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REVIEW ARTICLE

# A Practical Guide to Prescribing Long-Acting Injectable Medications: Clinically Informed Technological Aspects and Algorithmic Approaches for Enhanced Understanding and Implementation in Clinical Practice

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**Abstract**

It is very well documented and supported by the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study that patients with schizophrenia spectrum disorders do not adhere to medications adequately. Long-acting injectable (LAI) medications have been consistently shown to improve compliance with treatment in patients living with these disorders. However, the complexity of navigating the available long-acting injections and selective preference by providers has resulted in less-than-optimal use of these favorable formulations. In this paper, we summarize each medication available, represent computer generated graphics to aid understand the dosing logic as well as easy to follow algorithm in a hope to increase the prescription of LAI by community psychiatrist and advanced nonphysician psychiatric healthcare providers.

## Introduction

Schizophrenia is a chronic relapsing disorder characterized by impaired reality testing, disorganized thinking, and possible cognitive impairment [1]. Despite advances in treatment, predicting relapses remains a significant challenge. Since predicting the timing of a re lapse in schizophrenia and schizoaffective disorder is challenging, the emphasis must be on implementing effective prevention strategies. A crucial approach involves ensuring patient compliance with the prescribed medications; unfortunately, adherence among individuals with these disorders is notably low [2,3]. Factors contributing to poor compliance include medication side effects, lack of insight into the illness, and social or economic challenges [2-5]. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, for instance, revealed that approximately three-fourths of patients with schizophrenia discontinue their medication within the first year [4,5]. Non-adherence to medication regimens can significantly increase the risk of relapse in individuals with schizophrenia and schizoaffective disorders [3].

One highly effective strategy for improving medication adherence and reducing the risk of relapse in patients with schizophrenia and schizoaffective disorders is the utilization of long-acting injectable (LAI) antipsychotics [4,6]. LAI antipsychotics offer the advantage of sustained release over extended periods, typically ranging from two weeks to several months depending on the specific formulation [7-13]. Studies have demonstrated that LAI antipsychotics not only improve medication adherence but also lead to better overall treatment outcomes compared to oral medications alone [6,14]. The reduced frequency of dosing with LAIs can alleviate the burden of daily

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medication management for patients and caregivers, potentially enhancing treatment compliance and long-term stability [15] particularly in those with poor insight and judgment [5,6].

Various technologies have been employed to extend the duration of action of medications [16,17]. These include formulations utilizing biodegradable polymers for sustained release, implantable devices that gradually release drugs over time, and nanotechnology approaches to enhance patient compliance and therapeutic efficacy by reducing the frequency of dosing and maintaining consistent drug levels in the body over extended periods [16,17]. There are several long-acting injectable (LAI) antipsychotics currently available, each with unique characteristics and dosing schedules. Thus, establishing clear and straightforward guidelines could significantly enhance the adoption of LAIs among early career psychiatrists and residents. By providing accessible information on the technology to deliver the drug, dosage recommendations, administration techniques, and monitoring protocols for LAIs, early career mental healthcare professionals can feel more confident in prescribing these formulations. In this paper, our primary objective is to present user-friendly algorithms for each currently available long-acting injectable (LAI) antipsychotic medication. We will attempt to not only simplify the decision-making process but also reflect on the technological aspect of LAI consistency in clinical practice.

The development of LAIs began in the 1960s, with fluphenazine enanthate introduced in 1966 and fluphenazine decanoate in 1968 [18-22]. Fluphenazine decanoate formulations were noted for their extended duration of action and potentially lower side effects compared to enanthate formulations [20,23]. Clinical studies also suggested that fluphenazine enanthate did not consistently show superiority over oral fluphenazine [23]. Following these initial developments, a succession of other long-acting antipsychotics quickly emerged. This pioneering work not only expanded treatment options but also laid the groundwork for subsequent advancements in LAI technology. Currently, in the United States, the use of first-generation LAIs for the treatment of schizophrenia is limited to fluphenazine decanoate and haloperidol decanoate [24,25]. Other first-generation LAIs such as flupentixol decanoate, perphenazine decanoate, pipotiazine palmitate, and zuclopenthixol decanoate are not available in the United States market. Compared to first-generation LAI antipsychotics, however, a plethora of second-generation LAI antipsychotics are available, and the menu of options is increasing. In this paper, we will provide a brief summary of each LAI and the technology used, with a computer-generated schematic representation of the drug delivery mechanism. We hope the early career psychiatrist, advanced nurse practitioners, and residents will have a better understanding of how and why to select or dose a medication.

## What is in the Name?

Today, naming a drug is a prolonged and arduous process. In the United States, the American Medical Association (AMA) started a process to streamline names and eliminate confusion and 'medical quackery promotions' [26-28]. For example, in the case of Veracolate, a treatment promoted for indigestion, the AMA found it to be "semisecret in composition, unscientific in combination" and in the case of Oak Balm for vaginal tract ailments, there were no oak components [28]. Generic and brand names require two very different pathways. For generic names, in the United States, currently the American Medical Association (AMA), United States Pharmacopeial Convention (USP), and American Pharmacists Association (APhA) propose a name to the Food and Drug Administration (FDA) who approves or denies a generic name. AMA, USP and APhA created the United States Adopted Names (USAN) Program which assigns nonproprietary names i.e. generic names [26]. Internationally, the World Health Organization (WHO) publishes recommended International Nonproprietary Names (INN) which may or may not utilize USAN name [26]. The prefix tries to create a name that is user-friendly and the stem (the suffix) provides some information on how a drug may work [25,26]. In the "name imatinib, the -tinib stem refers to the drug's action as a tyrosine kinase (TYK) inhibitor" [26] while in a medicine such as sildenafil, the suffix of 'afil' refers to PDE5 inhibitor properties [25]. There are certain criteria for the prefix: Must be one to two syllabics, not contain letters difficult to pronounce in some languages (H, J, K, and W), not intended for marketing, and do not convey medical terminology [25,26]. Generic names use input from a variety of stakeholders to remove confusion and create user friendly names that are less prone to be promoted unethically. On the other hand, the generation of brand names is a more complex process requiring years of work by marketing companies. The companies create a long list of marketable yet distinct names, which are then vetted and reduced to one name to submit to the FDA and two names to be submitted to the WHO. The names are either accepted or rejected. Sometimes, the names can be quite surprising for example, EMSAM stands for Emily and Sam, two children of one of the employees of the manufacturer [28]. However, often many factors are accounted for such as trademarking, linguistic, interpretative potential, etc [29]. Generally, the drug name phonetically conveys positivity e.g. Viagrai, Ibrance, [29], Abilify, Prolixin, Consta, Invega, Sustenna, Maintenna, Initio [30].

## Haloperidol Decanoate

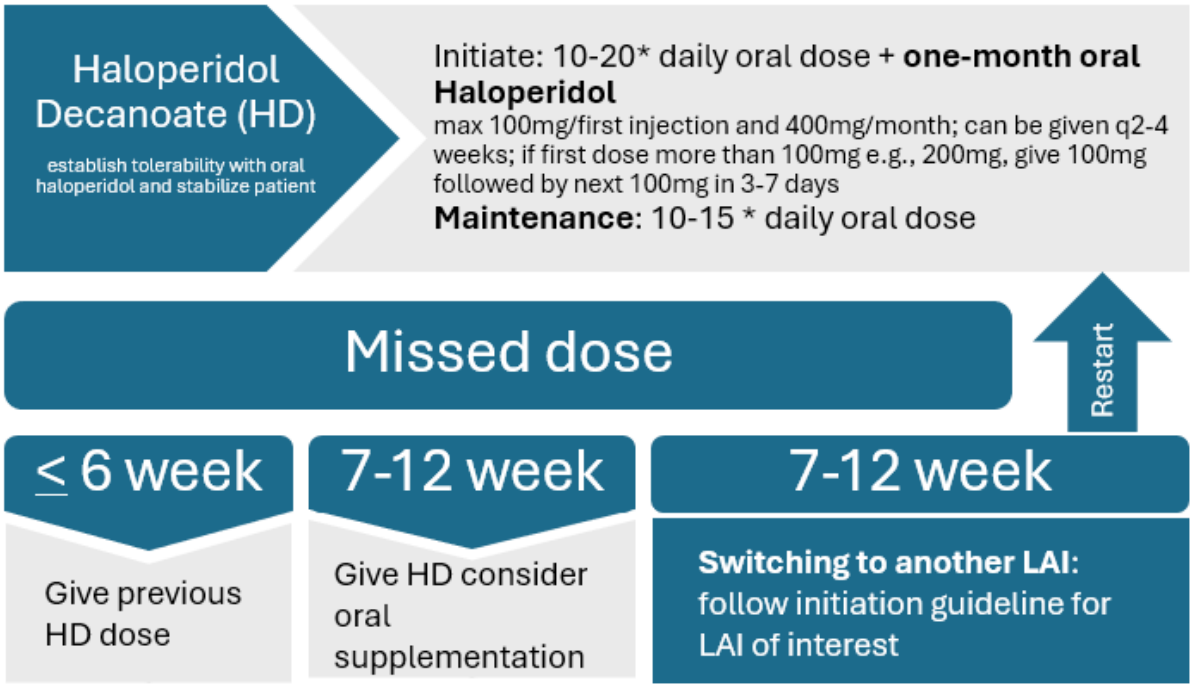
Haloperidol decanoate (HD) stands out as one of the most frequently prescribed first-generation long-acting injectable (LAI) medications in clinical practice. Its formulation offers an extended duration of action,

which can range from several weeks to a month depending on the dosing schedule [24]. The benefits of HD may mirror those of, for example, paliperidone and risperidone LAI at lower costs [30,31].

After injection, haloperidol decanoate (HD) undergoes slow hydrolysis of its ester component, leading to a gradual release of haloperidol over an extended period. This hydrolysis seems to occur more in the lymphatic system in close proximity the injected medication rather than the site of injection [32-34]. Interestingly, shortly after administration of HD, there may be some variability in plasma levels of haloperidol. However, clinical studies have consistently shown that these early fluctuations do not significantly impact treatment outcomes [35,36]. HD is diluted in sesame oil for injection. The lipophilic portion of HD, decanoate, remains anchored in the sesame oil, while the hydrophilic part, haloperidol, is oriented towards the interstitial surrounding (Figure 1). After injection, HD slowly leaves the sesame oil and is transported to other tissues, including lymph nodes where it is hydrolyzed enzymatically (e.g. by carboxylesterase) [37,38]. Yoshinori, et al. reported that in rats, there was no lymphatic absorption of haloperidol from the site of injection [33,34], with a scant amount of HD binding to macromolecules in interstitial fluids remaining at the side of injection for prolonged period. This suggests that hydrolysis of HD at the site of injection is less likely and most of the hydrolysis occurs in lymphocytes [34]. Consistent with this finding, there was a 4,600 times higher concentration of haloperidol in the lymph nodes closest to the site of injection compared to plasma levels [32]. Regarding excretion, about 90% of HD is eliminated from the body by day 42 [32].

In practical terms, the need for oral medications, thus far, remains a challenge. Traditionally, a patient will need to take oral haloperidol for at least several weeks before HD increases plasma levels of haloperidol to a meaningful level [36]. An alternative approach to administering HD involves the use of four weekly loading doses, which is typically sufficient to achieve therapeutic blood levels quickly without any oral supplementation [39,40].

**Haloperidol decanoate administration algorithm**




## Fluphenazine Decanoate

Fluphenazine decanoate (FD) is one of the pioneering first-generation long-acting injectable (LAI) medications available in the United States, specifically developed for the treatment of schizophrenia [10,22,41,42]. Its introduction marked a significant advancement in psychiatric pharmacotherapy, offering a sustained-release formulation that reduces the frequency of administration compared to oral medications. The efficacy of FD in managing symptoms of schizophrenia has been extensively studied and well-established through clinical trials and real-world use [30].

Despite its proven effectiveness, FD has faced challenges in widespread adoption, partly due to its historical underemphasis in psychiatric residency training programs. This lack of emphasis on FD and its side effect profile may have contributed to its underutilization in recent decades. However, FD remains an exceptional treatment option with benefits similar to haloperidol decanoate.

Similar to HD, FD is formulated as an ester that undergoes hydrolysis after injection, gradually releasing the active medication into the bloodstream over an extended period. This sustained release mechanism ensures stable therapeutic levels of fluphenazine (Figure 1).

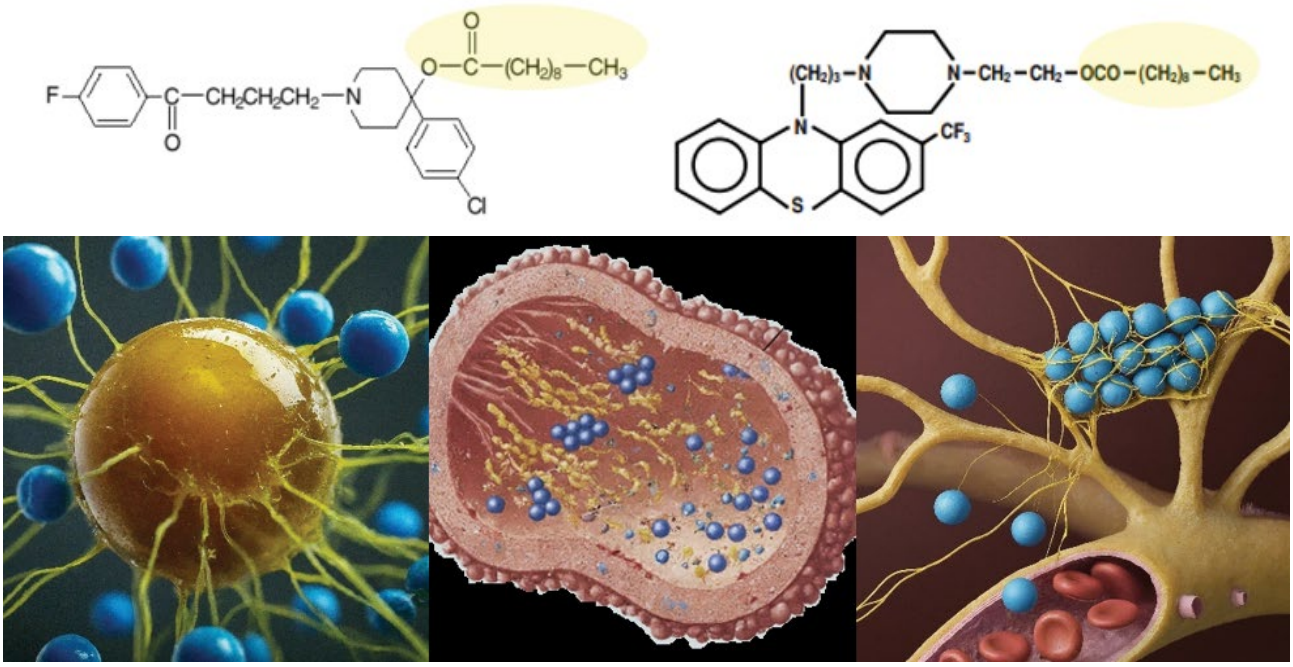
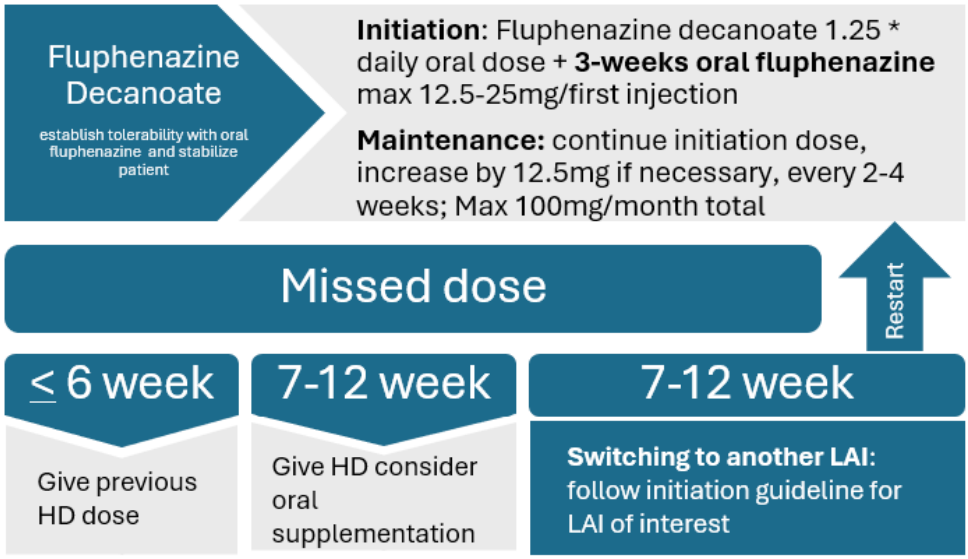


**Figure 1:** Top: Molecular structure of haloperidol decanoate (HD) [9] and fluphenazine decanoate (FD) [10] with decanoic acid highlighted. Bottom: Cartoon representation (Google Gemini produced) of HD/FD in sesame oil: The hydrophilic haloperidol/fluphenazine (blue ball) is anchored in sesame oil via hydrophobic decanoate (yellow string). HD/FD is taken up by (e.g.) lymph node where it is hydrolyzed by (e.g.) carboxylesterase to haloperidol/fluphenazine (free blue balls) released to circulation.

### Fluphenazine decanoate administration algorithm




## Risperidone

Risperidone, a pioneering long-acting second-generation antipsychotic, introduced a distinct mechanism for achieving sustained release. Unlike traditional oil-based medications, this second-generation formulation is water-soluble, resulting in injections that are less painful for patients [7,43]. Risperidone is available in three LAI formulations. The first one was released in 2004 [7] under the brand name Risperdal Consta®. In this formulation, risperidone molecules are encapsulated within micelles composed of biodegradable copolymer (Figure 2), polylactide coglycolide (PLG), using a static flow method to deliver the medication [7,43]. This co-polymer allows a drug delivery system with varied durations of action by different ratios of the constituent monomers [44,45]. These microspheres act as a protective shield, preventing immediate release of risperidone upon injection. Instead, the medication gradually releases over a period of three weeks as the external shell of the micelle is metabolized. Consequently, patients receiving this formulation will require oral supplementation with risperidone during the initial three-week period to maintain therapeutic levels (Figure 2). Peak plasma concentration is reached at 28 days and is sustained for 4-5 weeks followed by rapid reduction. No residual risperidone is measurable by the end of week 8 after the last injection [36].

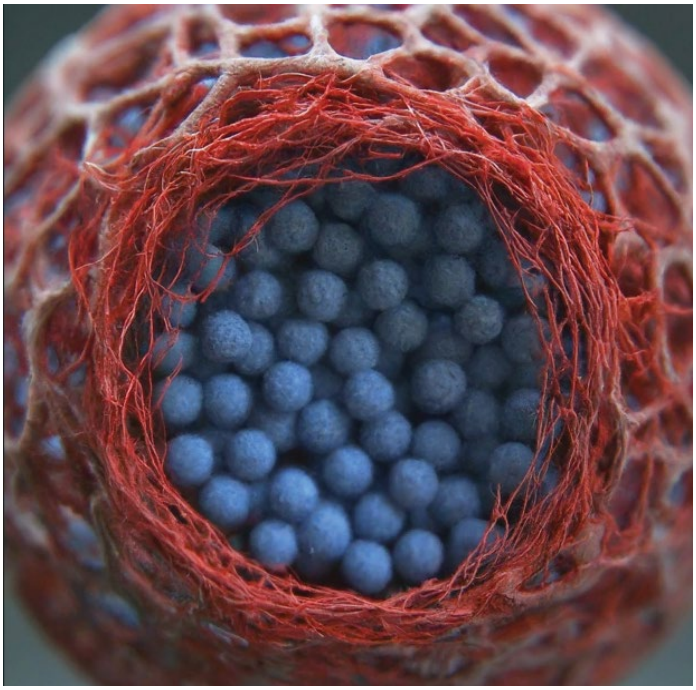
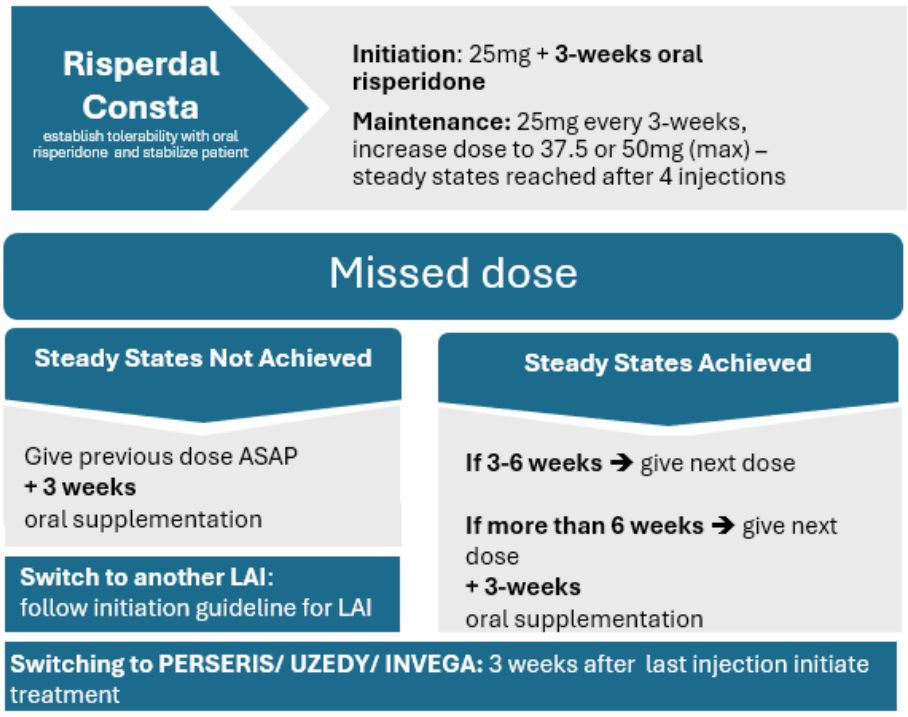


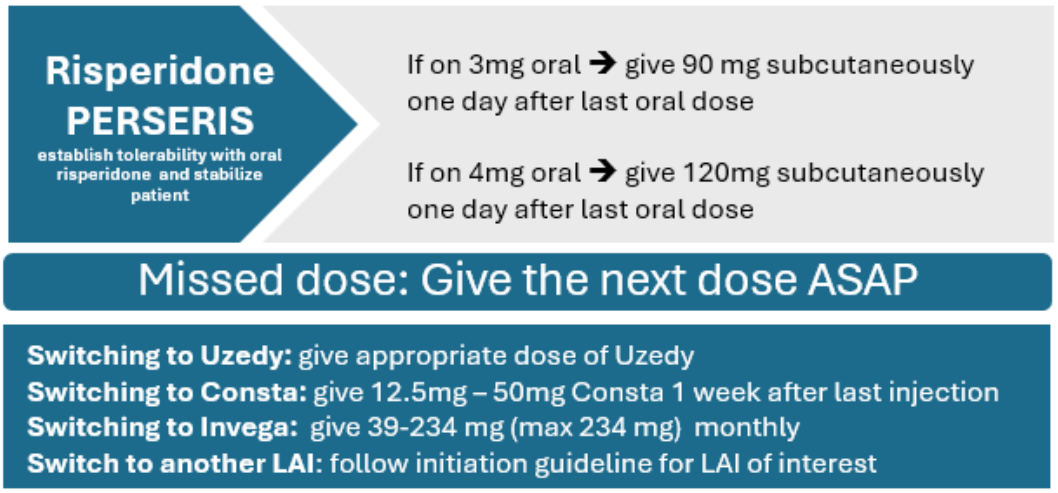
**Figure 2:** Computer generated representations of Risperdal Consta, microsphere of poly(lactic acid)-poly(ethylene glycol)-poly(lactic acid)-a structure similar to that of biodegradable surgical suture (red) containing risperidone (blue): Since the polymeric shell needs enzymatic degradation of 3-weeks, oral supplementation is necessary for first 3-weeks for Consta.

The second formation is marketed under the name PERSERIS™ where the biodegradable copolymer, poly(D,L-lactide-co-glycolide) (PLGA), is dissolved in an N-methyl-2-pyrrolidone (NMP) [8]. Upon contact with tissue, the NMP dissolves, and PLGA solidifies resulting in the slow release of risperidone [46]. PERSERIS is injected subcutaneously monthly; thus, there is no need for oral supplementation with PERSERIS. The third formulation uses yet another copolymer technology, poly(lactic acid)-poly(ethylene glycol)-poly(lactic acid) (PLA-PEG-PLA), to create microspheres that are injected subcutaneously [47,48]. This formulation [49], marked under the brand name UZEDY™ is available in monthly and bimonthly subcutaneous injections with slow release of risperidone. Similar to PERSERIS, UZEDY does not require oral supplementation.

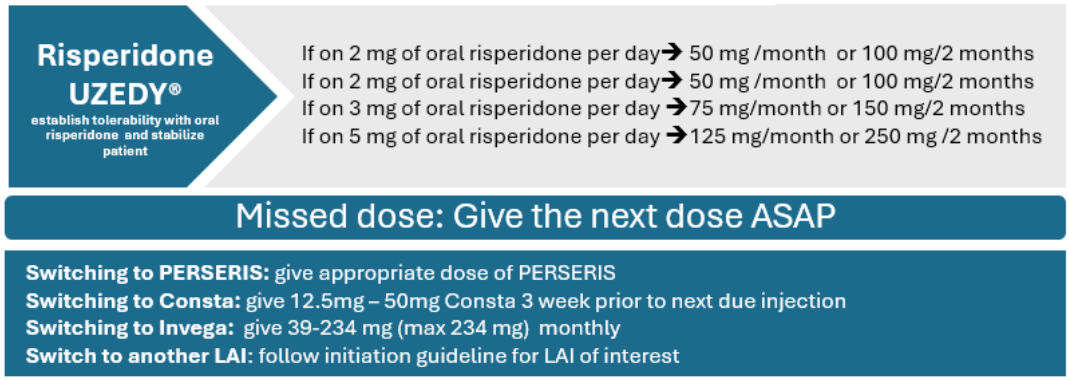
## Risperidone long-acting injection administration algorithms




**Risperidone PERSERIS®**




**UZEDY®**




## Olanzapine Pamoate

Approved in 2009, Olanzapine pamoate (OP), marketed as ZYPREXA RELPREVV, has been available in the United States for years [50-52]. In contrast to risperidone long-acting injectable (LAI), OP is formulated as a crystalline salt (Figure 3); OP is the first crystal-based LAI [36]. Peak plasma level is reached in 2-4 days with an apparent plasma half-life of 26 days [36]. Steady state is reached in 2-3 months. In biweekly injections, trough levels are half of peak levels (Figure 4), while in monthly injections they are ¾ of peak [36].

Very slowly, in the interstitial fluids, the salt microcrystals change to pamoic acid and an olanzapine free base which is rapidly absorbed [53]. This unique formulation eliminates the need for oral supplementation, offering a distinct advantage over other LAIs [55]. A cartoon representation of the compound can clarify the mechanism of delivery and explain why oral supplementation is unnecessary.

However, a notable concern is the occurrence of post-injection delirium/sedation syndrome (PIDSS), which has been reported in 0.07% of cases, prompting caution during its use. Consequently, patients receiving OP should be closely monitored for three hours post-injection.

The exact mechanism behind PIDSS is not fully understood, but there is evidence suggesting that elevated olanzapine levels in the blood of affected individuals may result from inadvertent intravascular injection. This risk can be mitigated by aspirating the syringe plunger before administering the medication to ensure it is not injected into a blood vessel. Physicians are strongly encouraged to participate in the ZYPREXA RELPREVV Patient Care Program [56] to enhance patient safety and minimize the occurrence of PIDSS. This program provides critical guidance on administration techniques and monitoring protocols tailored to reduce the risks associated with OP therapy.

**Figure 3:** Computer generated cartoon of olanzapine LAI microcrystals. Since, some of the microcrystals salts will release olanzapine, oral supplementation is not necessary, however, multiple initial injections are necessary.

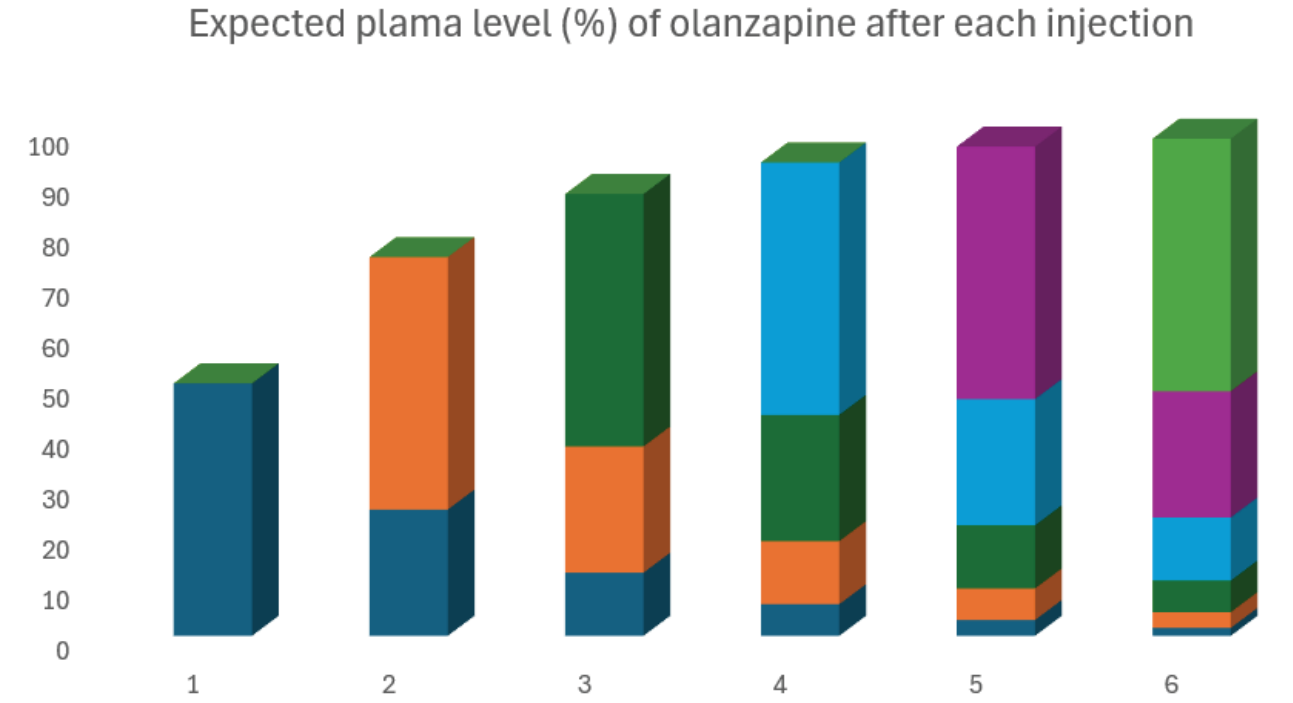
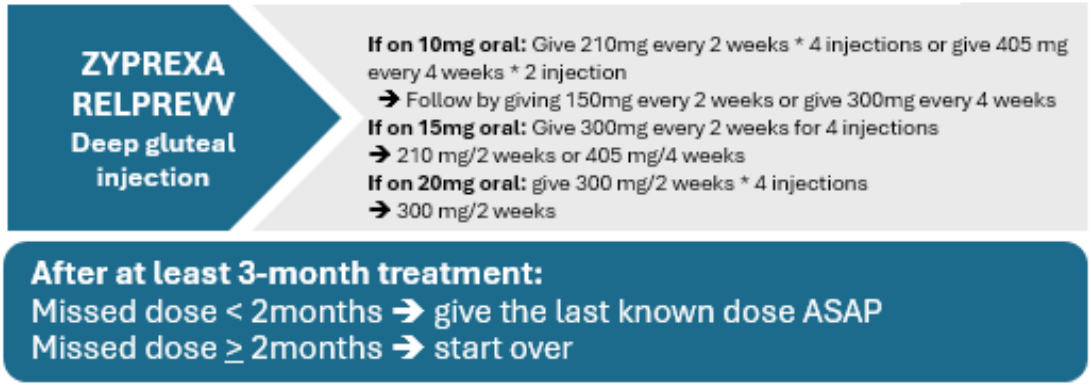



**Figure 4:** After each successive ejection, the plasma level waxes and wanes, however, after about 6 injections, the trough level reaches steady state [53]. After an injection, the micron-sized crystals of the pamoate salt slowly dissolve releasing olanzapine [36,54].

### Olanzapine long-acting injection administration algorithm




## Paliperidone Palmitate

Paliperidone palmitate is another crystalline salt (Figure 5) compound formulated as an aqueous suspension of

**Figure 5:** Computer generated (Google Gemini) cartoon depiction of paliperidone palmitate microcrystal: The breakdown of the surface microcrystals allows for the release of the active compound into the bloodstream; thus, oral supplementation is not necessary.

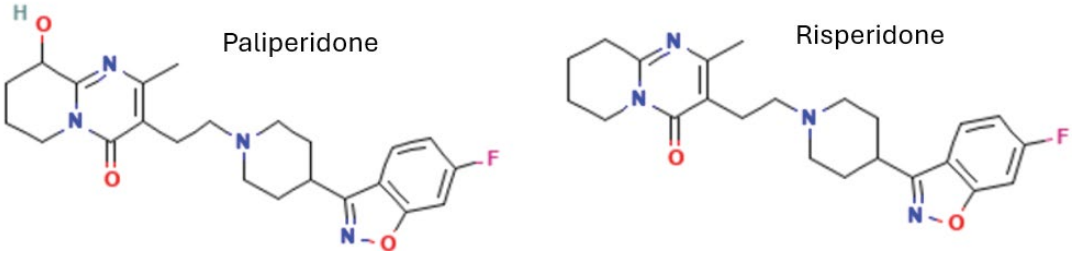



**Figure 6:** Chemical structres of risperdidone and paliperidone.

nanocrystals [36,43]. This injectable medication is derived from paliperidone, an active metabolite of risperidone [57,58], and is designed for extended-release administration. The nanocrystals in its formulation enhance its solubility and absorption properties, allowing for sustained delivery over extended periods [36].

Dissolution of the salt shell surrounding paliperidone palmitate nanocrystals facilitates the release of the active compound into the bloodstream, the formulation is structured to provide a steady release of paliperidone over weeks or months, depending on the formulation and dosing schedule [36,59]. Due to this extended-release mechanism, loading injections of paliperidone palmitate eliminate the need for oral supplementation. By bypassing the need for daily oral medications, paliperidone palmitate enhances convenience and potentially improves treatment adherence among patients with schizophrenia or related disorders [36,59,60]. Paliperidone (9-hydroxyrisperidone) is closely related to risperidone (Figure 6), however, there are some differences in pharmacodynamics, pharmacokinetics, as well as the mode of action of paliperidone [43]. However, this molecular similarity can allow a switch from oral risperidone to LAI paliperidone.

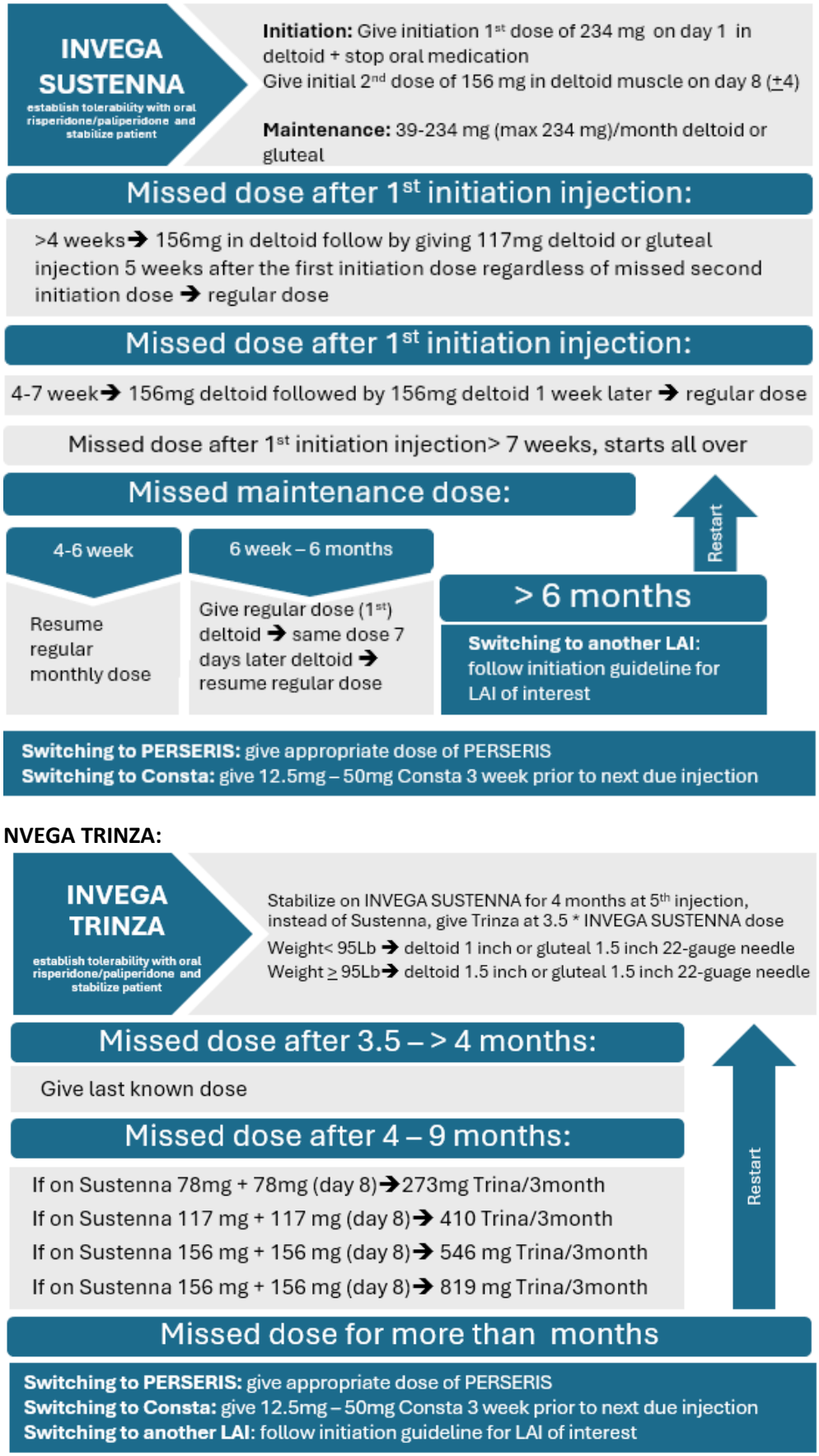
Paliperidone is an active metabolite of risperidone, yet their biological actions may exhibit variances despite their shared origin. These differences could stem from distinct pharmacokinetic profiles or unique interactions with synaptic receptors [49,60].

The three-month injection of paliperidone utilizes larger nanocrystals, which prolong the dissolution process, thereby enabling administration every three months. This extended-release formulation ensures sustained therapeutic levels in the bloodstream, offering convenience and enhancing treatment adherence compared to more frequent dosing schedules [11].

The paliperidone palmitate 6-month formulation is the only very long acting antipsychotic available on the market with comaprable effecacy to the paliperidone palmitate 3-month formulation [61]. The paliperidone palmitate 6-month formulation offers a cost effective alternative to both the paliperidone palmitate 3-month formulation and the paliperidone palmitate 1-month formulation [12].

## Paliperidone long-acting injection administration algorithm

**INVEGA SUSTENNA:**




**NVEGA TRINZA:**




**INVEGA HAFYERA:**

**INVEGA HAFYERA by** gluteal injection once every 6 months

On INVEGA SUSTENNA for at least 4 months (no equivalency for lower doses established)
For Sustenna of 156 mg ➔ give Hafyera of 1,092 mg
For Sustenna of 234 mg ➔ give Hafyera of 1,560 mg
On INVEGA TRINZA for at least one month (no equivalency for lower doses established)
For Trinza of 546 mg ➔ give 1,092 mg
For Trinza of 819 mg ➔ Give1,560 mg

Can be given 2 week before or 3 weeks after last injection

**Missed dose after 6 months +> 3 weeks:**

if 6 months + 3 week➔ reinitiate INVEGA HAFYERA with last dose of as follows:
If patient was on 1,092 mg ➔ give SUSTENNA 156 mg ➔ 1 month later give 1,092 mg
If patient was on 1,560 mg ➔ give SUSTENNA 234 mg ➔ 1 month later give 1,560 mg

**Switching to PERSERIS:** give appropriate dose of PERSERIS
**Switching to Consta:** give 12.5mg – 50mg Consta 3 week prior to next due injection
**Switching to another LAI:** follow initiation guideline for LAI of interest

## Aripiprazole

Aripiprazole monohydrate (Figure 7) is another compound that forms microcrystalline salts. Aripiprazole long-acting injection formulations employ techniques that create microcrystals of the drug, which dissolve gradually when administered, thereby extending the duration of action [62].

Aripiprazole monohydrates are monthly injections under the name of ABILIFY MAINTENA® and bimonthly under the name ABILIFY ASIMTUFII®. AM is released after 5 to 6 days, and release continues for an additional 36 days. Due to slow dissolution of these microcrystalline forms, it is necessary to provide 2 weeks of oral aripiprazole. It is considered disadvantage of both Maintenna and Asimtufii to rely on a patient who may not be able to take oral medication for a number of reasons.

### Aripiprazole lauroxil

Aripiprazole lauroxil (AL), marketed under ARISTADA® uses a different technology where a microcrystalline

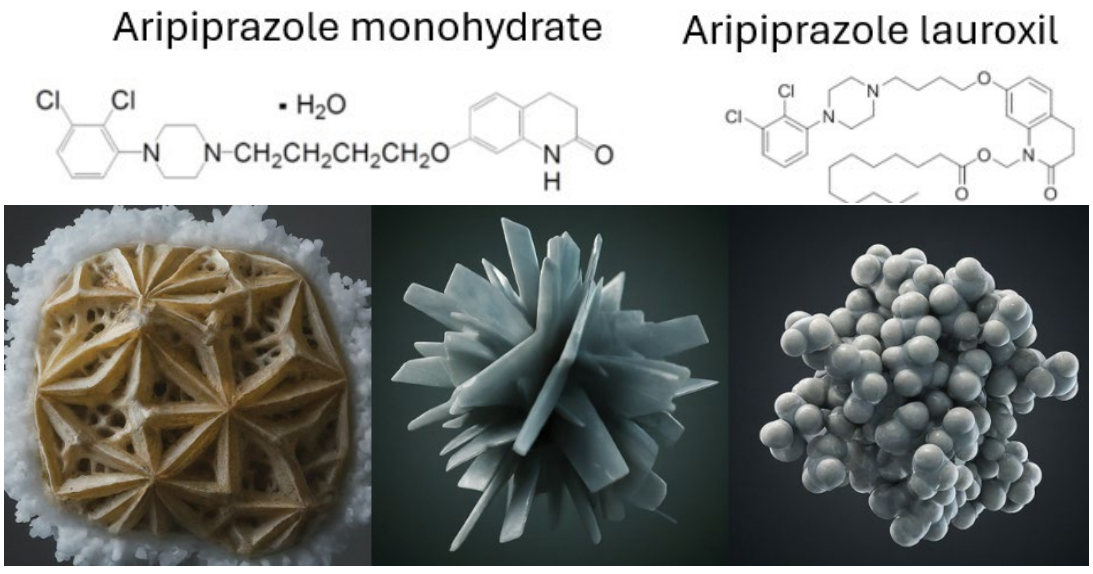
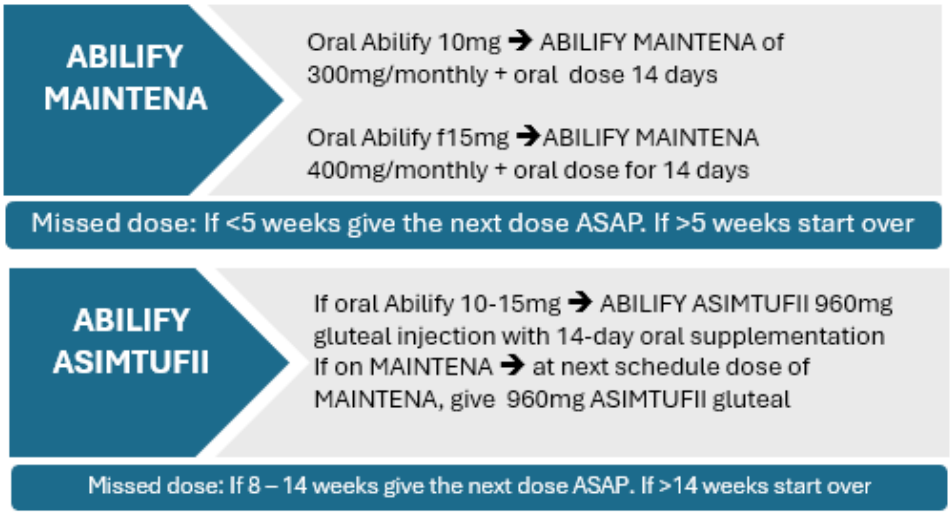



**Figure 7:** Top: Chemical structures of aripiprazole monohydrate (AM) and lauraxil (AL). Bottom: A computer-generated (Google Gemini) cartoon representation of AM microcrystals. Although AM and AL use different techniques, both produce slow releasing mechanisms in aqueous environments. The enzymatic degradation of the microcrystals will necessitate oral supplementation for 2 weeks. However, AL given with Initio® nanocrystal along with a single dose of oral aripiprazole will eliminate the need for continued oral supplementation with AL.

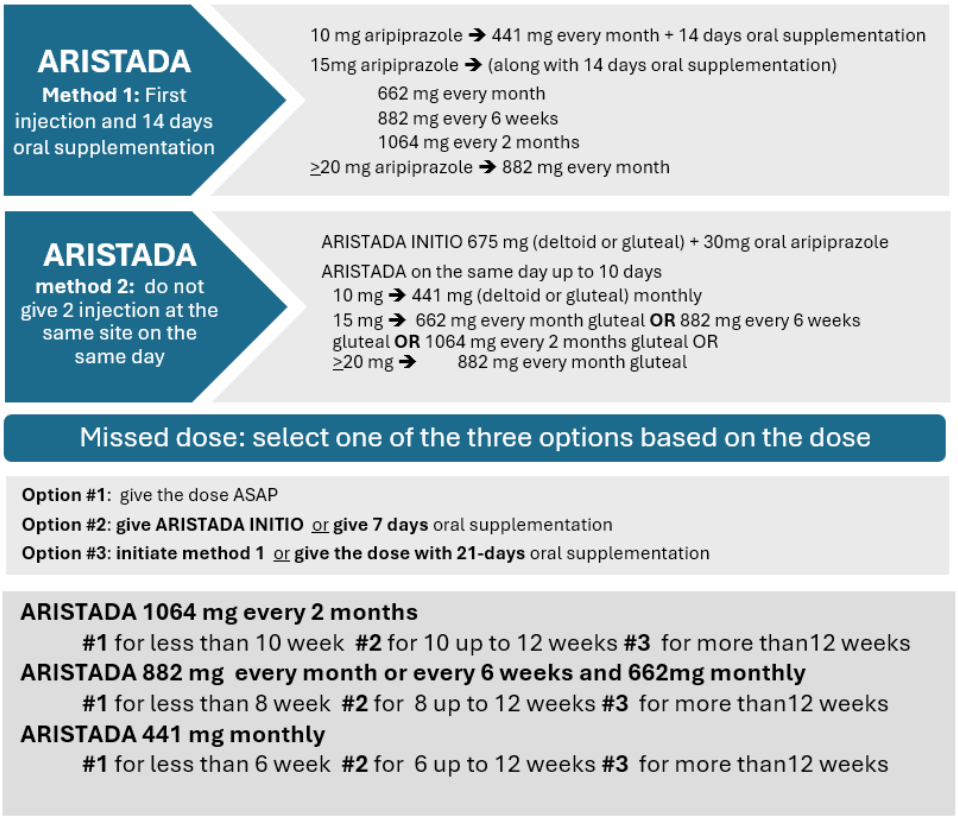
non-ester prodrug of aripiprazole is produced [63]. Aripiprazole lauraxil is very slowly metabolized enzymatically to *N*-hydroxymethyl aripiprazole and lauroxic acid (a fatty acid naturally present in breast milk). Subsequently, *N*-hydroxymethyl aripiprazole is spontaneously hydrolyzed to aripiprazole rapidly [63]. AL can be given monthly or every 6 weeks under the name of ARISTADA®. The slow increase in aripiprazole concentration after each injection necessitates the coadministration of oral aripiprazole for 21 days with the first injection [63].

Using nano-crystalline milled dispersion, AL NanoCrystal®Dispersion Technology (Aristada Initio®) enables a rapid increase in aripiprazole in plasma with only a single oral dose of 30 mg aripiprazole and provides sufficient release until microcrystals eventually provide sustained plasma levels [64]. This technique reduces the size of the microcrystals to nanocrystals, increasing surface area, which allows the poorly water-soluble drug to dissolve faster than the microcrystalline from of the salt [65]. Both the 882 mg dose every 6 weeks and 662 mg monthly provide sufficient coverage.

### Aripiprazole monohydrate long-acting injection administration algorithm




### Aripiprazole lauroxil long-acting injection administration algorithm

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8. FDA. PERSERIS (risperidone) for extended-release injectable suspension, for subcutaneous use.

9. FDA. HALDOL® Decanoate 50 (haloperidol) HALDOL® Decanoate 100 (haloperidol) For IM Injection Only.

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