DSH PSYCHOTROPIC MEDICATION
Operational Procedures

LONG-ACTING INJECTABLE (LAI) ANTIPSYCHOTIC MEDICATIONS:

I. Fluphenazine decanoate 25 mg IM Q-2 weeks is approximately equal to 10 to 20 mg per day of the oral formulation. This conversion factor should be used when calculating the total dosage of fluphenazine for patients receiving the injectable LAI form.

For example, a patient who was being converted to fluphenazine decanoate without oral cross-over who had been taking 20 mg orally per day would be loaded with 25 – 50 mg IM Q-7 days times three followed by 50 mg Q-14 days. Note that the 25 mg per week would likely produce a slightly lower plasma concentration than 20 mg per day orally, while 50 mg Q-7 days times three would produce a slightly higher plasma concentration than the oral dose at peak post-dose concentration.

Measurement of a plasma concentration before the first maintenance dose could be used to fine tune the dosing. In either case, the optimal plasma concentration range is thought to be 0.8 – 2.0 ng/mL for most patients, although a few treatment-resistant or refractorily ill patients may require plasma concentrations of up to 4.0 ng/mL. Plasma concentrations > 4.0 ng/mL likely represent a point of futility, as most D_2 dopamine receptors have been occupied by this concentration.

II. Haloperidol decanoate 100 mg Q-4 weeks is approximately equal to 5 mg per day of the oral formulation (i.e., 20:1 ratio). During haloperidol decanoate loading, the ratio should be calculated using a 10:1 ratio (i.e., with 10 mg PO per day being equivalent to 100 mg IM) Q-7 days times three.

For an average metabolizer of haloperidol, three weekly injections of haloperidol decanoate 100 mg will produce a trough post-loading concentration of 7.75 ng/mL. These conversion factors should be used when calculating the total maintenance and loading doses of haloperidol for patients receiving the LAI injectable form. [NOTE: Without loading, injections of haloperidol decanoate every 28 days would require about 105 days to reach steady-state.]

Optimal plasma concentrations are thought to range from 5 – 20 ng/mL, although some patients may require higher plasma concentrations. A plasma concentration of 30 ng/mL usually represents a point of futility in that most D_2 dopamine receptors are occupied by this concentration.

The cited range refers to the parent compound, not combined haloperidol and reduced haloperidol. Because haloperidol decanoate lacks a rapid release phase, a loading dose strategy is vital to avoid decompensation due to subtherapeutic plasma concentrations. [Please see the tables later in this chapter regarding initiation/loading strategies.]

III. LAI risperidone (Consta®) 25 mg given intramuscularly Q-2 weeks is approximately equal to 2 – 3 mg per day of the oral formulation.

Uzedy 50 mg given intramuscularly every month is equivalent to 2 mg of oral risperidone per day or given every two months is equivalent to 1 mg of oral risperidone per day. A range of doses up to 250 mg is available.

Similar data for paliperidone palmitate (Erzofri® or Invega Sustenna®) suggest that 234 mg given Q-28 days is approximately equivalent to 4 – 5 mg of risperidone orally per day. An additional LAI formulation of paliperidone (Invega Trinza®) is designed to be administered every three months but is restricted to patients who have responded to Q-4 weeks paliperidone palmitate and who have been on a stable dose for a minimum of four (4) months. A six (6) month formulation, Invega Hafyera®, is available for those on a stable dose of Invega Sustenna® for at least four (4) months or Invega Trinza® for at least three (3) months. Conversion from the Q-4 weeks (month) or three (3) month formulation to the Q-3 or 6-months formulation are as follows:

Erzofri® or Invega Sustenna®	**Invega Trinza®**	**Invega Hafyera®**
39 mg	no equivalent	No equivalent
78 mg	273 mg	No equivalent
117 mg	410 mg	No equivalent
156 mg	546 mg	1052 mg
234 mg	819 mg	1560 mg

IV. LAI olanzapine (Zyprexa Relprevv®) has not had oral equivalents established. The available doses are 150 mg, 210 mg, 300 mg, and 405 mg. The lower two doses can be administered every two weeks. However, the medication is designed for a Q-4 weeks dose interval. *DSH facilities are <u>not</u> registered to dispense LAI olanzapine (Zyprexa Relprevv®).*

V. LAI aripiprazole (Abilify Maintena®) is available as 300 mg and 400 mg. The usual dose is 400 mg Q-4 weeks. LAI aripiprazole 400 mg Q-28 days produces plasma concentrations comparable to 20 mg of oral aripiprazole per day.

Aripiprazole lauroxil (Aristada®) is available in doses of 441 mg, 662 mg, 882 mg, and 1064 mg. The 441 mg dose may be given by deltoid or gluteal routes, while the three higher doses must be given via the gluteal route. The lower two doses are intended to be given Q-4 weeks, while the 882 mg dose can be given Q-6 weeks. The 1064 mg dose can be given Q-8 weeks.

Lower doses may be appropriate in patients who are poor cytochrome P450 2D6 or 3A4 metabolizers. These formulations were not approved by the U.S. Food & Drug Administration for use in the demented elderly.

VI. Long-acting injectable (LAI) antipsychotic medications are not to be used without clinical evidence that the patient will likely respond to the medication and can tolerate the medication. This is particularly important for voluntary patients who have the right to refuse medications (e.g., those committed to DSH pursuant to PC 1370, PC 2684, PC 2962, PC 2972, PC 1026, or some civilly committed patients with no involuntary medication order). Because treatment with LAI antipsychotics imposes decreased ability

to withdraw medication in cases of adverse response, is inherently a more invasive form of treatment, and involves higher costs compared to oral preparations, all LAI antipsychotics should be reserved for those patients who meet one or more of the following criteria:

A. Are unable to take oral medications (e.g., due to malabsorption or inability to swallow);

B. Have a probability of non-adherence to oral antipsychotics;

C. Have a history of superior response to LAI antipsychotics; or

D. Have a clearly stated preference for treatment with LAI antipsychotic medications.

Despite the above parameters for long-acting injectable (LAI) antipsychotic use, it should be remembered that *LAI antipsychotics are superior in reducing violence,* maintaining stability, and improving longevity by circa 30% compared to their oral counterparts.

VII. LAI risperidone (Consta®), paliperidone palmitate (Erzofri® or Invega Sustenna®), or paliperidone palmitate (Invega Trinza®) or Invega Hafyera® must be reserved for those individuals who meet one or more of the above criteria and also have shown:

A. A documented history of clearly superior clinical improvement of psychiatric symptoms with oral risperidone or paliperidone compared to other antipsychotic medications, respectively, and there are adherence problems which cannot be addressed by alternate approaches; or

B. Have a demonstrated history of failure to respond to or have a demonstrated history of intolerance (e.g., development of moderate to severe tardive dyskinesia) to other conventional LAI antipsychotic medications.

VIII. LAI aripiprazole (Abilify Maintena® or Aristada®) must be reserved for those patients with demonstrated positive response to oral aripiprazole and for whom oral aripiprazole treatment is contraindicated (e.g., by non-adherence, inability to swallow oral medications, etc.). Tolerance and positive response to oral aripiprazole must be based on reliable data (i.e., not via unreliable history alone). This is required because aripiprazole has a very high affinity for dopamine D_2 receptors (i.e., 0.3 nM) and because LAI aripiprazole has a very long half-life. This means that at therapeutic doses for psychosis, aripiprazole will block the access of dopamine antagonist antipsychotics to D_2 receptors, rendering them ineffective until the aripiprazole has had time to decline following discontinuation.

IX. Continued combined use of oral and LAI forms of the same medication for more than 90 days requires Medication Review Committee (MRC) or Therapeutic Review

Committee (TRC) consultation or review. Please see the chapter of these policies regarding MRC or TRC policies.

X. Recommended LAI Antipsychotic Initiation (Loading) Strategies:

LAI Antipsychotic	Comments on Initiation/Loading
Aripiprazole	There are two ways to initiate Abilify Maintena®: 1-day initiation: Administer two intramuscular injections of Abilify Maintena® 400 mg in two different injection sites (deltoid or gluteal muscle), and one dose of oral aripiprazole 20 mg on the first day of treatment with Abilify Maintena®. Do not administer both injections into the same muscle. 14-day initiation: 400 mg intramuscularly Q-28 days, with continuation of oral aripiprazole 10 – 20 mg for the first 14 days after the initial injection. There are two ways to initiate Aripiprazole lauroxil (Aristada®): Option 1: Administer one intramuscular injection of Aristada Initio® 675 mg (deltoid or gluteal muscle) and one dose of oral aripiprazole 30 mg in conjunction with the first Aristada® injection. The first Aristada® injection may be administered on the same day as Aristada Initio® or up to 10 days thereafter. Option 2: Aripiprazole lauroxil (Aristada®) is initiated at 441 mg, 662 mg, 882 mg, or 1064 mg, with the three higher doses requiring gluteal administration. Oral aripiprazole must be continued for the first 21 days of aripiprazole lauroxil treatment. Lower doses are used for cytochrome P450 2D6 or 3A4 poor metabolizers or in patients taking weak to moderate 2D6 or 3A4 inhibitors. Combined use with strong 2D6 or 3A4 inhibitors (e.g., fluoxetine or paroxetine) is not recommended.
Fluphenazine	For each 10 mg of oral fluphenazine per day, give 25 mg of fluphenazine decanoate IM Q-1 week times three and then continue Q-2 weeks at 12.5 mg to a maximum of 100 mg as guided by plasma concentration measurements. Note that fluphenazine decanoate exhibits both an immediate and delayed release from its vehicle, requiring initial reduction or discontinuation of oral dosing in some individuals to avoid post-injection emergence of EPS.

Haloperidol	Because haloperidol decanoate has no immediate release phase, a loading dose strategy is required to avoid need for prolonged co-administration of an oral antipsychotic. That is, administration at a fixed dose would require three to four months to reach steady-state. Give 100 – 300 mg IM Q-1 week times two to three doses. Measurement of a plasma concentration before the third loading dose will assist in determining whether the third loading dose is needed. Measurement of a plasma concentration shortly before the first maintenance dose will be helpful in fine tuning ongoing dosing. Maintenance dosing should begin 14 days after the last loading injection. Optimal plasma concentrations are thought to range from 5 to 20 ng/mL of the parent compound. For maintenance, give on average 200 mg Q-4 weeks per 10 mg of oral daily dose. If the maintenance dose exceeds 300 mg, then divide the dose and administer every 14 days.
Olanzapine (<u>not</u> available in DSH facilities)	There is no need for oral cross-over or loading. Note, however, that a 0.1 – 0.2% risk of delirium, obtundation, and coma follows each dose. Direct nursing observation is required for a minimum of three hours following each injection. *LAI olanzapine is <u>not</u> available in DSH facilities.*
Paliperidone	*For Erzofri® give an initial dose of 351 mg in the deltoid muscle. For Invega Sustenna®* give an initial dose of 234 mg followed by a second initiation dose of 156 mg after one week. Initial doses should be deltoid. Maintenance doses may be deltoid or gluteal. The modal maintenance dose is 117 mg Q-4 weeks, with a dose range of 39 – 234 mg. Oral risperidone or paliperidone is not required after the initiation phase. Note: Although the paliperidone palmitate package insert states that oral cross-over is not required when initiating paliperidone palmitate and no clinical studies have identified an elevated risk of post-initiation decompensation, due to the pharmacokinetics of the paliperidone palmitate initiation (loading) protocol, it may be prudent to consider oral overlap to avoid psychiatric decompensation in some patients. This is accomplished by prescribing risperidone 4 to 6 mg po starting on the day that 234 mg IM deltoid injection is given and continuing for 7 days. Risperidone oral supplementation at 2 to 3 mg/day would then

<table>
<tr><td></td><td>continue another 7 days starting on the day of the second paliperidone IM deltoid injection.

Paliperidone palmitate extended-release (Invega Trinza®) is restricted to patients who have received effective and stable treatment with paliperidone palmitate (Invega Sustenna®) for a minimum of four (4) months. At the time the next dose of paliperidone palmitate would be due, give the equivalent dose of paliperidone palmitate extended-release (Invega Trinza® or Invega Hafyera®). Invega Hafyera® must be given by the gluteal route only.</td></tr>
<tr><td>Risperidone</td><td>Initiate LAI risperidone (Consta®) at 25 – 50 mg Q-2 weeks while continuing oral risperidone treatment. After three weeks have passed since the initial injection, taper and discontinue oral risperidone.

Each 25 mg of Consta® produces plasma concentrations of risperidone plus 9-hydroxy-risperidone comparable to 2 – 3 mg of oral risperidone.

Uzedy® does not require oral cross-over and may be initiated at the target dose. Uzedy® is initiated at 50 mg to 125 mg once monthly or 100 mg to 250 mg once every 2 months (abdominal or upper arm subcutaneous (SC) injections).

<table>
<tr><th>Comparable Daily Oral Risperidone Dose</th><th>Uzedy® Dose Once Monthly</th><th>Uzedy® Dose Once Every 2 months</th></tr>
<tr><td>2 mg</td><td>50 mg</td><td>100 mg</td></tr>
<tr><td>3 mg</td><td>75 mg</td><td>150 mg</td></tr>
<tr><td>4 mg</td><td>100 mg</td><td>200 mg</td></tr>
<tr><td>5 mg</td><td>125 mg</td><td>250 mg</td></tr>
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A. Loading strategies would likely not be needed if switching from a longer-acting LAI medication (e.g., haloperidol decanoate, paliperidone palmitate, or olanzapine pamoate). Use of a loading strategy would not be needed to switch from LAI risperidone to paliperidone palmitate. Use of a loading strategy might be prudent, depending on dose timing, in switching from fluphenazine decanoate to a different LAI antipsychotic.

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