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CME Review Article

Long-Acting Injectable Antipsychotics: What, When, and How

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- Identify patients who may benefit from transition to a long-acting injectable (LAI) antipsychotic
- Apply evidence-based practices when initiating LAI antipsychotics in the treatment of schizophrenia

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Long-acting injectable antipsychotics: what, when, and how

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Review

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Abstract

Current guidelines for the treatment of patients with schizophrenia advocate that patients receive treatment with a long-acting injectable (LAI) antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence. Available LAI formulations in the United States include first-generation antipsychotics (fluphenazine decanoate and haloperidol decanoate), risperidone/paliperidone containing products (risperidone microspheres, paliperidone palmitate, and risperidone subcutaneous), aripiprazole containing products (aripiprazole monohydrate and aripiprazole lauroxil), and olanzapine pamoate. LAI antipsychotics can address the guesswork about adherence status and patients may prefer them if they are offered this as a choice, including individuals early in their disease course. Additional approved indications in the United States for LAI antipsychotics include bipolar I disorder maintenance treatment for risperidone microspheres and aripiprazole monohydrate, and schizoaffective disorder for paliperidone palmitate once monthly. Differences and similarities among the different products are discussed, including guidance regarding optimal treatment selection. Tips are provided to enhance effective patient communication to maximize the likelihood of acceptance of this treatment modality.

Introduction

Antipsychotics are the foundational treatment for schizophrenia and schizoaffective disorder, and an important option for the treatment of bipolar disorder. However, even if a medication can reduce symptoms and is tolerable for that individual,[1] adherence issues often emerge.[2] Long-acting injectable (LAI; depot) formulations of antipsychotics can assist with adherence, leading to better outcomes. Many patients prefer LAI formulations, especially after gaining some experience with this modality.[3] In the most recent iteration of the guidelines for the treatment of patients with schizophrenia published by the American Psychiatric Association, the authors advocate that patients receive treatment with a LAI antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence.[4] Regarding the latter, nonadherence to oral antipsychotic medication treatment (defined by some investigators as a failure to take at least 80% of prescribed medication) is common and has been observed in approximately half of all patients with schizophrenia, schizoaffective disorder, and bipolar disorder.[5-7] Lack of adherence extends out to treatments targeting comorbidities, especially when the underlying psychiatric disorder remains poorly managed.[8,9] Given the consequences of nonadherence to antipsychotic medication, including relapse, hospitalization, aggressive behavior, suicide, substance abuse, and disease progression,[10-18] efforts to identify and address poor adherence is crucial. LAI antipsychotics can eliminate the guesswork about adherence status and allow the clinician to focus on other reasons why symptoms may be exacerbated, such as psychosocial stressors or substance use. In the end, preventing a relapse today can make a difference for a lifetime.

What are the available LAI options?

In the United States, there are several LAI antipsychotics to select from and they are listed in Table 1.[19-21] Older first-generation antipsychotics such as fluphenazine decanoate (administered every 2 weeks) and haloperidol decanoate (administered every 4 weeks) remain available.[19] Both can be injected in either the deltoid or gluteal muscle. They are dissolved in sesame seed oil and may be more challenging to inject than the second-generation intramuscular LAI formulations which are all suspended in water. Nevertheless, fluphenazine decanoate and haloperidol decanoate are relatively inexpensive and commonly prescribed. For fluphenazine decanoate the initial dose is 12.5 to 25 mg and can be increased in increments of 12.5 mg but the total amount administered at one time should not exceed 100 mg.[22] The initial dose for haloperidol decanoate should be 10 to 20 times the previous daily dose in oral haloperidol equivalents but the initial injection is limited to 100 mg, followed by the balance

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Table 1. Long-Acting Injectable Antipsychotics Available in the United States as of December 2020

- First-generation antipsychotics
  - Haloperidol decanoate
  - Fluphenazine decanoate
- Second-generation antipsychotics
  - Risperidone- or paliperidone-containing formulations
    - Risperidone microspheres
    - Risperidone subcutaneous
    - Paliperidone palmitate monthly
    - Paliperidone palmitate every 3 months
  - Aripiprazole-containing formulations
    - Aripiprazole monohydrate
    - Aripiprazole lauroxil
  - Olanzapine pamoate

Table 2. Long-Acting Injectable Antipsychotics: "Amenities of Care"

- How often are the injections administered?
- What is the needle gauge?
- What is the injection volume?
- Is there a choice of injection site?
- Does this product require reconstitution?
- Is oral supplementation required?
- Does storage of this product require refrigeration?
- Are there any special requirements for post-injection observation?
- Are there any important drug–drug interactions, and can they be remedied?
- Missed doses: What is the "grace period?"
- Is reimbursement an issue if used "off-label"?
- In case of reimbursement obstacles, can I easily access a patient-assistance program?

3 to 7 days later. The usual maintenance range is 10 to 15 times the previous daily dose in oral haloperidol equivalents depending on clinical response. Clinical experience with haloperidol decanoate at doses greater than 450 mg/month is limited.[23] Other first-generation LAI antipsychotics have been available outside the United States (eg, flupentixol, perphenazine, pipotiazine, and zuclopenthixol).[24] The biggest limitation to using first-generation LAI antipsychotics is the common occurrence of drug-induced parkinsonism and thus the use of anticholinergic medication. This contributes to an increased risk of developing tardive dyskinesia.[25] In addition, anticholinergic medications can also be associated with worsened cognitive impairment.[26] Drug-induced parkinsonism and the need for anticholinergic medications can be minimized by using second-generation LAI antipsychotics.

There are three different second-generation antipsychotics currently available in LAI formulations: risperidone/paliperidone, aripiprazole, and olanzapine. For each of these second-generation antipsychotic categories, there may be several different products to consider. The different formulations containing the same active molecule can be differentiated in terms of their "amenities of care" such as dosing intervals (eg, every 2, 4, 6, 8, or 12 weeks), availability of different dose strengths, choice of injection site, size of the needle, injection volume, storage and reconstitution requirements, need for oral supplementation, guidance regarding early or late dosing, and approved indications. A list of these pragmatic considerations is contained in Table 2.

Risperidone/paliperidone containing formulations

Table 3 outlines the four different formulations available that contain risperidone or paliperidone. They differ broadly in approved indications, dosage forms/strengths, reconstitution requirements, injection sites, needle gauge/length, injection volume, injection interval, requirement for oral supplementation, need for refrigeration when stored, and instructions for early or late dosing.

In 2003, risperidone microspheres became the first second-generation antipsychotic to be available in a LAI formulation.[27,28] In addition to the indication for schizophrenia, risperidone microspheres are also approved as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder.[20,29] Of note, storage of the product requires refrigeration.[29] Because the main release of the drug does not begin until 3 weeks after administration, supplemental oral risperidone is required for 21 days after the first injection and after any dose increase.[29] After mixing the risperidone microspheres powder with the supplied aqueous diluent, it can be administered in the deltoid or gluteal muscle. The recommended starting dose is 25 mg/2 weeks, and the maximum recommended dose is 50 mg/2 weeks. With respect to total exposure, injections of 25, 50, or 75 mg every 2 weeks were found to be equivalent to daily oral doses of 2, 4, or 6 mg of risperidone, respectively.[30] Another formulation of an intramuscular risperidone LAI is under development (risperidone ISM); although reconstitution of risperidone ISM is needed and the maximum dose is limited to the equivalent of oral risperidone 4 mg/day, it can be administered monthly and does not require oral supplementation or loading doses.[31,32]

The use of risperidone microspheres administered every 2 weeks has been replaced in many instances with paliperidone palmitate administered monthly or every 3 months. Paliperidone (9-OH risperidone) is the main active metabolite of risperidone and a once-monthly injectable formulation became available in the United States in 2009.[33-35] In contrast to risperidone microspheres which must be reconstituted as well as stored in a refrigerator, paliperidone palmitate is an aqueous suspension that comes in prefilled syringes and does not require refrigeration. The product has relatively small needle bores to choose from. Instead of using oral supplementation, the initiating doses are all by injection: 234 mg on treatment day 1 and 156 mg 1 week later (±4 days), both administered in the deltoid muscle. Although the recommended monthly maintenance dose is 117 mg for the treatment of schizophrenia, the maintenance doses can be within the range of 39 to 234 mg, equivalent to the dose range of 3 to 12 mg/day for oral paliperidone.[33] When converting from oral risperidone to paliperidone palmitate, oral risperidone doses of 1, 2, 3, 4, and 6 mg/day result in similar exposures as 39, 78, 117, 156, and 234 mg of paliperidone palmitate, respectively.[36] The regular monthly maintenance doses can be administered in either the deltoid or gluteal muscle. In addition to the indication for treatment of schizophrenia, paliperidone palmitate once monthly received approval for use in schizoaffective disorder as monotherapy or as an adjunct to mood stabilizers or antidepressants.[20,33,35] In 2015, a 3-month formulation was approved for the treatment of schizophrenia in individuals who have been treated with the once-monthly formulation of paliperidone palmitate for ≥4 months.[20,37] In contrast to the once-monthly preparation, this longer-acting formulation of paliperidone palmitate does not have approval for schizoaffective disorder at the present time. The 3-month formulation is packaged in water-based prefilled syringes; however, the product is denser than the once-monthly formulation and has a larger particle size.[38] The doses that are available remain sufficiently small in volume so that they can be administered in the deltoid muscle, although gluteal injection remains an option. Dose for the 3-month formulation is calculated by multiplying the once-monthly dose by 3.5.

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Table 3. Summary of Characteristics of Risperidone- or Paliperidone-Containing Long-Acting Injectable Antipsychotics Commercially Available in the United States

	Risperidone Microspheres	Paliperidone Palmitate Once Monthly	Paliperidone Palmitate Every 3 mo	Risperidone Subcutaneous
Brand name (United States)	Risperdal Consta	Invega Sustenna	Invega Trinza	Perseris
Year commercialized	2003	2009	2015	2018
Active moiety	Risperidone and paliperidone	Paliperidone	Paliperidone	Risperidone and paliperidone
Approved indications (all adult)	Schizophrenia; bipolar I disorder maintenance treatment (monotherapy or adjunctive to lithium or valproate) (2009)	Schizophrenia; schizoaffective disorder (monotherapy or adjunctive to mood stabilizers or antidepressants) (2014)	Schizophrenia	Schizophrenia
Contraindications	Known hypersensitivity to risperidone, paliperidone, or to any excipients in the product	Known hypersensitivity to paliperidone, risperidone, or to any excipients in the product	Known hypersensitivity to paliperidone, risperidone, or to any excipients in the product	Known hypersensitivity to risperidone, paliperidone, or other components in the product
Dosage forms/strengths	Vial kits: 12.5, 25, 37.5, and 50 mg	Injectable suspension: 39, 78, 117, 156, and 234 mg	Injectable suspension: 273, 410, 546, and 819 mg	Syringe kits: 90 and 120 mg
Requires adding diluent/liquid	Yes	No	No	Yes
Injection type	Intramuscular	Intramuscular	Intramuscular	Subcutaneous
Approved injection sites	Deltoid or gluteal muscle	Deltoid or gluteal muscle	Deltoid or gluteal muscle	Abdomen
Needle gauge and length	20G/2-inch, 21G/1-inch	22G/1.5-inch, 23G/1-inch	22G/1 or 1.5-inch	18G/0.625-inch
Injection volume	Approximately 2 mL	156 mg/mL; range 0.25 mL (39 mg) to 1.5 mL (234 mg)	312 mg/mL; range 0.9 mL (273 mg) to 2.6 mL (819 mg)	0.6 mL (90 mg), 0.8 mL (120 mg)
Injection interval (wk)	2	4	12	4
Starting dose	25 mg	234 mg day 1 and 156 mg day 8 (deltoid)	After treatment with 1-mo paliperidone palmitate for ≥4 months: 273 mg, 410 mg, 546 mg, 819 mg (3.5 times the last dose of the once monthly formulation)	90 or 120 mg
Maintenance dose	25 mg, maximum 50 mg/2 wk	117 mg, range 39 to 234 mg/4 wk	Same as above	90 or 120 mg
Oral dose equivalent	25, 50 or 75 mg every 2 weeks are equivalent to daily oral doses of 2, 4 or 6 mg of risperidone, respectively	Maintenance doses of 39 mg to 234 mg are equivalent to the dose range of 3 to 12 mg/d for oral paliperidone; when converting from oral risperidone to paliperidone palmitate, oral risperidone doses of 1, 2, 3, 4, and 6 mg/d result in similar exposures as 39, 78, 117, 156, and 234 mg of paliperidone palmitate, respectively	See data regarding paliperidone once-monthly and the corresponding doses with 3-mo paliperidone palmitate as above	90 and 120 mg administered monthly are equivalent to oral risperidone 3 or 4 mg/d, respectively
Half-life	3 to 6 d	25 to 49 d	84 to 95 d (deltoid), 118 to 139 d (gluteal)	9 to 11 d
Oral supplementation?	21 d after the initial injection and after any change in dose	No	No	No
Missed dose grace period[a]	No data	2 wk	4 wk	No data
Early dosing permitted?	No data	21 d after last injection	2.5 mo after last injection	No data
Stored refrigerated?	Yes	No	No	Yes
Mandated observation period post injection?	No	No	No	No

[a]Defined as the amount of time that can elapse after an injection is due before any supplemental oral medication is required (risperidone microspheres), or in the case of LAI antipsychotics where oral supplementation is not used, the amount of time that can elapse after an injection is due before any extra dose(s) of LAI antipsychotic is required (paliperidone palmitate).

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The 3-month formulation requires the use of special-purpose thin-walled needles that come packaged with the product and these needles cannot be interchanged with those supplied with the once-monthly formulation or with other regular commercially available needles. A 6-month version of paliperidone palmitate is under development (NCT03345342, NCT04072575).

In 2018, a sustained release of risperidone was approved for subcutaneous injection in the abdomen.[21,39] This is a novel method of administration for psychiatric medications (although fluphenazine decanoate is also approved for subcutaneous use, it is generally thought of as an intramuscular medication). Storage of the product requires refrigeration. The injection process requires preparing the product by mixing the risperidone powder with the liquid vehicle using two syringes coupled together. The needle itself is 18 gauge but short (5/8 inch). The available doses strengths are 90 and 120 mg administered monthly, which are equivalent to oral risperidone 3 or 4 mg/day, respectively. Another formulation of a subcutaneous risperidone LAI is under development (TV-4600); reconstitution of TV-4600 is not required, and injections can be administered every 1 or 2 months.[32]

Aripiprazole containing formulations

Table 4 outlines the three different formulations available that contain aripiprazole, with one of them (aripiprazole lauroxil nanocrystal dispersion) reserved for the initiation of aripiprazole lauroxil.[20,40-46] Principal differences between the formulations include approved indications, dosage forms/strengths, reconstitution requirements, injection sites, needle gauge/length, injection volume, injection interval, requirement for oral supplementation, concomitant use instructions with CYP3A4 inducers, and instructions for early or late dosing.

Aripiprazole monohydrate became available in the United States in 2013.[19,20,40,43] Following reconstitution with water using either a vial kit or a pre-filled dual-chambered syringe, the monthly injection can be administered in either the deltoid or gluteal muscle. Oral supplementation with aripiprazole or any other antipsychotic is required for 14 days after the initial injection. In Canada and the EU, but not in the US, product labeling permits initiation of aripiprazole monohydrate by administering two separate injections of 400 mg at different injection sites, along with one 20 mg dose of oral aripiprazole, all on the first day of treatment (https://www.newswire.ca/news-releases/health-canada-approves-otsuka-and-lundbeck-s-abilify-maintena-r-aripiprazole-for-prolonged-release-injectable-suspension-alternative-initiation-regimen-850848524.html). The recommended initial and maintenance doses are 400 mg, although a reduction to 300 mg can be considered to manage tolerability concerns. Blood levels achieved with aripiprazole monohydrate 400 mg are comparable with those of oral aripiprazole 15 to 20 mg/day.[47] In addition to being approved for the treatment of schizophrenia, aripiprazole monohydrate is also approved for maintenance monotherapy treatment of bipolar I disorder.[20,43] A 2-month formulation of aripiprazole monohydrate is under development (NCT04030143).

Aripiprazole lauroxil was introduced in the United States in 2015.[20,40,44] Aripiprazole lauroxil is supplied in prefilled syringes as an aqueous suspension.[44] Once injected into the deltoid muscle (approved for the 441 mg dose) or gluteal muscle (approved for any of the doses), the conversion of aripiprazole lauroxil to aripiprazole is governed by the slow dissolution of aripiprazole lauroxil and subsequent enzyme-mediated cleavage by esterases. When the product was launched, dose strengths of 441, 662, and 882 mg were initially available. These doses, when administered monthly, yield exposures to aripiprazole equivalent to oral aripiprazole 10, 15, and ≥20 mg/day, respectively. The dose of 882 mg administered every 6 weeks yields similar exposures as 662 mg administered monthly. In 2017, a dose strength of aripiprazole lauroxil 1064 mg administered every 2 months became available and yields equivalent exposures as 662 mg monthly or 882 mg every 6 weeks. Instructions for the use of aripiprazole lauroxil suggest that any dose can be initiated, including 1064 mg every 2 months (in contrast to 3-month paliperidone palmitate which must be preceded by ≥4 months of exposure to 1-month paliperidone palmitate). Initiation of aripiprazole lauroxil requires either 21 days of supplementation with oral aripiprazole or the use of the aripiprazole lauroxil nanocrystal dispersion (ALNCD) formulation, available since 2018.[41,42,45,46] ALNCD contains nanometer-sized particles instead of the micrometer-sized particles contained in standard aripiprazole lauroxil; the smaller particles have faster dissolution properties when injected into the muscle.[42] An injection of the ALNCD formulation into either the deltoid or gluteal muscle, plus administration of oral aripiprazole 30 mg that same day, can substitute for the 21 days of oral supplementation that would otherwise be required when starting aripiprazole lauroxil.[46] The first injection of standard aripiprazole lauroxil may be administered on the same day as the ALNCD formulation or up to 10 days thereafter. The ALNCD formulation can also be used in lieu of oral supplementation when the regularly scheduled injection is unduly delayed.[44] Because there is only one strength of the ALNCD formulation available (675 mg), adjustments to the dose are not possible in the presence of potential drug–drug interactions, such as with strong CYP2D6 or CYP3A4 inhibitors and strong CYP3A4 inducers, and thus the ALNCD formulation cannot be used under those circumstances and a 21-day oral supplementation period will then be necessary.[44,45]

Olanzapine containing formulations

Table 5 outlines the characteristics of olanzapine pamoate.[48-50] There are currently no alternative LAI formulations of olanzapine commercially available. Olanzapine pamoate was approved in the United States in 2009. It differs from the other LAI antipsychotics in that its use is governed by a Risk Evaluation and Mitigation Strategy program (United States) or Risk Minimization Plan (Europe), requiring a 3-hour post-injection monitoring period after each injection.[50] This is to better manage the potential risk of Post-injection Delirium Sedation Syndrome (PDSS), as described below.

Olanzapine pamoate is a crystalline salt formulation composed of olanzapine and pamoic acid.[48,49] After reconstitution in water, it is injected into the gluteal muscle and the salt slowly dissolves, releasing olanzapine over a period of weeks. However, when olanzapine pamoate comes into contact with a substantial amount of blood or plasma, the salt dissolves more quickly, resulting in the release of a larger amount of olanzapine, potentially leading to PDSS characterized by sedation, confusion, slurred speech, altered gait or unconsciousness. PDSS can be expected to occur in approximately 0.07% of injections and is time-limited but may require symptomatic treatment.[51,52] Because there are no clear identifiable risk factors, olanzapine pamoate can only be provided at registered healthcare facilities and patients must be monitored by appropriately qualified staff for at least 3 hours after injection. In the United States, there is the additional requirement that patients must be

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Table 4. Summary of Characteristics of Aripiprazole-Containing Long-Acting Injectable Antipsychotics Commercially Available in the United States

	Aripiprazole Monohydrate	Aripiprazole Lauroxil	Aripiprazole Lauroxil Nanocrystal Dispersion
Brand name (United States)	Abilify Maintena	Aristada	Aristada Initio
Year commercialized	2013	2015	2018
Active moiety	Aripiprazole and dehydro-aripiprazole	Aripiprazole and dehydro-aripiprazole	Aripiprazole and dehydro-aripiprazole
Approved indications (all adult)	Schizophrenia; bipolar I disorder maintenance treatment (monotherapy) (2017)	Schizophrenia	Schizophrenia
Contraindications	Known hypersensitivity to aripiprazole	Known hypersensitivity to aripiprazole	Known hypersensitivity to aripiprazole
Dosage forms/strengths	Vial kits and dual-chambered prefilled syringes: 300 and 400 mg	Injectable suspension: 441, 662, 882, and 1064 mg	Injectable suspension: 675 mg
Requires adding diluent/liquid	Yes	No	No
Injection type	Intramuscular	Intramuscular	Intramuscular
Approved injection sites	Deltoid or gluteal muscle	Deltoid (441 mg only) or gluteal muscle	Deltoid or gluteal muscle
Needle gauge and length	21G/2-inch, 22G/1.5-inch, or 23G/1-inch	20G/1.5 or 2-inch, 21G/1-inch	20G/1.5 or 2-inch, 21G/1-inch
Injection volume	200 mg/mL; range 0.8 mL (160 mg) to 2 mL (400 mg)	276 mg/mL: range 1.6 mL (441 mg) to 3.9 mL (1064 mg)	2.4 mL
Injection interval (wk)	4	4, 6, or 8	Not applicable
Starting dose	400 mg	441 mg/4 wk, 662 mg/4 wk, 882 mg/4 wk, 882 mg/6 wk, 1064 mg/8 wk	Not applicable
Maintenance dose	300 or 400 mg/4 wk (adjust for CYP2D6 or CYP3A4 inhibitors; cannot give with CYP3A4 inducers)	Same as above (adjust for CYP2D6 or CYP3A4 modulators)	Not applicable
Oral dose equivalent	Blood levels achieved with aripiprazole monohydrate 400 mg are comparable with those of oral aripiprazole 15 to 20 mg/d	Aripiprazole lauroxil 441 mg monthly is equivalent to oral aripiprazole 10 mg/d; 662 mg monthly, 882 mg every 6 wk, or 1064 mg every 2 mo is equivalent to oral aripiprazole 15 mg/d; 882 mg monthly is equivalent to oral aripiprazole ≥20 mg/d	Not applicable
Half-life	29.9 d (300 mg), 46.5 d (400 mg)	53.9 to 57.2 d	15 to 18 d
Oral supplementation?	14 d after the initial injection (option to shorten to 1 day with 2 injections in Canada and EU - see text)	21 d after the initial injection or 1 day when used with the nano-crystal dispersion formulation	One day of aripiprazole 30 mg
Missed dose grace period[a]	Up to 2 wk	Up to 4 wk	Not applicable
Early dosing permitted?	26 d after last injection	14 d after last injection	Not applicable
Stored refrigerated?	No	No	No
Mandated observation period post injection?	No	No	No

[a]Defined as the amount of time that can elapse after an injection is due before any supplemental oral medication (or aripiprazole lauroxil nano-crystal dispersion) is required. Details may vary depending on the dose of the last injection (as with aripiprazole lauroxil) or may vary by how many consecutive injections have already been administered (as with aripiprazole monohydrate).

accompanied to their next destination upon leaving the facility. Because the risk of PDSS is cumulative, patients receiving olanzapine pamoate every 2 weeks can decrease their risk of PDSS by 50% by switching to monthly injections. PDSS is not common; from a provider perspective, a clinic with 60 patients receiving an injection every 2 weeks might expect approximately one event per year.[51]

Initiation of olanzapine pamoate does not require oral supplementation. The recommended starting and maintenance dose is dependent on the dose of oral olanzapine required for stabilization: for patients requiring olanzapine 10 mg/day, the starting olanzapine pamoate dose is 210 mg every 2 weeks or 405 mg every 4 weeks, and then if clinically indicated, patients can be evaluated 2 months later for a reduction to a maintenance dose of 150 mg every 2 weeks or 300 mg every 4 weeks; for patients requiring oral olanzapine 15 mg/day, the starting olanzapine pamoate dose is 300 mg every 2 weeks, and then if clinically indicated, patients can be evaluated 2 months later for a reduction to a maintenance dose of 210 mg every 2 weeks or 405 mg every 4 weeks; for patients

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Table 5. Summary of Characteristics of Olanzapine-Containing Long-Acting Injectable Antipsychotics Commercially Available in the United States

	Olanzapine Pamoate
Brand name (United States)	Zyprexa Relprevv
Year commercialized	2009
Active moiety	Olanzapine
Approved indications (all adult)	Schizophrenia
Contraindications	None
Dosage forms/strengths	Vial kits: 210, 300, and 405 mg
Requires adding diluent/liquid	Yes
Injection type	Intramuscular
Approved injection sites	Gluteal muscle
Needle gauge and length	19G/1.5-inch
Injection volume	150 mg/mL; range 1.0 mL (150 mg) to 2.7 mL (405 mg)
Injection interval (wk)	2 or 4
Starting dose	210 mg/2 wk, 405 mg/4 wk, 300 mg/2 wk
Maintenance dose	150 mg/2 wk, 300 mg/4 wk, 210 mg/2 wk, 405 mg/4 wk, 300 mg/2 wk
Oral dose equivalent	For oral olanzapine 10 mg/d, the starting olanzapine pamoate dose is 210 mg every 2 wk or 405 mg every 4 wk, with a maintenance dose of 150 mg every 2 wk or 300 mg every 4 wk; for olanzapine 15 mg/d, the starting olanzapine pamoate dose is 300 mg every 2 wk, with a maintenance dose of 210 mg every 2 wk or 405 mg every 4 wk; for oral olanzapine 20 mg/d, the starting and maintenance dose of olanzapine pamoate is 300 mg every 2 wk
Half-life	30 d
Oral supplementation?	No
Missed dose grace period	No data
Early dosing permitted?	No data
Stored refrigerated?	No
Mandated observation period post injection?	Yes—3 h

requiring oral olanzapine 20 mg/day, the recommended starting and maintenance dose of olanzapine pamoate is 300 mg every 2 weeks.[48]

Acute treatment: what is the evidence?

Oral risperidone/paliperidone, aripiprazole, and olanzapine are all efficacious medications when used to manage individuals with acute exacerbations of schizophrenia. They have been well characterized, with their major differences being their tolerability profiles when comparing groups enrolled in clinical trials.[53,54] For example, olanzapine is associated with greater weight gain and metabolic abnormalities, aripiprazole with higher rates of akathisia, and risperidone/paliperidone with elevation in prolactin levels. However, there is considerable individual variation in how people respond to or tolerate antipsychotics.

It would be expected that the LAI formulations would be as efficacious in the acute setting as their oral counterparts. Efficacy in acutely exacerbated patients with schizophrenia has been formally evaluated for once-monthly paliperidone palmitate,[55-58] olanzapine pamoate,[59] aripiprazole monohydrate,[60] aripiprazole lauroxil,[61] and risperidone subcutaneous injection.[62] Although the initiation procedures vary among the different products, starting a LAI antipsychotic while hospitalized with an acute exacerbation of schizophrenia consistently demonstrated robust superiority over placebo in reducing psychotic symptoms. Of additional interest is the ability to reduce hostility and agitation.[63,64]

Aside from potential adverse effects related to the injection itself (such as pain, redness, induration), it would be expected that the LAI formulations would have similar tolerability profiles in the acute setting as their oral counterparts. Number need to harm (NNH) vs placebo can be used to indirectly compare risk for weight gain, sedation, and akathisia (Table 6).[21,29,33,39,43,44,48,65-69] NNH values less than 10 denote events that would be more commonly encountered; this would be the case for weight gain ≥7% from baseline for risperidone subcutaneous injection, aripiprazole monohydrate, and olanzapine pamoate, as calculated from their short-term acute registration studies. The weight gain data is counter-intuitive for risperidone subcutaneous injection and aripiprazole monohydrate and appears to differ somewhat from what has been calculated from registration studies of the oral formulations of risperidone and aripiprazole, where the NNH vs. placebo estimates for weight gain ≥7% were 18 and 21, respectively[66,68]; this could be a reflection of study design where patients remained hospitalized throughout the study and potential skewing of the characteristics of the study participants towards those more prone to weight gain.[60,62]

Prevention of relapse: what is the evidence?

Although LAI antipsychotics can be used acutely, LAI antipsychotics are more often considered as part of a long-term treatment

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Table 6. Rates and Number Needed to Harm vs Placebo for Weight Gain, Somnolence/Sedation, and Akathisia, for Approved Long-Acting Injectable Second-Generation Antipsychotics and Their Oral Counterparts in Adults as Observed in Acute Short-Term Studies for Schizophrenia (Doses Pooled)

	Weight Gain ≥7% from Baseline			Somnolence/Sedation Adverse Events			Akathisia Adverse Events		
	Rate (%)			Rate (%)			Rate (%)		
Antipsychotic, Length of Study(ies)	Placebo	Drug	NNH (95% CI)	Placebo	Drug	NNH (95% CI)	Placebo	Drug	NNH (95% CI)
Risperidone/paliperidone formulations									
Risperidone microspheres, 12 wk	6	9	33 (ns)	3[a]	5.4[a]	42 (ns)	6[b]	7.6[b]	69 (ns)
Risperidone subcutaneous, 8 wk	18.0	37.6	6 (4–10)	0[a]	7.3[a]	14 (10–26)	4.2	4.7	199 (ns)
Risperidone oral, up to 8 mg/d, up to 8 wk	2.9[c]	8.7 [c]	18 (13–30)	2	10	13 (9–23)	3	10	15 (10–32)
Paliperidone palmitate, 9 and 13 wk	3.3	8.7	19 (13–33)	3[a]	8.7[a]	59 (ns)	3	3.1	1839 (ns)
Paliperidone oral, 3 to 12 mg/d, up to 6 wk	5	7.9	35 (ns)	7[a]	9.4[a]	42 (ns)	3.9	6.5	40 (ns)
Aripiprazole formulations									
Aripiprazole monohydrate, 12 wk	8.5	21.5	8 (5–21)	1.2	5.4	24 (13–225)	3.5	11.4	13 (8–43)
Aripiprazole lauroxil, 12 wk	5.8	9.2	30 (ns)	1.4	2.2	139 (ns)	4.3	11.6	14 (9–33)
Aripiprazole oral, 2 to 30 mg/d, up to 6 wk	3.2	8.1	21 (14–42)	8.0	11.0	34 (ns)	6.8	10.0	31 (16–622)
Olanzapine formulations									
Olanzapine pamoate, 8 wk	12.4	28.6	7 (5–13)	7[a]	11.3[a]	24 (ns)	NR	NR	NR
Olanzapine oral, 2.5 to 20 mg, up to 6 wk	22.2[c]	3[c]	6 (NC)	15.3	26.2	10 (6–41)	5	1	25 (14–134)

Abbreviations: CI, confidence interval; NC, the 95% CI is not calculable as denominators were not provided in product labeling; NNH, number needed to harm; NR, not reported (did not meet threshold for reporting); ns, not significant at the $P < .05$ threshold and thus the 95% CI is not shown.
[a]Pooled term of somnolence/sedation as reported in the product label.
[b]Pooled term of akathisia/restlessness as reported in the product label.
[c]Pooled schizophrenia and bipolar as reported in the product label.

strategy. Evidence supporting this goes back to the notion of the need to improve adherence to medication treatment in order to optimize outcomes. Real-world prospective and retrospective studies comparing LAI antipsychotics vs oral antipsychotics generally demonstrate decreases in relapse, hospitalization, and all-cause discontinuation for patients receiving LAI antipsychotics.[70]

Although not without controversy,[71] placebo-controlled randomized withdrawal study designs are often used to establish efficacy for the maintenance indication. The typical study design would be one where patients with the disease of interest are stabilized on the test medication and then subsequently randomized to either continue the test medication or receive placebo. The primary outcome measure is usually time to relapse, impending relapse, or recurrence, depending on the disorder and the study. This has been formally assessed vs. placebo in registration studies in individuals with schizophrenia for paliperidone palmitate administered monthly[72] or every 3 months,[73] olanzapine pamoate,[74] and aripiprazole monohydrate.[75] Registration studies were also done in individuals with bipolar disorder for risperidone microspheres (monotherapy or adjunctive use)[76,77] and aripiprazole monohydrate (monotherapy),[78] and in individuals with schizoaffective disorder for once monthly paliperidone palmitate (monotherapy or adjunctive use).[79] Number needed to treat vs placebo for prevention of relapse or recurrence for any of the tested medications for any of the indications range from 4 to 8, with overlap of the 95% confidence intervals (Table 7).[20,34,35,40,49,50,80] These effect sizes are consistent with the broader literature in schizophrenia.[81]

When should LAIs be offered?

Although LAI antipsychotics are often thought of as a last resort for chronically ill individuals who have been unable to adhere to oral medications, there is strong evidence supporting the use of LAI antipsychotics earlier in the disease process.[82,83] Early episode patients may have the most to gain from LAI antipsychotics, at a time when schizophrenia is most treatable and when avoidance of recurrences and rehospitalizations may lead to the biggest improvements in outcome. Using LAI antipsychotics may potentially decrease the percentage of time spent experiencing psychotic symptoms, reduce disability, and perhaps avoid some of the decrease in treatment response that can occur with subsequent exacerbations. Neuropathological brain changes can progress with subsequent clinical episodes.[84] The first 2 to 3 years of illness may be the most critical.[85] LAI antipsychotics allows for the swift identification of overt nonadherence and can eliminate covert nonadherence.

The evidence supporting the early use of LAI antipsychotics is from both real-world studies and from controlled clinical trials. For example, in a nationwide cohort study in Finland of 2588 patients diagnosed with schizophrenia following a first hospitalization, the risk of rehospitalization for patients receiving LAI antipsychotics was about one-third of that for patients receiving oral antipsychotics.[86] This is not surprising given that relapse rates are as high as about 80% within 5 years of initial recovery from first-episode schizophrenia,[87] often related to stopping medication.[88] The case for using LAI antipsychotics in first-episode or early-phase schizophrenia has also been supported by randomized clinical trials of risperidone microspheres,[89] paliperidone palmitate,[90] and aripiprazole monohydrate.[91]

Of interest is the inclusion in treatment guidelines of the importance of patient preference when selecting medications, including LAI formulations.[4] However, LAI antipsychotics are not being consistently offered and thus patients who may want them may not even know of the existence of this modality of treatment. In a

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Table 7. Prevention of Relapse or Recurrence as Quantified Using Number Needed to Treat vs Placebo (or vs. 45 mg/4 wk for Olanzapine Pamoate), Data from U.S. Registration Studies

		Relapse or Recurrence		
		Rate (%)		
Disorder	Antipsychotic	Placebo	Drug	NNT (95% CI)
Schizophrenia	Paliperidone palmitate monthly, flexibly dosed, 39 to 156 mg/4 wk	34.0	9.6	5 (4–7)
	Paliperidone palmitate 3-Month, flexibly dosed, 273 to 819 mg/12 wk	29.0	8.8	5 (4–9)
	Aripiprazole monohydrate, 400 mg/4 wk	39.6	10.0	4 (3–5)
	Olanzapine pamoate 150 mg/2 wk	29.2	15.7	8 (5–26)
	Olanzapine pamoate 300 mg/2 wk	29.2	5.0	5 (4–7)
	Olanzapine pamoate 405/4 wk	29.2	12.3	6 (4–12)
Schizoaffective disorder	Paliperidone palmitate monthly, flexibly dosed, 78 to 156 mg/4 wk	33.5	15.2	6 (4–11)
Bipolar Disorder	Risperidone microspheres, as adjunctive therapy, flexibly dosed, 25 to 50 mg/2 wk	45.8	23.1	5 (3–16)
	Risperidone microspheres, as monotherapy, flexibly dosed, 25 to 50 mg/2 wk	56.3	30.0	4 (3–7)
	Aripiprazole monohydrate, 400 mg/4 wk	51.1	26.5	5 (3–8)

Abbreviations: CI, confidence interval; NNT, number needed to treat.

survey of attitudes towards LAI antipsychotics among patients, relatives, and psychiatrists in Switzerland, about 67% of the patients did not receive information about depot antipsychotics from their psychiatrist and less than 10% of psychiatrists offer depot treatment after a first psychotic episode.[92] This is a disservice because data suggests that once provided, patients receiving LAI antipsychotics want to continue them. In a survey conducted in France in patients with schizophrenia who had received at least 3 months' treatment with a LAI antipsychotic, injections were the favored dosage form, and 67% said they felt better having received an injectable treatment than they felt before, with about half the patients (51%) considered injectable therapy to be more effective than other medication.[3] Moreover, 70% felt better supported in their illness by virtue of regular contact with the doctor or nurse who administered their injection.

How to offer LAIs

Motivational interviewing can be a useful method of encouraging active participation in treatment planning and increase levels of adherence to whatever decision is reached.[93,94] This technique is not unique to psychiatry, as motivational interviewing is also encouraged for the management of hypertension[95] where levels of treatment nonadherence are also as high as 50%.[96,97] In addition to "meeting patients where they are," shedding negative attitudes toward LAI antipsychotics is important, as evidenced in a study examining psychiatrists' ambivalence regarding the value of LAI antipsychotics and the perceived difficulty with patient acceptance of this modality of treatment.[98]

A useful opening is asking "How would you like to receive your medication once a month (or every 2 months) (or every 3 months)? I know I would!" Other remarks that can be made include:

- "You know, I have high blood pressure and take pills for that, and sometimes I forget. How often does that happen to you with your pills?"
- "It must be hard to hear your Mother constantly ask all day long if you have taken your medicine…"
- "It must be hard to remember if you had taken your medicine last night."

The injection process can be perceived as stigmatizing by some patients who have received intramuscular medication for behavioral emergencies and over their objection; in this instance, the voluntary nature of routine maintenance treatment will need to be emphasized. It can be helpful to "normalize" injection treatments in general by mentioning that many people with diabetes need insulin injections and that depot medications have been used for other purposes in medical care, such as hormonal treatments and opioid use disorder. Another source of stigma may be that the patient has received care in settings where only the most severely ill received LAI antipsychotics; in this case it would be helpful for the patient to converse with a peer advocate who has been successful with LAI antipsychotic treatment.

Demystification of the injection process can be accomplished by showing the syringe and needle to be used, and in the case of intramuscular administration, discussing the similarities with the mechanics of a routine "flu shot." Concerns over gluteal injection can often be allayed by mentioning that it can be administered in the upper outer quadrant of the buttocks, which is relatively easy to access without disrobing, and is also a far quicker process than injection in the deltoid muscle during the cold winter months when they are all bundled up in multiple layers of clothing.

Ultimately if acceptance of the LAI antipsychotic appears tenuous, there is no harm done by suggesting "Would you like to give it a try? If you do not want it again, you do not have to have it."

Patient and family education on schizophrenia, schizoaffective disorder and bipolar disorder, and the risks of relapse/recurrence are important. The National Alliance on Mental Illness (NAMI) make a Family-to-Family educational program available in many communities in the United States (see https://www.nami.org/Support-Education/Mental-Health-Education/NAMI-Family-to-Family).

Lastly, who gives the injection can also be a driver for both the offer of a LAI antipsychotic by the treating clinician, and the acceptance of this treatment by the patient. Several options exist as to who administers the injection: the prescriber, another member of the office staff, another provider in the building that has agreed to do this, or the pharmacist in States that allow this.

It needs to be acknowledged that LAI antipsychotics are not for everyone. Since LAI antipsychotics are usually administered every 2 to 12 weeks, depending on the product, this prevents the flexibility

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that is ordinarily present with dosing of oral medications and when optimal dose for the individual is not known. There are some patients with delusions of being controlled and for whom LAI antipsychotics seem to be particularly threatening, no matter how strong the therapeutic alliance. In the event of adverse reactions, slow distribution from the muscle or subcutaneous tissue may lead to prolonged effects, making management of side effects challenging.[99] Some individuals may be sensitive to injection site reactions—pain, erythema, swelling and discomfort, particularly with sesame oil-based products such as fluphenazine decanoate or haloperidol decanoate.

More about choices

The simplest scenario is if the patient is already receiving an antipsychotic that is available as a LAI formulation. Then it is a matter of educating the patient (and caregiver) about the availability of this different way of receiving medication. If there are competing LAI formulations for the same or related molecule, then a review of the "amenities of care" (Table 2) is in order. There may be a preference for a specific injection interval that is available with only some of the products. Patients and caregivers sometimes need to be reassured that a longer interval between injections does not necessarily mean that visits will be scheduled less often.

In some situations, it may be unrealistic to expect adherence to oral supplementation and alternatives should be considered. Some choices require an infrastructure (refrigeration for storage of risperidone microspheres or risperidone subcutaneous injection, examination table for administering risperidone subcutaneous injection in the abdomen, ability to observe the patient for 3 hours after each injection of olanzapine pamoate). For patients receiving oral fluphenazine or haloperidol and a switch to a LAI is being considered, despite the relatively low cost of haloperidol decanoate or fluphenazine decanoate, the clinician needs to weigh the potential disadvantages of using concomitant oral anticholinergics as discussed earlier. On occasion, the supply chain for older generic medications sometimes gets interrupted[100]; the American Society of Health-System Pharmacists maintains a web resource that tracks drug shortages and is available at https://www.ashp.org/Drug-Shortages/Current-Shortages.

If the patient is receiving acute treatment, paliperidone palmitate, risperidone subcutaneous, and olanzapine pamoate are options that can be administered in the inpatient setting and no oral medication is required upon their initiation. However, the other options, notably aripiprazole monohydrate and aripiprazole lauroxil, have demonstrated robust efficacy in the acute setting, provided that supplemental medication be administered after the first injection: 14 days for aripiprazole monohydrate (or 1 day in Canada or the EU if the two-injection start regimen is used), and either 1 day or 21 days for aripiprazole lauroxil depending if the ALNCD formulation is used. Prior knowledge of tolerability and efficacy is important, because once injected, the medication cannot be withdrawn. Oral or intramuscular short acting antipsychotic medications are in most situations the most prudent way to initiate antipsychotic treatment in an individual who is treatment-naïve or if a medication history cannot be reliably obtained. In general, weight gain and metabolic adverse effects are a common concern with second-generation antipsychotics, especially with olanzapine; first-generation LAI antipsychotics could possibly be considered under these circumstances and where a switch among the second-generation LAIs was not helpful. If prolactin-related adverse effects are a clinical concern, one of the aripiprazole LAI formulations would be the first choice; to be avoided under these circumstances would be paliperidone palmitate, risperidone microspheres, or the first-generation LAI antipsychotics.

Cost considerations for branded products are sometimes obstacles to their use and access to patient-assistance programs can be helpful in many instances.

Conclusion

Poor adherence to antipsychotic medication is common and this can result in suboptimal outcomes. LAI antipsychotics can address the guesswork about adherence status and patients may prefer them if they are offered this as a choice, including individuals early in their disease course. Although not every oral antipsychotic is available in a LAI formulation, there are now more options than existed 20 years ago. Choosing among the different LAI antipsychotics is partly based on pragmatic concerns. For example, olanzapine pamoate would not be a practical option if the mandatory 3-hour post-injection observation period cannot be provided. For patients receiving oral risperidone, using risperidone microspheres can be inconvenient as that formulation is administered every 2 weeks, requires refrigeration and reconstitution, and must be accompanied by oral supplementation for the first 3 weeks after the initial injection. Instead of risperidone microspheres, paliperidone palmitate can be considered as it does not require oral supplementation, entails less frequent injections (either monthly or every 3 months), is supplied in prefilled syringes, has a needle gauge as small as 23G, a small injection volume, and does not need to be refrigerated. Regarding aripiprazole LAI, there are 2 competing formulations available in the United States; they differ in terms of oral supplementation, frequency of injections, requirement for reconstitution, and needle gauge. Additional approved indications in the US for LAI antipsychotics include bipolar I disorder maintenance treatment for risperidone microspheres and aripiprazole monohydrate, and schizoaffective disorder for paliperidone palmitate once monthly.

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In the past 12 months, speaker: AbbVie, Acadia, Alkermes, Allergan, Angelini, Eisai, Intra-Cellular Therapies, Janssen, Lundbeck, Merck, Neurocrine, Noven, Otsuka, Sage, Shire, Sunovion, Takeda, Teva, and CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and Universities and Professional Organizations/Societies.

Stocks (small number of shares of common stock): Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer purchased >10 years ago.

Royalties: Wiley (Editor-in-Chief, International Journal of Clinical Practice, through end 2019), UpToDate (reviewer), Springer Healthcare (book), Elsevier (Topic Editor, Psychiatry, Clinical Therapeutics).

In the past 5 years Leslie Citrome has engaged in collaborative research with, or received consulting or speaking fees, from: AbbVie, Acadia, Alexza, Alkermes, Allergan, Angelini, Astellas, AstraZeneca, Avanir, Axsome, BioXcel, Boehringer Ingelheim, Bristol-Myers Squibb, Cadent Therapeutics, Eisai, Eli Lilly, Forum, Genentech, Impel, Indivior, Intra-Cellular Therapies, Janssen, Jazz, Karuna, Lundbeck, Luye, Lyndra, Medavante-Prophase, Meiji, Merck, Medivation, Mylan, Neurocrine, NeuroRx, Novartis, Noven, Osmotica, Otsuka, Pfizer, Reckitt Benckiser, Relmada, Reviva, Sage, Shire, Sunovion, Takeda, Teva, University of Arizona, Valeant, Vanda, and one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research.

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References

1. Volavka J, Citrome L. Oral antipsychotics for the treatment of schizophrenia: heterogeneity in efficacy and tolerability should drive decision-making. *Expert Opin Pharmacother.* 2009;**10**(12):1917–1928.
2. Valenstein M, Ganoczy D, McCarthy JF, *et al.* Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review. *J Clin Psychiatry.* 2006;**67**(10):1542–1550.
3. Caroli F, Raymondet P, Izard I, *et al.* Opinions of French patients with schizophrenia regarding injectable medication. *Patient Prefer Adherence.* 2011;**5**:165–171.
4. Keepers GA, Fochtmann LJ, Anzia JM, *et al.* The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. *Am J Psychiatry.* 2020;**177**(9):868–872.
5. Lacro JP, Dunn LB, Dolder CR, *et al.* Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry.* 2002;**63**(10):892–909.
6. Joshi K, Lin J, Lingohr-Smith M, *et al.* Treatment patterns and antipsychotic medication adherence among commercially insured patients with schizoaffective disorder in the United States. *J Clin Psychopharmacol.* 2016;**36**(5):429–435.
7. Jawad I, Watson S, Haddad PM, *et al.* Medication nonadherence in bipolar disorder: a narrative review. *Ther Adv Psychopharmacol.* 2018;**8**(12):349–363.
8. Dolder CR, Lacro JP, Jeste DV. Adherence to antipsychotic and nonpsychiatric medications in middle-aged and older patients with psychotic disorders. *Psychosom Med.* 2003;**65**(1):156–162.
9. Shafrin J, Silverstein AR, MacEwan JP, *et al.* Using information on patient adherence to antipsychotic medication to understand their adherence to other medications. *P T.* 2019;**44**(6):350–357.
10. Law MR, Soumerai SB, Ross-Degnan D, *et al.* A longitudinal study of medication nonadherence and hospitalization risk in schizophrenia. *J Clin Psychiatry.* 2008;**69**(1):47–53.
11. Weiden PJ, Kozma C, Grogg A, *et al.* Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. *Psychiatr Serv.* 2004;**55**(8):886–891.
12. Morken G, Widen JH, Grawe RW. Non-adherence to antipsychotic medication, relapse and rehospitalisation in recent-onset schizophrenia. *BMC Psychiatry.* 2008;**8**:32.
13. Lindenmayer JP, Liu-Seifert H, Kulkarni PM, *et al.* Medication nonadherence and treatment outcome in patients with schizophrenia or schizoaffective disorder with suboptimal prior response. *J Clin Psychiatry.* 2009;**70**(7):990–996.
14. Alia-Klein N, O'Rourke TM, Goldstein RZ, *et al.* Insight into illness and adherence to psychotropic medications are separately associated with violence severity in a forensic sample. *Aggress Behav.* 2007;**33**(1):86–96.
15. Herings RM, Erkens JA. Increased suicide attempt rate among patients interrupting use of atypical antipsychotics. *Pharmacoepidemiol Drug Saf.* 2003;**12**(5):423–424.
16. Ascher-Svanum H, Faries DE, Zhu B, *et al.* Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. *J Clin Psychiatry.* 2006;**67**(3):453–460.
17. Hong J, Reed C, Novick D, *et al.* Clinical and economic consequences of medication non-adherence in the treatment of patients with a manic/mixed episode of bipolar disorder: results from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study. *Psychiatry Res.* 2011;**190**(1):110–114.
18. Haddad PM, Brain C, Scott J. Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. *Patient Relat Outcome Meas.* 2014;**5**:43–62.
19. Citrome L. New second-generation long-acting injectable antipsychotics for the treatment of schizophrenia. *Expert Rev Neurother.* 2013;**13**(7):767–783.
20. Citrome L. Long-acting injectable antipsychotics update: lengthening the dosing interval and expanding the diagnostic indications. *Expert Rev Neurother.* 2017;**17**(10):1029–1043.
21. Citrome L. Sustained-release risperidone via subcutaneous injection: a systematic review of RBP-7000 (PERSERIS) for the treatment of schizophrenia. *Clin Schizophr Relat Psychoses.* 2018;**12**(3):130–141.
22. APP Pharmaceuticals. Fluphenazine decanoate injection, USP. Prescribing Information, Revised September 2010. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/071413s019lbl.pdf. Accessed December 24, 2020.
23. Janssen. HALDOL Decanoate 50 (haloperidol), HALDOL Decanoate 100 (haloperidol), For IM Injection Only. Prescribing Information, Revised November 2020. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/HALDOL+Decanoate-pi.pdf. Accessed December 24, 2020.
24. Taylor D. Psychopharmacology and adverse effects of antipsychotic long-acting injections: a review. *Br J Psychiatry Suppl.* 2009;**52**:S13–S19.
25. Citrome L. Clinical management of tardive dyskinesia: five steps to success. *J Neurol Sci.* 2017;**383**:199–204.
26. Vinogradov S, Fisher M, Warm H, *et al.* The cognitive cost of anticholinergic burden: decreased response to cognitive training in schizophrenia. *Am J Psychiatry.* 2009;**166**(9):1055–1962.
27. Ehret MJ, Fuller MA. Long-acting injectable risperidone. *Ann Pharmacother.* 2004;**38**(12):2122–2127. Erratum in: Ann Pharmacother. 2005; 39(1):201.
28. Harrison TS, Goa KL. Long-acting risperidone: a review of its use in schizophrenia. *CNS Drugs.* 2004;**18**(2):113–132.
29. Janssen. RISPERDAL CONSTA (risperidone) LONG-ACTING INJECTION. Prescribing Information, Revised July 2020. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/RISPERDAL+CONSTA-pi.pdf. Accessed December 24, 2020.
30. Eerdekens M, Van Hove I, Remmerie B, *et al.* Pharmacokinetics and tolerability of long-acting risperidone in schizophrenia. *Schizophr Res.* 2004;**70**(1):91–100.
31. Correll CU, Litman RE, Filts Y, *et al.* Efficacy and safety of once-monthly Risperidone ISM in schizophrenic patients with an acute exacerbation. *NPJ Schizophr.* 2020;**6**(1):37.
32. Clark I, Taylor D. Newer formulations of risperidone: role in the management of psychotic disorders. *CNS Drugs.* 2020;**34**(8):841–852.
33. Janssen. INVEGA SUSTENNA (paliperidone palmitate) extended-release injectable suspension, for intramuscular use. Prescribing Information, Revised January 2019. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVEGA+SUSTENNA-pi.pdf. Accessed December 24, 2020.
34. Citrome L. Paliperidone palmitate—review of the efficacy, safety and cost of a new second-generation depot antipsychotic medication. *Int J Clin Pract.* 2010;**64**(2):216–239.
35. Greenberg WM, Citrome L. Paliperidone palmitate for schizoaffective disorder: a review of the clinical evidence. *Neurol Ther.* 2015;**4**(2):81–91.
36. Russu A, Kern Sliwa J, Ravenstijn P, *et al.* Maintenance dose conversion between oral risperidone and paliperidone palmitate 1 month: practical guidance based on pharmacokinetic simulations. *Int J Clin Pract.* 2018; **72**(6):e13089.
37. Janssen. INVEGA TRINZA (paliperidone palmitate) extended-release injectable suspension, for intramuscular use. Prescribing Information, Revised January 2019. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVEGA+TRINZA-pi.pdf. Accessed December 24, 2020.
38. Ravenstijn P, Remmerie B, Savitz A, *et al.* Pharmacokinetics, safety, and tolerability of paliperidone palmitate 3-month formulation in patients with schizophrenia: a phase-1, single-dose, randomized, open-label study. *J Clin Pharmacol.* 2016;**56**(3):330–339.
39. Indivior. PERSERIS (risperidone) for extended-release injectable suspension, for subcutaneous use. Prescribing Information, Revised December 2019. https://www.perserishcp.com/prescribing-information.pdf. Accessed December 24, 2020.
40. Citrome L. Aripiprazole long-acting injectable formulations for schizophrenia: aripiprazole monohydrate and aripiprazole lauroxil. *Expert Rev Clin Pharmacol.* 2016;**9**(2):169–186.
41. Ehret MJ, Davis E, Luttrell SE, *et al.* Aripiprazole lauroxil nanocrystal dispersion technology (Aristada Initio). *Clin Schizophr Relat Psychoses.* 2018;**12**(2):92–96.

https://doi.org/10.1017/S1092852921000249 Published online by Cambridge University Press

42. Hard ML, Wehr A, von Moltke L, *et al.* Pharmacokinetics and safety of deltoid or gluteal injection of aripiprazole lauroxil nanocrystal dispersion used for initiation of the long-acting antipsychotic aripiprazole lauroxil. *Ther Adv Psychopharmacol.* 2019;**9**:2045125319859964.
43. Otsuka. ABILIFY MAINTENA (aripiprazole) for extended-release injectable suspension, for intramuscular use. Prescribing Information, Revised June 2020. https://www.otsuka-us.com/sites/g/files/qhldwo2966/files/media/static/Abilify-M-PI.pdf. Accessed December 24, 2020.
44. Alkermes. ARISTADA (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use. Prescribing Information, Revised October 2020. https://www.aristadahcp.com/downloadables/ARISTADA-PI.pdf**.** Accessed December 24, 2020.
45. Alkermes. ARISTADA INITIO (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use. Prescribing Information, Revised October 2020. https://www.aristadahcp.com/downloadables/ARISTADA-INITIO-PI.pdf. Accessed December 24, 2020.
46. Hard ML, Wehr AY, Du Y, *et al.* Pharmacokinetic evaluation of a 1-day treatment initiation option for starting long-acting aripiprazole lauroxil for schizophrenia. *J Clin Psychopharmacol.* 2018;**38**(5):435–441.
47. Raoufinia A, Peters-Strickland T, Nylander AG, *et al.* Aripiprazole once-monthly 400 mg: comparison of pharmacokinetics, tolerability, and safety of deltoid versus gluteal administration. *Int J Neuropsychopharmacol.* 2017;**20**(4):295–304.
48. Lilly. ZYPREXA RELPREVV (olanzapine) for extended release injectable suspension. Prescribing Information, Revised July 2020. http://pi.lilly.com/us/zyprexa_relprevv.pdf. Accessed December 24, 2020.
49. Citrome L. Olanzapine pamoate: a stick in time? A review of the efficacy and safety profile of a new depot formulation of a second-generation antipsychotic. *Int J Clin Pract.* 2009;**63**(1):140–150.
50. Citrome L. Patient perspectives in the development and use of long-acting antipsychotics in schizophrenia: focus on olanzapine long-acting injection. *Patient Prefer Adherence.* 2009;**3**:345–355.
51. Detke HC, McDonnell DP, Brunner E, *et al.* Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection, I: analysis of cases. *BMC Psychiatry.* 2010;**10**:43.
52. Luedecke D, Schöttle D, Karow A, *et al.* Post-injection delirium/sedation syndrome in patients treated with olanzapine pamoate: mechanism, incidence, and management. *CNS Drugs.* 2015;**29**(1):41–46.
53. Leucht S, Cipriani A, Spineli L, *et al.* Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;**382**(9896):951–962. Erratum in: Lancet. 2013;382 (9896):940.
54. Huhn M, Nikolakopoulou A, Schneider-Thoma J, *et al.* Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet*. 2019;**394**(10202):939–951. Erratum in: Lancet. 2019;394(10202):918.
55. Pandina GJ, Lindenmayer JP, Lull J, *et al.* A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia. *J Clin Psychopharmacol*. 2010;**30**(3):235–244. Erratum in: J Clin Psychopharmacol. 2010;30(4):364.
56. Gopal S, Hough DW, Xu H, *et al.* Efficacy and safety of paliperidone palmitate in adult patients with acutely symptomatic schizophrenia: a randomized, double-blind, placebo-controlled, dose-response study. *Int Clin Psychopharmacol.* 2010;**25**(5):247–256.
57. Nasrallah HA, Gopal S, Gassmann-Mayer C, *et al.* A controlled, evidence-based trial of paliperidone palmitate, a long-acting injectable antipsychotic, in schizophrenia. *Neuropsychopharmacology.* 2010;**35**(10): 2072–2082.
58. Kramer M, Litman R, Hough D, *et al.* Paliperidone palmitate, a potential long-acting treatment for patients with schizophrenia. Results of a randomized, double-blind, placebo-controlled efficacy and safety study. *Int J Neuropsychopharmacol.* 2010;**13**(5):635–647.
59. Lauriello J, Lambert T, Andersen S, *et al.* An 8-week, double-blind, randomized, placebo-controlled study of olanzapine long-acting injection in acutely ill patients with schizophrenia. *J Clin Psychiatry*. 2008;**69**(5): 790–799. Erratum in: J Clin Psychiatry. 2011;72(8):1157.
60. Kane JM, Peters-Strickland T, Baker RA, *et al.* Aripiprazole once-monthly in the acute treatment of schizophrenia: findings from a 12-week, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry.* 2014; **75**(11):1254–1260.
61. Meltzer HY, Risinger R, Nasrallah HA, *et al.* A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. *J Clin Psychiatry.* 2015;**76**(8):1085–1090.
62. Nasser AF, Henderson DC, Fava M, *et al.* Efficacy, safety, and tolerability of RBP-7000 once-monthly risperidone for the treatment of acute schizophrenia: an 8-week, randomized, double-blind, placebo-controlled, multicenter phase 3 study. *J Clin Psychopharmacol.* 2016;**36**(2):130–140.
63. Citrome L, Du Y, Risinger R, Stankovic S, *et al.* Effect of aripiprazole lauroxil on agitation and hostility in patients with schizophrenia. *Int Clin Psychopharmacol.* 2016;**31**(2):69–75.
64. Citrome L, Volavka J. Specific anti-hostility effects of atypical antipsychotics in persons with schizophrenia: from clozapine to cariprazine. *Harv Rev Psychiatry.* 2021;**29**(1):20–34.
65. Citrome L. Activating and sedating adverse effects of second-generation antipsychotics in the treatment of schizophrenia and major depressive disorder: absolute risk increase and number needed to harm. *J Clin Psychopharmacol.* 2017;**37**(2):138–147.
66. Janssen. RISPERDAL (risperidone) tablets, for oral use; RISPERDAL (risperidone) oral solution; RISPERDAL M-TAB (risperidone) orally disintegrating tablets. Prescribing Information, Revised January 2020. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/RISPERDAL-pi.pdf. Accessed December 25, 2020.
67. Janssen. INVEGA (paliperidone) Extended-Release Tablets. Prescribing Information, Revised January 2019. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVEGA-pi.pdf. Accessed December 25, 2020.
68. Otsuka. ABILIFY (aripiprazole) Tablets; ABILIFY DISCMELT (aripiprazole) Orally Disintegrating Tablets; ABILIFY (aripiprazole) Oral Solution; ABILIFY (aripiprazole) Injection FOR INTRAMUSCULAR USE ONLY. Prescribing Information, Revised June 2020. https://www.otsuka-us.com/sites/g/files/qhldwo2966/files/media/static/Abilify-PI.pdf. Accessed December 25, 2020.
69. Lilly. ZYPREXA (olanzapine) Tablet for Oral use; ZYPREXA ZYDIS (olanzapine) Tablet, Orally Disintegrating for Oral use; ZYPREXA Intra-Muscular (olanzapine) Injection, Powder, For Solution for Intramuscular use. Prescribing Information, Revised April 2020. https://pi.lilly.com/us/zyprexa-pi.pdf. Accessed December 25, 2020.
70. Kirson NY, Weiden PJ, Yermakov S, *et al.* Efficacy and effectiveness of depot versus oral antipsychotics in schizophrenia: synthesizing results across different research designs. *J Clin Psychiatry.* 2013;**74**(6):568–575.
71. Emsley R, Fleischhacker WW, Galderisi S, *et al.* Placebo controls in clinical trials: concerns about use in relapse prevention studies in schizophrenia. *BMJ.* 2016;**354**:i4728.
72. Hough D, Gopal S, Vijapurkar U, *et al.* Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. *Schizophr Res.* 2010;**116**(2–3):107–117.
73. Berwaerts J, Liu Y, Gopal S, *et al.* Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia: a randomized clinical trial. *JAMA Psychiatry.* 2015;**72**(8): 830–839.
74. Kane JM, Detke HC, Naber D, *et al.* Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. *Am J Psychiatry.* 2010;**167**(2):181–189.
75. Kane JM, Sanchez R, Perry PP, *et al.* Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry.* 2012;**73**(5):617–624.
76. Macfadden W, Alphs L, Haskins JT, *et al.* A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who relapse frequently. *Bipolar Disord.* 2009;**11**(8):827–839.
77. Quiroz JA, Yatham LN, Palumbo JM, *et al.* Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. *Biol Psychiatry.* 2010;**68**(2):156–162.

https://doi.org/10.1017/S1092852921000249 Published online by Cambridge University Press

78. Calabrese JR, Sanchez R, Jin N, *et al.* Efficacy and safety of aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: a double-blind, placebo-controlled, 52-week randomized withdrawal study. *J Clin Psychiatry.* 2017;**78**(3):324–331.
79. Fu DJ, Turkoz I, Simonson RB, *et al.* Paliperidone palmitate once-monthly reduces risk of relapse of psychotic, depressive, and manic symptoms and maintains functioning in a double-blind, randomized study of schizoaffective disorder. *J Clin Psychiatry.* 2015;**76**(3):253–262.
80. US Food and Drug Administration. Drug Approval Package, Zyprexa Relprevv (olanzapine) for Extended Release Injectable Suspension 210 mg, 300 mg, and 405 mg, Company: Eli Lilly and Company, Application No.: 022173, Approval Date: 12/11/2009. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022173_zyprexa_relprevv_toc.cfm. Accessed December 25, 2020.
81. Ceraso A, Lin JJ, Schneider-Thoma J, *et al.* Maintenance treatment with antipsychotic drugs for schizophrenia. *Cochrane Database Syst Rev.* 2020; **8**:CD008016
82. Stahl SM. Long-acting injectable antipsychotics: shall the last be first? *CNS Spectr.* 2014;**19**(1):3–5.
83. Gardner KN, Nasrallah HA. Managing first-episode psychosis: rationale and evidence for nonstandard first-line treatments for schizophrenia. *Current Psychiatry.* 2015;**14**(7):33, 38–45, e3.
84. Lieberman JA, Alvir JM, Koreen A, *et al.* Psychobiologic correlates of treatment response in schizophrenia. *Neuropsychopharmacology.* 1996;**14** (3 Suppl):13S–21S.
85. Birchwood M, Todd P, Jackson C. Early intervention in psychosis. The critical period hypothesis. *Br J Psychiatry Suppl.* 1998;**172**(33):53–59.
86. Tiihonen J, Haukka J, Taylor M, *et al.* A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. *Am J Psychiatry.* 2011;**168**(6):603–609. Erratum in: Am J Psychiatry. 2012;169(2):223.
87. Robinson D, Woerner MG, Alvir JM, *et al.* Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry.* 1999;**56**(3):241–247.
88. Robinson DG, Woerner MG, Alvir JM, *et al.* Predictors of medication discontinuation by patients with first-episode schizophrenia and schizoaffective disorder. *Schizophr Res.* 2002;**57**(2–3):209–219.
89. Subotnik KL, Casaus LR, Ventura J, *et al.* Long-acting injectable risperidone for relapse prevention and control of breakthrough symptoms after a recent first episode of schizophrenia. A randomized clinical trial. *JAMA Psychiatry.* 2015;**72**(8):822–829.
90. Schreiner A, Aadamsoo K, Altamura AC, *et al.* Paliperidone palmitate versus oral antipsychotics in recently diagnosed schizophrenia. *Schizophr Res.* 2015;**169**(1–3):393–399.
91. Kane JM, Schooler NR, Marcy P, *et al.* Effect of long-acting injectable antipsychotics vs usual care on time to first hospitalization in early-phase schizophrenia: a randomized clinical trial. *JAMA Psychiatry.* 2020;**77**(12): 1–8. Erratum in: doi:10.1001/jamapsychiatry.2020.3302.
92. Jaeger M, Rossler W. Attitudes towards long-acting depot antipsychotics: a survey of patients, relatives and psychiatrists. *Psychiatry Res.* 2010; **175**(1–2):58–62.
93. Haque SF, D'Souza A. Motivational interviewing: The RULES, PACE, and OARS. *Current Psychiatry.* 2019;**18**(1):27–28.
94. Lewis-Fernández R, Coombs AA, Balán IC, *et al.* Motivational interviewing: overcoming disparities in pharmacotherapy engagement. *J Clin Psychiatry.* 2018;**79**(3):18ac12150.
95. Ren Y, Yang H, Browning C, *et al.* Therapeutic effects of motivational interviewing on blood pressure control: a meta-analysis of randomized controlled trials. *Int J Cardiol.* 2014;**172**(2):509–511.
96. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. *Am J Med.* 2012;**125**(9):882–7.e.1.
97. Briesacher BA, Andrade SE, Fouayzi H, *et al.* Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy.* 2008;**28**(4):437–443.
98. Weiden PJ, Roma RS, Velligan DI, *et al.* The challenge of offering long-acting antipsychotic therapies: a preliminary discourse analysis of psychiatrist recommendations for injectable therapy to patients with schizophrenia. *J Clin Psychiatry.* 2015;**76**(6):684–690.
99. Remington GJ, Adams ME. Depot neuroleptic therapy: clinical considerations. *Can J Psychiatry.* 1995;**40**(3 Suppl 1):S5–S11.
100. Demers MF, Bilodeau I, Laberge L, *et al.* SU112. The dark side of haloperidol decanoate shortage in Canada. *Schizophr Bull.* 2017;**43** (Suppl 1):S201–S202.

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Optional Posttest and CME Certificate

CME Credit Expires: February 18, 2024

Posttest Study Guide

The posttest can only be submitted online. The below posttest questions have been provided solely as a study tool to prepare for your online submission.

1. Michelle is a patient with schizophrenia considering a transition from oral to long-acting injectable (LAI) antipsychotic treatment. Research supports which of the following statement(s) comparing outcomes of LAI versus oral antipsychotic treatment?
   A. Decrease in relapse with LAI
   B. Decrease in hospitalizations with LAI
   C. Decrease in all-cause discontinuation with LAI
   D. All of the above

2. Blake has early-episode schizophrenia with prominent agitation and delusions of being controlled by the government. Which characteristic of Blake's illness poses the greatest concern for a successful transition to long-acting injectable (LAI) antipsychotic treatment?
   A. Schizophrenia diagnosis
   B. Early-episode illness status
   C. Agitation
   D. Delusions of being controlled

3. Greg, a patient with bipolar I disorder, was treated with lithium during an initial manic episode. He will begin treatment with an adjunctive long-acting injectable (LAI) antipsychotic for maintenance of his symptoms. Which LAI antipsychotic is approved for use as an adjunctive to lithium in patients with bipolar I disorder?
   A. Paliperidone palmitate once monthly
   B. Risperidone microspheres
   C. Aripiprazole monohydrate
   D. Aripiprazole lauroxil

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