported that monthly medication costs of LAIAs were significantly higher than those of oral antipsychotics and that there were no significant differences in total medical costs between groups receiving LAIAs and oral antipsychotics.⁵⁵

Tech Talk: Patient Assistance Programs

Patients who cannot afford their medication may be eligible for various patient assistance programs. The process differs depending on the pharmaceutical company's requirements. Advise patients that they will need to provide financial information, and most programs require the prescriber to complete some paperwork.

When working with people who have schizophrenia who are interested in applying for patient assistance, patience is a virtue. Many patients have case managers—health care professionals whose job is to identify patients' needs, goals, strengths/abilities, and preferences in their treatment and recovery. Patients who have mental health challenges usually know who their case managers are, and how to contact them.

Often, calling the case manager and explaining the situation—whether it's a costly prescription or a behavioral challenge in the pharmacy—can open the door for productive discussion and better understanding of the patient's needs.

The table to the right lists specific patient assistance programs for LAIAs.

LAIA	Patient Assistance Program
Haloperidol decanoate Invega Sustenna Invega Trinza Risperdal Consta	Janssen Prescription Assistance 1-800-526-7736 http://www.janssenprescriptionassistance.com
Abilify Maintena	Assure Otsuka Patient Support 1-855-242-7787 https://www.assure.com/patient/abilify-maintena/tools-resources?_ga=2.150738742.1017984916.1572029585-943857923.1571857782
Aristada	Aristada Care Support 1-866-274-7823 https://www.aristadacaresupport.com
Zyprexa Relprevv	ZYPREXA RELPREVV Patient Care Program 1-877-772-9390 https://www.zyprexarelprevvprogram.com/public/contactus.aspx
Perseris	Insupport 1-844-INSPRT https://www.insupport.com/hcp

Emerging Opportunities for Pharmacists

Discussions with mental health providers reveal that LAIA are not widely used due to the lack of accessible injection services. LAIAs have typically been administered by nurses in physician offices and/or clinics. However, busy physician practices, limited office hours, transportation difficulties, and other related challenges can potentially limit patient access. Having other trained professionals who are more available and accessible to administer the LAIAs can help patients avoid some logistical issues and receive injections in a safe, convenient, efficient way. Trained community pharmacists are well positioned to add LAIA administration to the clinical services they provide. Nearly all states have pharmacy practice regulations that indicate specific situations under which they allow pharmacists to administer injectable drugs.⁵⁶

Pharmacists interested in administering LAIAs should explore their state regulations to see if they allow them to administer specific medications and/or have language allowing pharmacists and prescribers to develop a collaborative practice agreement (CPA). CPAs describe a specific relationship between a pharmacist and prescriber and what the medication support activities a pharmacist is allowed to do with the prescriber's patients. For example, in Connecticut, several CPAs have been developed that allow pharmacists to administer LAIAs to the prescriber's patients. Nebraska's existing legislation allows

payment to pharmacists for LAIA injection services. While exploring these regulations, pharmacy staff should review the specific regulatory requirements so they can ensure compliance before setting up the service.

For example, regulations may specify the need for private space for injections and a documentation process to capture patient symptoms, side effects and any other concerns. Some regulations may specify that the first dose of the LAIA be administered in the physician's office. In addition to careful review of the regulations, the pharmacy may want to consider having a male and a female pharmacist trained in administering the injections to allow for patient-specific requests for a certain gender. Also, pharmacy staff may want to create forms to document patient consent to a specific LAIA and specify how they will communicate with the prescriber about the injections and other updates.

Some strategies may reduce prescriber and nurse resistance to the pharmacist's expanded role. First, pharmacists might suggest they are performing the service to improve LAIA access for patients. They should emphasize this role in situations where prescribers employ no on-site nurses and therefore lack staff or time. Second, pharmacists can indicate they are happy to work with nurses as a back-up or as an additional resource for times when nurses are unavailable. This safety net model highlights the pharmacy as a part of the team

making the LAIA available and accessible when the patient needs or is able to receive it.

To start the process of considering a CPA, it is also critical for LAIA-trained pharmacists to initiate conversations with psychiatrists in their area and describe their expertise and interest. If you don't know the psychiatrists in the area, you may need to arrange 1:1 meetings and/or use letters to promote the service. In addition, several manufacturers have developed programs to allow nurses to administer LAIAs at pharmacies in areas where state laws prohibit pharmacists from doing so. Alkermes, Janssen, and Ostuka America Pharmaceuticals have sponsored past and/or current programs. Pharmacists interested in becoming injection/local care centers can contact one or more of these companies to learn the status of the opportunity and next steps.

Pharmacy Team's Role

Pharmacy staff can help patients with schizophrenia or bipolar illness feel significantly more comfortable using LAIAs if they engage in a few key best practices.

- 1. Create a stigma-free environment.** Provide an inviting, supportive culture around the care of those with mental health needs. Avoid language that labels the person as mentally ill and try to use person-first language. For example, saying "an individual with schizophrenia" is kinder and less defining than saying "a schizophrenic." Also, use language that empowers individuals towards hope and recovery and advocates for their needs and right to be informed and supported about their treatment. Pharmacy staff needs to initiate discussion and reach out to individuals with mental health needs and avoid assuming patients are uninterested or unreceptive to discussion. Listening with empathy and openness may require considerable patience. Simply, staff needs to show a willingness and desire to engage.
- 2. Provide education and ongoing monitoring.** Individuals with mental illnesses desire as much information about their medications as those with physical illnesses. In many cases, they may be particularly anxious about their treatments and worry about side effects and drug interactions. It is also critical to be proactive about medication adherence. Help them stay on track with their medications and seek solutions for situations contributing to their nonadherence. Prevention of medication nonadherence may prevent treatment disruption and negative clinical outcomes. It can also reduce costs.
- 3. Engage mental health specialists and advocates in your community.** Pharmacy staff should reach out to various community mental health specialists and mental health advocates and tell them about their interest in being a resource for medication information and other treatment services such as administering LAIAs. This may involve attending community health fairs or setting up appointments at prescriber offices, or community mental health centers. Pharmacies need to learn their colleagues' level of interest in engaging pharmacists trained in administering LAIAs, and referring their patients to pharmacies to receive LAIA injections. Pharmacies can also offer themselves as a resource to mental health specialists who are trying to manage the complexities of integrating medications they are prescribing with those patients received from primary care prescribers and other specialists. Such navigation may require pharmacy staff to determine the patient's most accurate medication list (medication reconciliation), encourage deprescribing (removal of unnecessary medications), highlight critical drug interactions, engage in proactive side effect and efficacy monitoring, and active outreach to share clinical concerns with prescribers.
- 4. Prepare the pharmacy for administering LAIAs.** As with any new service, the pharmacy must be properly set up to carry out the service efficiently. The associated tasks must fit within the point-of-service workflow. As noted earlier, individuals will need to be trained in safe LAIA administration. The pharmacy will need space to administer LAIAs privately and equipment to adhere to best practices for administration discussed above. Ideally, they should have an organized way to document each injection administered and to maintain that documentation in a private, secure location. Further, this documentation should specify what LAIA was administered (lot number and expiration date), administration date and time, route, injection site, who administered it, and any concerns associated with administration. To maximize the service's clinical value, pharmacy staff can also record the patient's weight, blood pressure, pulse and respiratory rate, and clinical observations of the patient's appearance, affect, and interactions (eye contact, level of engagement in conversation, etc.). In addition, the staff should ask patients about sleep and appetite, side effects, and emergence of new behaviors. The pharmacy should also establish a consistent process of faxing or sharing such notes with prescribers after visits and letting prescribers know when patients do not appear for appointments. Pharmacies should also develop and retain drug-specific consent forms that patients sign.

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We integrated some experiences into several sections of the present manuscript.*

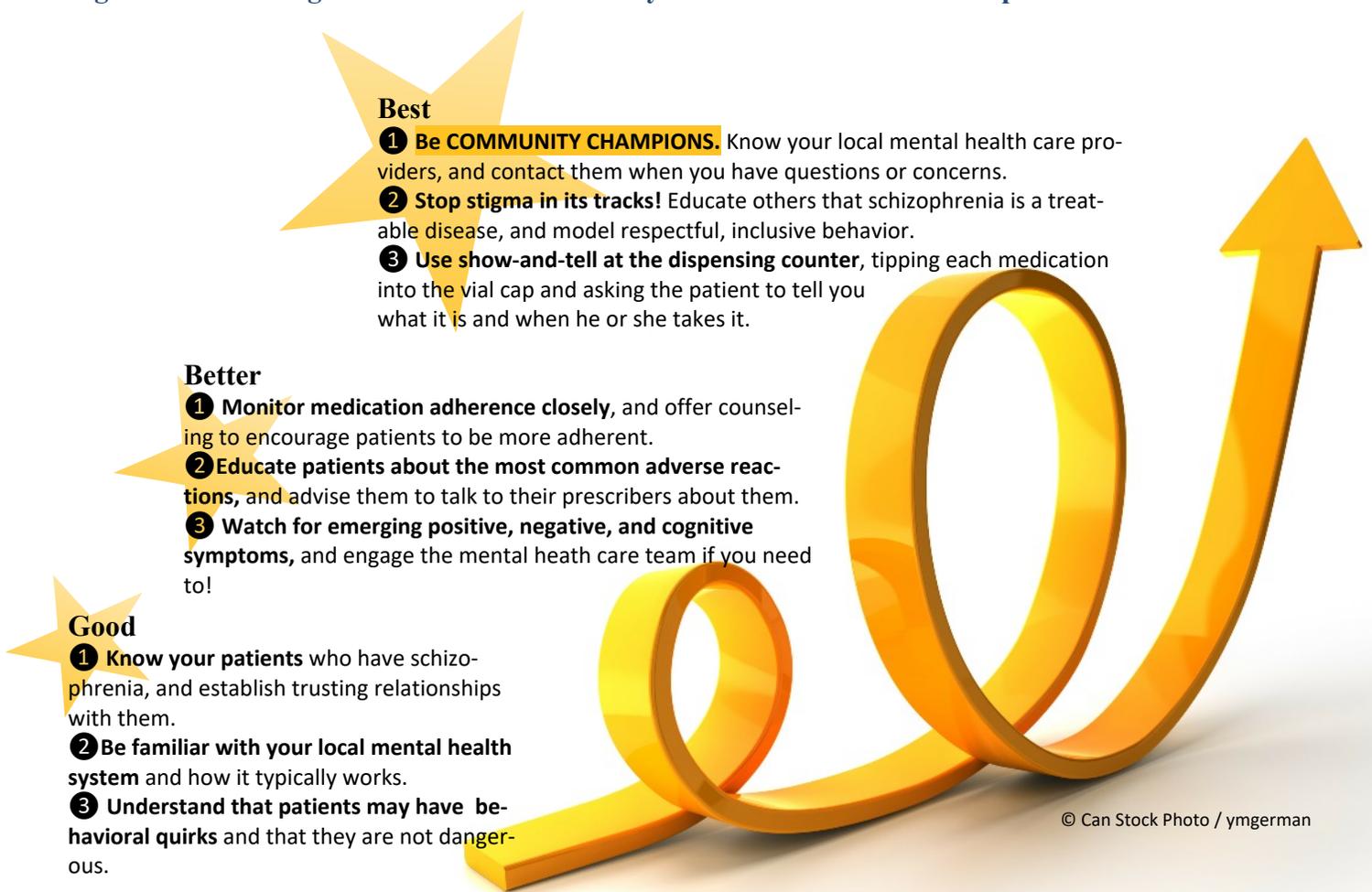
5. **Collect feedback about new services and seek ways to ensure sustainability.** To make the new service more effective and impactful, pharmacy staff might consider developing a survey, conducting interviews, and/or holding focus groups to assess patient and prescriber experiences. The pharmacy may wish to work with a school of pharmacy to develop these measures and evaluate the results. Informing pharmacy associations and state-level pharmacy organizations about the results lets them use the results to leverage new legislation that might support reimbursement and service continuity.

Figure 1 summarizes important steps in becoming involved and “indispensable.”

CONCLUSION

Schizophrenia can be difficult to manage due to stigma, symptom management, side effects, and high risk of medication non-adherence. Newer medications such as the SGAs have better musculoskeletal side effect profiles than the older FGAs but, unfortunately, are associated with other side effects such as weight gain, dyslipidemias, and diabetes. Several new LAIAs can significantly improve medication adherence, and reduce the risk of relapse and relapse-related hospitalizations. Administering the LAIAs is a new opportunity for pharmacist and technician involvement in patient care. By reducing stigma and other treatment barriers, pharmacists and technicians can facilitate a more engaged and proactive patient and healthcare team that is consistently committed to advancing the safe, efficient, and effective treatment of schizophrenia.

Figure 1. Advancing Pharmacist and Pharmacy Technician Roles in Schizophrenia Care



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