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LONG-ACTING INJECTABLE ANTIPSYCHOTICS IN SCHIZOPHRENIA

Antipsychotics serve as the cornerstone of pharmacological treatment for schizophrenic disorders, including both the management of acute episodes and the prevention of relapse. Long-acting injectable antipsychotics (LAIAs) are intended to improve treatment compliance, thereby reducing the risk of relapse and hospitalization. The marketing of LAIAs has increased over the past few years, consequently expanding the range of active substances and extending dosing intervals (bi-weekly, monthly, quarterly and semi-annually). This new situation represents a qualitative change in the available therapeutic approaches for schizophrenia, although a risk/benefit assessment is required, and the prescribing efficiency from an overall patient health perspective needs to be studied.

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INTRODUCTION

Antipsychotics (APs) are employed to reduce or eliminate the symptoms of psychosis (hallucinations, delirium, disorganised thinking or behaviour)[1].The use of these medications has been approved, among other indications, for the acute-phase and maintenance treatment of schizophrenia .Although antipsychotic treatment is typically an essential element for patients with schizophrenia, such treatment must also encompass psychosocial interventions such as cognitive-behavioural therapy, psycho-education, social skills training and workplace support[2].

APs have traditionally been classified into two primary groups, namely typical and atypical.

- Typical, or first-generation, APs are characterised by a strong D2 dopaminergic receptor antagonism at both cortical and striatal levels. In turn, they are subdivided into high-potency types (e.g. Haloperidol) and low-potency types (e.g. chlorpromazine).
- Atypical, or second-generation, APs are characterised by their potent D2 receptor blockade, combined with acting as antagonists for 5HT2A serotonergic, alpha-1, muscarinic and histaminergic receptors.

The differentiation between typical and atypical APs in terms of adverse effects is debatable[3], as intragroup differences in adverse effects, as well as some similarities in adverse effect profiles among APs from different groups, have been described. Consequently, the pharmacological properties, therapeutic effects and adverse effects must be evaluated individually for each drug (Table 1).

Systematic reviews and meta-analyses have failed to find any significant differences in efficacy among the different APs available on the market for managing acute episodes of schizophrenia, with the esception of clozapine[3,4]. Given its greater efficacy, clozapine stands as the drug of choice for harmacologically treating treatment-refractory schizophrenia. Refractory schizophrenia is most commonly defined by the presence of at least three moderate psychotic symptoms and functional deterioration, des-

Table 1. Main adverse effects of the APs used in Spain[6–8].

		WEIGHT GAIN	BLOOD GLUCOSE ALTERATIONS	HYPERLIPIDEMIA	AKATHISIA	PARKINSONISM	DYSTONIA	TARDIVE DYSKINESIA	ELEVATED PROLACTIN	SEDATION	ANTICHOLINERGIC EFFECT	ORTHOSTATIC HYPOTENSION	QTC PROLONGATION
1st Generation antipsychotics	Chlorpromazine+	++	++	+	++	++	++	+++	+	+++	+++	+++	+++
	Flufenazine ↗	++	+	+	+++	+++	+++	+++	+++	+	+	+	+
	Haloperidol	++	+	+	+++	+++	+++	+++	+++	+	+	+	++ (p.o.)/ +++ (i.v.)
	Loxapine	+	+	+	++	++	++	++	++	++	++	++	*
	Perphenazine	++	+	+	++	++	++	++	++	++	++	++	*
	Pimozide	+	+	+	+++	+++	++	+++	+++	+	+	+	++
	Tioridazine++	++	+	+	+	+	+	+	++	+++	+++	+++	++
	Zuclopenthixol ↗	++	+	+	++	++	++	+	+++	++	++	+	*
2nd Generation antipsychotics	Aripiprazole ↗	+	+	+	++	+	+	+	+	+	+	+	*
	Asenapine	++	++	++	++	+	++	++	++	++	+	++	+
	Brexpiprazol¶	+	+	++	++	+	+	+	+	++	+	+	*
	Cariprazine¶	++	+	+	++	+	+	+	+	++	++	+	*
	Clozapine+++	+++	+++	+++	+	+	+	+	+	+++	+++	+++	++
	Lurasidone	+	++	++	++	++	++	++	+	++	+	+	*
	Olanzapine ↗	+++	+++	+++	++	++	+	+	++	+++	++	++	++
	Paliperidone ↗	++	+	++	++	++	++	++	+++	+	+	++	+
	Quetiapine	++	++	+++	+	+	+	+	+	+++	++	++	++
	Risperidone ↗	++	++	+	++	++	++	++	+++	++	+	++	++
	Ziprasidone	+	+	+	++	+	+	+	++	++	+	++	+++

Incidence/Severity
(+) Low
(++) Moderate
(+++) High
(*) Not detected in preliminary studies or reported in the summary of product characteristics
(p.o.) Oral administration
(i.v.) Intravenous

+Chlorpromazine: Increased photosensitivity and skin rashes.
++Thioridazine: Dose-dependent relationship with development of retinitis pigmentosa, as well as increased photosensitivity and skin rashes.
+++Clozapine : May cause agranulocytosis (1%), increases the risk of myocarditis and venous thromboembolism.
↗ Active substance for which a long-acting intramuscular presentation (LAIA) exists.

pite having received at least two lines of treatment at therapeutic doses for a period of more than six weeks[5].

Oral APs present a hepatic first-pass effect before reaching systemic circulation. Injectable APs are divided into two categories depending on duration of action: immediate and long-acting. Immediate-action injectable APs have quicker effects but with briefer duration, whereas long-acting injectable antipsychotics (LAIAs) release active substance gradually, thus allowing extended administration intervals (spanning 2 weeks and 6 months).

The gradual and extended release of LAIAs recommends their usage in patients with treatment-efficacy problems related to non-adherence to oral APs. It should be noted that a total or partial lack of treatment compliance occurs in up to 60% of patients with schizophrenia[9-11].A lack of treatment compliance is an important risk factor for relapse[12], and may lead to an increase in the number of hospital admissions and care needs, a higher risk of behavioural disturbances or suicidal ideation, and a worsened disease prognosis[10,13].

As such LAIAs should mainly be used in schizophrenia patients who initially responded well to oral AP treatment but who have suffered a relapse due to non-compliance[14,15]. Although the prescription of a LAIA does not guarantee treatment compliance in the long term, it allows healthcare staff to determine the patient's degree of compliance.Patient preferences should also be taken into account, as they may prefer the administration of a LAIA over daily oral forms.Similarly, LAIA use may have other advantages and disadvantages with regard to oral APs (Table 2).

Antipsychotic treatment involves multiple factors

Pharmacological properties, therapeutic effects and adverse effects should be evaluated individually for each medication

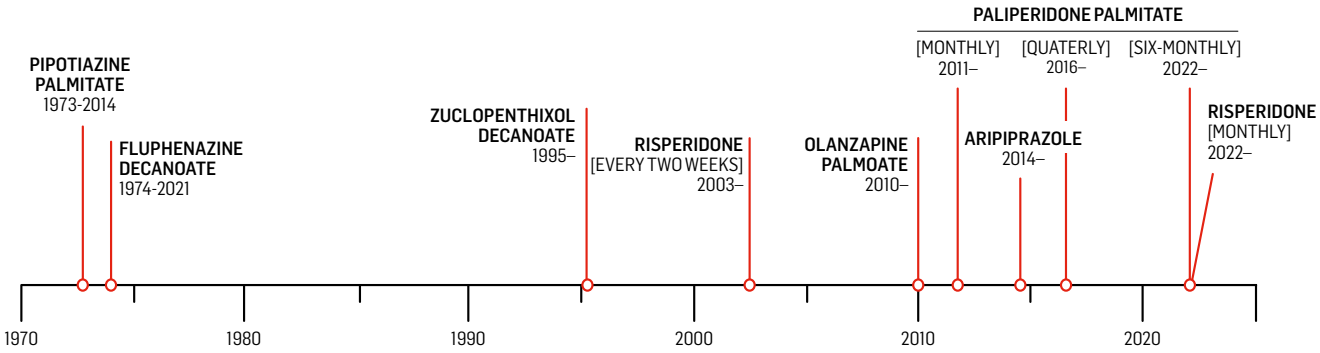
The first LAIAs were developed in the 1970s. Typical LAIAs (fluphenazine decanoate, pipotiazine palmitate and zuclopenthixol decanoate) were first developed, followed by their atypical counterparts (risperidone, olanzapine pamoate, paliperidone palmitate and aripiprazole) during the early years of the 21st century[18,21] (Figure 1).

Table 2. Advantages and disadvantages of LAIAs with respect to oral APs.

ADVANTAGES LAIA	DISADVANTAGES LAIA
✓ They improve compliance[14,15].	✗ The effectiveness and safety/tolerability should be compared to the oral presentation prior to use[16].
✓ They allow regular monitoring of the psycho-pathological status, compliance and possible adverse effects by the healthcare personnel administering the drug[16].	✗ Given their long half-life, any adverse effect that appears after administration of a LAIA is likely to persist over time.They should be avoided in patients with a history of severe adverse effects (e.g. neuroleptic malignant syndrome)[16].
✓ LAIAs are more effective than oral APs for preventing hospitalisation or relapse[17].	✗ The number of active substances available is much lower than for oral formulations[18].
	✗ The LAIAs marketed in Spain are more expensive than the oral presentation and the cost of the same LAIA may be higher the longer its period of action (six-monthly or quarterly presentation vs. monthly)[19].
	✗ They are administered in health centres and the intervention of healthcare staff is required[20].
	✗ They may produce adverse effects at the injection site.
	✗ They are not an efficient option in patients with good pharmacological compliance.

All prescribers must be aware that the patient is undergoing antipsychotic treatment due to the potential risk of interactions.

Figure 1. LAIAs marketed in Spain. Modified from Arango et al., 201921 with data available from the Spanish Agency for Medicines and Medical Devices[18].



The following general recommendations should be taken into account when prescribing a LAIA[16]:

- Conduct a response and tolerance test with the oral presentation prior to administering a LAIA. In patients who have never received antipsychotic treatment, it is recommended to administer the oral presentation with the same active substance as the LAIA for at least 2 weeks.
- Consider the characteristics of the LAIA to ensure an appropriate induction period, in other words the period during which supplementation with oral APs may be necessary.
- Prescribe the lowest feasible therapeutic dose initially.
- The frequency of administration should be the longest possible interval established in the summary of product characteristics.
- Dose adjustment should only be performed after an appropriate evaluation period as release of the antipsychotic results in a steady increase in plasma levels, with stable levels being reached after 6–8 weeks.

CHARACTERISTICS OF LAIAS

Monthly aripiprazole[22]

This is an atypical LAIA for the maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.

Comparative efficacy

In the only published comparative trial, aripiprazole depot was shown non-inferiority to oral aripiprazole in terms of efficacy. Statistically significant differences were found in favor of aripiprazole depot as regards the main study endpoints , namely change on the scales: total PANSS (positive and negative syndrome scale):–2.24 (–4.23 to –0.25), CGI-I (clinical global impression of improvement):–0.17 (–0.31 to –0.04) and CGI-S (clinical global impression of severity) and in time to relapse23. No significant differences were found between the 400 mg and 300 mg doses and oral aripiprazole in the results for the secondary endpoints, namely time to relapse, proportion of responders (stabilised at 38 weeks) and percentage of patients who achieve remission.

Loading dose and start of treatment

Two starting regimens can be followed for prolonged release aripiprazole.

Starting regimens for prolonged release aripiprazole	**Slow CYP2D6* metabolisers**	**Slow CYP2D6* metabolisers and a potent CYP3A4 inhibitor**
One IM injection of 400 mg 10–20 mg/day orally for 14 days	One IM injection of 300 mg 10–20 mg/day orally for 14 days	One IM injection of 200 mg 10–20 mg/day orally for 14 days
Two IM injections of 400 mg 20 mg orally as a single dose	Two IM injections of 300 mg 20 mg orally as a single dose	Not recommended

(*) Determined by way of genomic tests that are not currently carried out in clinical practice.

Maintenance dose

The usual maintenance dose is 400 mg administered intramuscularly once a month.

Adjustment of maintenance dose in patients receiving concomitant treatment with enzyme inhibitors/inducers for >14 days

	Aripiprazole LAIA 300 mg	Aripiprazole LAIA 400 mg
Potent CYP2D6 or CYP3A4 inhibitor	200 mg	300 mg
Potent CYP2D6 and CYP3A4 inhibitor	160 mg	200 mg
CYP3A4 inducer	Do not use	Do not use

Adverse effects profile

The most frequently observed effect with aripiprazole is akathisia and psychomotor agitation.

It exhibits a low incidence of other extrapyramidal effects, sedation and orthostatic hypotension.

It does not produce weight gain or metabolic syndrome, and is not associated with hyperprolactinaemia or prolongation of the QTc interval.

There is no affinity for muscarinic cholinergic receptors, and there is a low incidence of anticholinergic effects[22].

Non-compliance with treatment is an important risk factor for relapse, and LAIAs offer and advantage by enhancing adherence

Pharmacokinetics and pharmacogenomics

Monthly aripiprazole exhibits poor solubility and a slow and prolonged absorption.This absorption is somewhat faster in the deltoid (4 days to peak) than in the gluteus muscle (5–7 days). Steady levels are achieved after four administrations.

Therapeutic reference ranges are approximately 100–350 mg/mL for aripiprazole and 150–500 ng/mL for its active metabolite (dehydroaripiprazole)[24]. Concentrations achieved with the monthly administration of 400 mg aripiprazole are equivalent to the oral administration of 15–20 mg daily[25].

Drug exposure depends on the CYP2D6 pharmacogenetic profile, therefore the dose needs to be adjusted if the patient is known to be a slow CYP2D6 metabolizer.

A new presentation containing an injectable aripiprazole salt, namely aripiprazole lauroxil, allowing for longer intervals between doses, is expected to be marketed in Spain shortly[26].It is currently marketed in the USA.

Fluphenazine decanoate[22]

This is a typical LAIA for the treatment of paranoid schizophrenia and psychosis, as well as maintenance therapy in chronic patients with problems following the oral regimen. Since it´s not available in the Spainish arket, it must be imported from abroad.

Loading dose and start of treatment

No loading dose is required.The optimal dose and frequency of administration should be adjusted based on the patient's symptoms.

Adverse effects profile

High incidence of extrapyramidal reactions.

Minimal sedative and hypotensive effects.

Mild anticholinergic effects.

Monthly olanzapine pamoate

This is an atypical LAIA for the maintenance treatment of schizophrenia in adult patients stabilized during acute treatment with oral olanzapine.

Comparative efficacy

Two pivotal studies were performed for approval. The first evaluated short-term efficacy (8 weeks) in patients with acute psychotic symptoms versus placebo[27]. A significant improvement in the PANSS score was achieved. It should be noted that supplementation with oral antipsychotics was not not allowed in this study. The second study investigated switching from oral olanzapine to the injectable form in patients previously stabilized with oral olanzapine[28]. The primary endpoint was the presence of exacerbations, as measured by worsening on the BPRS positive scale derived from the PANSS and hospital admissions due to the worsening positive psychotic symptoms. The change to the intramuscular form was found to benon-inferior to continuing with the oral form.

Adverse effects profile[29]

Post-Injection Syndrome: Intramuscular administration of olanzapine lead to symptoms resembling an overdos, such as drowsiness and confusion. This is very uncommon (<1 out of every 1000 injections) between the first and third hour, and even rarer (<1 out of every 10,000 injections) after 3 hours. Consequently, the patient must be monitored for 3 hours post-administration.

The most common effects are weight gain, glucose intolerance, dyslipidaemia and sedation.

It may produce hyperprolactinaemia and prolongation of the QTc interval.

One of the disadvantages of LAIAs is that, given their long half-life, any adverse effect that appears after administration is likely to endure

Low incidence of dystonia and tardive dyskinesia.

In general, it produces mild and transitory anticholinergic effects.

Pharmacokinetics

The active substance in the prolonged release presentation is olanzapine pamoate which, given its low solubility, forms a suspension that dissolves slowly in the intramuscular compartment, releasing olanzapine. However, the salt dissolves rapidly if it comes into direct contact with the blood, thus leading to supra-therapeutic concentrations that lead to symptoms of olanzapine overdose (sedation and/or delirium)[22,30].

Peak plasma concentrations are reached at 2–6 days post-administration, with a half-life of 30 days and stable levels for 3 months. A target concentration range of 20–80 mg/mL has been reported[24].

Loading dose and start of treatment

The initial dose of olanzapine depot will depend on the dose of oral olanzapine with which the patient is stabilised:

Oral olanzapine	Initial depot dose (IM) first 2 months	Maintenance depot dose (IM) (after 2 months)
10 mg/day	210 mg / 2 weeks or 405 mg / 4 weeks	150 mg / 2 weeks or 300 mg / 4 weeks
15 mg/day	300 mg / 2 weeks	210 mg / 2 weeks or 405 mg / 4 weeks
20 mg/day	300 mg / 2 weeks	300 mg / 2 weeks

Monthly, quarterly and six-monthly paliperidone palmitate[22]

This active metabolite of risperidone is an atypical LAIA indicated for the maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or oral risperidone. Additionally, the monthly presentation can also be used without the need for prior stabilisation with oral treatment if the patient has previously responded to paliperidone or oral risperidone and the psychotic symptoms are mild or moderate and treatment with a LAIA is required.

The quarterly presentation of paliperidone is indicated for those patients stabilized with the monthly presentation, and the six-monthly presentation for those patients stabilised with the monthly and/or quarterly presentation.

Transitioning to quarterly or six-monthly paliperidone should only occur after stabilization with the monthly presentation, using the appropriate equivalent dose

Comparative efficacy

For approval of the monthly presentation, studies were conducted to assess its efficacy in acute treatment of schizophrenia and its ability to mantain symptom control and delay the relapse of schizophrenia. In the context of acute treatment, four short-term trials (9–13 weeks) were carried out in patients admitted due to acute relapse of schizophrenia versus placebo[31-34].The monthly presentation demonstrated a significant reduction on the PANSS scale. In terms of symptom control, a placebo-controlled, flexible-dose, double-blind study was carried out over a longer period in which 849 non-elderly adult subjects who met the DSM-IV criteria for schizophrenia took part[35]. This study included an acute open phase of 33 weeks and a stabilisation phase, a double-blind, placebo-controlled randomised phase to observe relapse, and an open-label phase of 52 weeks.The trial was suspended prematurely due to efficacy reasons, as a significantly longer time to relapse was observed in patients treated with monthly paliperidone in comparison with placebo.

The quarterly presentation was approved after the publication of two pivotal studies. The first study compared it with the monthly presentation over a 48-week period after a 16-week stabilization phase with the latter[36]. No statistically significant differences were found in the relapse rate or scores on the PANSS, CGI-S and PSP scales. The second study evaluated the prevention of relapse in previously stabilized patients who had received oral paliperidone, both monthly and a quarterly dose[37].These patients were randomised to continue with quarterly paliperidone or placebo injections.The study was terminated prematurely as a higher relapse rate was detected in the placebo group compared to patients treated with paliperidone.

The six-monthly presentation was approved in the basis of a single, pivotal, non-inferiority trial in which time to relapse and evolution on the PANSS scale was compared versus the quarterly formulation in patients previously stabilzsed with the monthly (at least 4 months) or quarterly formulation (at least one injection). Six-monthly paliperidone was found to be not inferior to both variables[38].

A systematic Cochrane review[39] concluded that intramuscular paliperidone and risperidone are comparable in terms of efficacy and tolerability. No comparative studies with other LAIAs are available[40].

Loading dose and start of treatment

Monthly paliperidone is initiated at a dose of 150 mg on the first day of treatment, followed by 100 mg one week later.The third dose should be administered one month after the second starting dose.

The maintenance dose range is between 25 and 150 mg, depending on the tolerability and/or efficacy in each individual patient.

Quarterly and six-monthly paliperidone are commenced without loading dose, aligning with the next scheluded administration of injectable paliperidone.

Change from other treatments to paliperidone LAIA

Oral prolonged release paliperidone

Oral paliperidone	Monthly injectable paliperidone
3 mg/day	25-50 mg/month
6 mg/day	75 mg/month
9 mg/day	100 mg/month
12 mg/day	150 mg/month

Fortnightly risperidone

No loading dose is necessary

Fortnightly injectable risperidone*	Monthly injectable paliperidone
25 mg / 2 weeks	50 mg/month
37.5 mg / 2 weeks	75 mg/month
50 mg / 2 weeks	100 mg/month

(*) The equivalence of fortnightly risperidone and the quarterly and six-monthly paliperidone presentations is not described in the summary of product characteristics.

Quarterly and six-monthly paliperidone

No loading dose is necessary

Monthly injectable paliperidone	Quarterly injectable paliperidone	Six-monthly injectable paliperidone
50 mg/month	175 mg/quarter	No equivalent dose
75 mg/month	263 mg/quarter	No equivalent dose
100 mg/month	350 mg/quarter	700 mg/six months
150 mg/month	525 mg/quarter	1000 mg/six months

Adverse effects profile[29]

High incidence of elevated prolactin levels.

May produce extrapyramidal reactions, weight gain, hypertriglyceridaemia and orthostatic hypotension.

Pharmacokinetics and pharmacogenomics

The monthly presentation is formulated as paliperidone palmitate within an aqueous suspension of nanocrystals. These crystals dissolve slowly and release the active substance from day 1, with peak plasma concentrations being reached after an average of 13 days and a steady state at 8 months. Absorption differences may occur depending on the administration site, with the deltoid region presenting better absorption, particularly in obese patients. Therefore, this region is recommended[41].

The quarterly and six-monthly presentations[42,43] differ from the monthly one as regards the size of the particles and the fact that the volume administered is greater, thus resulting in a more prolonged release[44]. Release starts from the first day of administration and continues for between 18 months and four years.The peak plasma concentration is reached at 30–33 days and stable levels at 15 months.

Target therapeutic levels coincide with those for risperidone, namely 20–60 mg/mL24, and no pharmacogenetic marker affecting the response has been found.

Fortnightly or monthly risperidone[22]

This is an atypical or second-generation LAIA. It is available as both fortnightly and monthly formulations, both indicated for the maintenance treatment of schizophrenia in adult patients, provided the tolerability and effectiveness with oral risperidone has been established. Patient stabilization is not necessary for the monthly presentation as therapeutic levels are achieved without a loading dose, and it is also indicated in acute treatment[22].

Comparative efficacy

For approval, the fortnightly presentation was compared with placebo and oral risperidone in clinical non-inferiority trials in stable patients[22].The monthly presentation was compared to placebo in a double-blind, randomised, multicentre, 12-week phase II study in which patients with an acute worsening or relapse of schizophrenia were included. A statistically significant improvement in the change of total PANSS score,from baseline to 85 days, favored monthly risperidone[45].

Loading dose and start of treatment

No loading dose is required.

Change to fortnightly risperidone:

Not currently with risperidone	**Consider prior stabilisation with oral risperidone**	
Currently oral risperidone	≤ 4 mg/day oral	25 mg/ 2 weeks IM
	> 4 mg/day oral	37.5 mg/ 2 weeks IM

Change to monthly risperidone:

Never risperidone	Adjustment of 14 days with oral risperidone	
Risperidone previously but not currently	Adjustment of 6 days with oral risperidone	
Currently oral risperidone	<4 mg/ day oral	75 mg/ 4 weeks IM
	≥4 mg/ day oral	100 mg/ 4 weeks IM

Change to monthly risperidone from fortnightly risperidone:

Currently fortnightly risperidone	
37.5 mg/ 2 weeks IM	75 mg/ 4 weeks IM
50 mg/ 2 weeks IM	100 mg/ 4 weeks IM

Adverse effects profile

Common elevation of prolactin levels.

Extrapyramidal reactions proportional to dose administered.

Very few anticholinergic effects.

Weight gain and prolongation of the QTc interval.

Pharmacokinetics and pharmacogenomics

The two available formulations of long-acting injectable risperidone differ in terms of their pharmacokinetic characteristics, thus resulting in both different dosage regimens and different therapeutic strategies.

In the fortnightly presentation, risperidone is encapsulated in microspheres.The degradation profile for these microspheres has a release peak at 4 to 6 weeks post-administration, with minimal risperidone release in the preceding weeks. As such, oral supplementation is required for 8–13 days to ensure plasma levels within the therapeutic range. In this presentation, stable concentrations are reached after the fourth dose and are maintained for 4–5 weeks after the final administration[46].

For the monthly presentation, risperidone is suspended in a polymer that solidifies in contact with tissue. In this presentation, a risperidone release peak is achieved at 4–6 hours post-administration, followed by a second peak 10–14 days later.This means that risperidone does not need to be supplemented orally in the first administration period. Stable values are reached before the third injection[47].

In both instances, the target therapeutic levels are the same as for the oral forms, namely 20–60 ng/mL of risperidone and its active metabolite (9-OH-R, paliperidone)[24]. The majority of pharmacokinetic studies show efficacy in the range 20–30 ng/mL for the injectable forms of risperidone, with sustained concentrations staying within this interval[48].

The role played by pharmacogenetics in risperidone treatment is debatable[47].Thus, some studies show no clinically relevant differences depending in the CYP2D6 genotype, whereas others show different efficacy and safety profiles depending on this gene, which is responsible for transforming risperidone into paliperidone.The Dutch Pharmacogenetics Working Group recommends the need to adjust the dose for both the ultrafast metabolising phenotype CYP2D6 (target dose of 75 mg IM every two weeks) and for slow metabolisers (dose of 50–67% of the standard)[49]. According to data from the PHARMANAGEN study, 4% of the population in Navarre (Spain) presents an ultrafast metabolising phenotype, whereas 5% are slow metabolisers[50].

Fortnightly or monthly zuclopenthixol decanoate[22]

This is a typical LAIA for the treatment of chronic and sub-chronic schizophrenia, especially in patients in which compliance is difficult to establish with an oral form.

Loading dose and start of treatment

No loading dose is required.The dose ranges from 200 to 400 mg, with intervals of two to four weeks, depending on each patient´s individual response.

Changes from other treatments to zuclopenthixol decanoate

Prior treatment	Zuclopenthixol decanoate dose	Comments
Oral zuclopenthixol daily	8 times the oral dose every 2 weeks or 16 times the oral dose every 4 weeks	Maintain oral zuclopenthixol at a reduced dose for the first week
Zuclopenthixol acetate IM daily	200–400 mg together with the last injection of zuclopenthixol acetate and then every 2 weeks	Zuclopenthixol acetate and decanoate can be mixed and administered as a single injection

Adverse effects profile

Marked sedative effect at treatment initiation, although tolerance develops rapidly.

The risk of orthostatic hypotension is low.

Possible risk of prolonged QTc interval.

May produce hyperprolactinaemia.

Elevated propensity to induce extrapyramidal reactions, very few anticholinergic effects[22].

Pharmacokinetics and pharmacogenomics

This LAIA contains zuclopenthixol decanoate dissolved in an oil-based medium. After intramuscular administration, peak levels are achieved at 3–7 days, with a half-life of 19 days[30]. Some guidelines suggest the need to perform dose adjustment depending on the CYP2D6 phenotype. In slow metabolisers, a dose 50% of the standard dose is recommended, with this value increasing to 75% in intermediate metabolisers, whereas in ultra-fast metabolisers the possible inefficacy of the drug should be monitored, with dose adjustment if deemed necessary[51].

Table 3. Mechanisms of action of LAIAs[52,53].

Antipsychotic	D2 Receptor	5-HT2A Receptor	M1 Receptor	H1 Receptor	5-HT1A Receptor	D1 Receptor	D3 Receptor
Risperidone	++++	++++	++	+++	++++	+±+	+++
Olanzapine	++++	++++	++++	++++	++++	±±±	±±
Paliperidone	++++	++++	++	++	±	±	±
Aripiprazole	±±±	±±±	±	±	+++	±	±
Zuclopenthixol	++++	±	±	±±	-	-	-
Flufenazine	++++	-	-	-	-	-	-

D2 Dopamine receptor. **5-HT2A** Serotonin receptor. **M1** Muscarine receptor. **H1** Histamine receptor.

The "+" symbols indicate the affinity of the antipsychotic for the corresponding receptor, with "++++" being the highest affinity and "+" the lowest.The "-" symbol indicates that the antipsychotic has a very low or no affinity for the corresponding receptor.The "±" symbol indicates that the drug exhibits partial agonism for that receptor.

Table 4. Main characteristics of the LAIAs used in Spain[22,54].

Active substance	Aripiprazole	Fluphenazine	Olanzapine	Paliperidone palmitate			Risperidone		Zuclopenthixol
Presentation	Abilify Maintena®	Not marketed in Spain	Zypadhera®	Xeplion®	Trevicta®	Byannli®	Risperdal® Consta	Okedi®	Clopixol depot®
Generation	Second generation (atypical)	First generation (typical)	Second generation (atypical)	Second generation (atypical)	Second generation (atypical)	Second generation (atypical)	Second generation (atypical)	Second generation (atypical)	First generation (typical)
Indication approved in SPC	Maintenance of schizophrenia	Treatment and maintenance of schizophrenia and paranoid psychosis	Maintenance of schizophrenia	Maintenance of schizophrenia			Maintenance of schizophrenia	Schizophrenia	Chronic and sub-chronic schizophrenia
Prior stabilisation with oral forms	Yes	Yes	Yes	Not required if prior response to risperidone or paliperidone and mild or moderate symptoms	Not applicable	Not applicable	Yes	Yes. At least 6–14 days if changing from other APs depending on prior response to risperidone	Yes
Prior stabilisation with depot forms	Not applicable	Not applicable	Not applicable	Not applicable	With monthly form	With monthly (100 or 150 mg) or quarterly form (350 or 525 mg)	Not applicable	Not required	Not applicable
Doses available per unit	300 mg and 400 mg	25 mg	210 mg, 300 mg and 405 mg	25 mg, 50 mg, 75 mg, 100 mg and 150 mg	175 mg, 263 mg, 350 mg and 525 mg	700 mg and 1000 mg	25 mg, 37,5 mg and 50 mg	75 mg and 100 mg	200 mg
Administration frequency	Monthly	Every 4–6 weeks	Every 2–4 weeks	Monthly	Quarterly	Six-monthly	Every two weeks	Monthly	Every 2–4 weeks
Maximum recommended dose	400 mg/month	100 mg/4 weeks	300 mg/2 weeks	150 mg/month	525 mg/3 months	1000 mg/six months	50 mg/2 weeks	100 mg/month	400 mg/2 weeks
Location of intramuscular injection	Gluteus or deltoids	Gluteus or deltoids.Also administered subcuta-neously	Gluteus	Gluteus or deltoids	Gluteus or deltoids	Gluteus	Gluteus or deltoids	Gluteus or deltoids	Gluteus
Precautions	Monitor QTc	Tardive dyskinesia, neuroleptic malignant syndromeMonitor QTc	Post-injection syndromeMonitor QTc and prolactin	Monitor QTc and prolactin			Monitor QTc and prolactin		Neuroleptic malignant syndrome, dementia patientsMonitor QTc
Latency period	Between 14 and 46 days	Between 1 and 4 days		Between 8 and 13 days			Between 3 and 6 weeks	2 hours	Between 3 and 7 days
Storage conditions	Room temperature	Room temperature	Room temperature	Room temperature	Room temperature	Room temperature	Cold (2–8ºC)	Room temperature	Room temperature
Cost patient/year*	3785 € - 4101 €	62 € - 234 €	3563 € - 7147 €	1624 € - 3672 €	1839 € - 5117 €	3372 € - 4768 €	3736 € - 5233 €	3386 € - 4021 €	111 € - 429 €

(*) Calculation performed assuming loading dose.

SPECIAL POPULATIONS

Paediatric population

The safety and efficacy of any LAIA in children and adolescents aged < 18 years have not been established. No data areavailable.

Elderly patients

The safety and efficacy has not been established for LAIAs in elderly patients aged > 65 years.

An increase in stroke has been observed in dementia patients.

Special approval is required to dispense LAIAs in pharmacies to patients over 75 years except for zuclopenthixol.

- Paliperidone and aripiprazole: the same dose as in young adults is recommended if kidney function is normal[22].
- Olanzapine: not recommended unless an effective and well-tolerated dosage regimen has been established with oral olanzapine or in patients older than 75 years. A lower starting dose (150 mg/4 weeks) is not usually indicated but should be considered in patients aged 65 years or more when suggested by clinical factors[22].
- Monthly risperidone: tolerability to a daily oral dose of ≥ 3 mg risperidone should be established prior to administration. A higher incidence of mortality in elderly dementia patients treated simultaneously with furosemide and risperidone was observed in trials.The risks and benefits of starting risperidone in elderly dementia patients in treatment with furosemide or other potent diuretics should be evaluated, especially in situations of dehydration[22].
- Fortnightly risperidone: no dose adjustment required[22].
- Zuclopenthixol: should receive the lower dose in the range[22].

Kidney failure (KF)

- Paliperidone: in patients with mild KF (creatinine clearance ≥50 to <80 mL/min), it is recommended to start monthly paliperidone at a dose of 100 mg on the first day of treatment, followed by 75 mg one week later. Both doses should be administered into the deltoid muscle.The recommended monthly maintenance dose is 50 mg, with a range of 25 to 100 mg, depending on individual tolerability and/or efficacy.Not recommended in patients with moderate of severe KF (creatinine clearance <50 mL/min)[22].
- Monthly aripiprazole:no dose adjustment required22.
- Olanzapine:a lower starting dose should be considered (150 mg every 4 weeks)[22].
- Monthly risperidone: patients with mild KF (creatinine clearance of 60–89 mL/min) exhibited a similar exposure to patients with normal kidney function.No data are available for moderate or severe KF[22].
- Fortnightly risperidone: not studied. If a total daily oral dose of at least 2 mg is well tolerated, an injection of 25 mg can be administered every 2 weeks[22].
- Zuclopenthixol: no dose adjustment required[22].

Liver failure (LF)

- Paliperidone: no dose adjustment is required in patients with mild or moderate LF .As it has not been studied in severe LF, caution is recommended in these patients[22].
- Monthly aripiprazole: no dose adjustment is required in patients with mild or moderate LF. In patients presenting severe LF, the dose should be controlled carefully and the oral presentation should preferably be used[22].
- Olanzapine: in moderate liver LF (cirrhosis, class A or B insufficiency on the Child–Pugh scale), the starting dose should be 150 mg every 4 weeks and should be increased with care.There are no data in Child–Pugh C[22].
- Fortnightly risperidone: not studied.If a total daily oral dose of at least 2 mg is well tolerated, an injection of 25 mg can be administered every 2 weeks[22].
- Monthly risperidone: not studied.It is recommended to confirm tolerability with an oral dose of at least 3 mg before starting treatment with 75 mg.
- Zuclopenthixol: careful dosing is recommended and, if possible, serum levels should be monitored[22].

The risk-benefit balance must be evaluated if the patient is considering pregnancy

Pregnancy

Use during pregnancy is not recommended unless strictly necessary, as there are insufficient data in this regard. If prescribed, the newborn should be monitored carefully as, in the event of exposure to APs during the third trimester of pregnancy, there is a risk of adverse reactions, including extrapyramidal symptoms and/or withdrawal syndrome, the severity and duration of which after birth may vary. Cases of restlessness, hypertony, hypotonia, tremor, drowsiness, breathing difficulties and eating disorders have been reported.

Quarterly paliperidone can be detected in plasma for up to 18 months after administering a single dose[27]. In the case of six-monthly paliperidone, plasma exposure after a single dose is expected to be 4 years[22].

Breast-Feeding

All LAIAs are excreted in breast milk. As a risk to the newborn cannot be ruled out, use during breast-feeding should be avoided. Exposure up to 18 months and 4 years has been detected after a single administration of quarterly and six-monthly paliperidone, respectively, therefore the newborn may be at risk even if the drug was administered a long time before breast-feeding.

Fertility

No relevant effects have been observed for the majority of LAIAs in non-clinical studies and they do not appear to affect fertility, as per reproductive toxicity data. However, side-effects such as elevated prolactin levels, galactorrhea, amenorrhea or decreased libido, which are common for many LAIAs, may have a negative impact on male and/or female sexual function and fertility.

The following table summarises the treatment initiation guidelines for monthly LAIAs.

Table 5. Monthly LAIA treatment initiation guidelines.

LAIA	Parenteral loading dose	Oral supplementation
Risperidone	Not required	3 weeks with the fortnightly presentation
Olanzapine	Different dose in first 2 months	Not required
Paliperidone	Day 1: 150mg Day 8: 100mg	Not required
Aripiprazole	Day 1: 400mg Day 1: 800mg	Days 1-14: 20mg/día Day 1: 20mg
Zuclopenthixol	Not required	First week
Flufenazine	Not required	Not required

CURRENT SITUATION FOR LAIA PRESCRIBING IN NAVARRE

After the prescription of treatment by a psychiatrist from the SNS-O (Navarre Health Service), the LAIA will be administered by nursing staff from the different resources of the Navarre Mental health Network (RSMNa) or, exceptionally, at a primary care centre. Administration is recorded in the patient's electronic medical records, thus allowing control of appointment attendance and ensuring continuation of the treatment prescribed. LAIAs are dispensed by the SNS-O Pharmacy Services and do not need to be collected from the pharmacy office.

The number of patients (Figure 1) and number of defined daily doses (DDDs; Figure 2) for the different LAIAs prescribed in Navarre over the past 5 years are shown below. An increase in the prescription of LAIAs from 2018 to 2021 can be seen, with the level stabilising in 2022.S imilarly, an increase in DDDs during the first 4 years and a reduction in 2022 can also be seen. Figure 3 shows the annual cost for the first year of treatment.

Figure 1. Number of patients prescribed a LAIA (2018–2022).

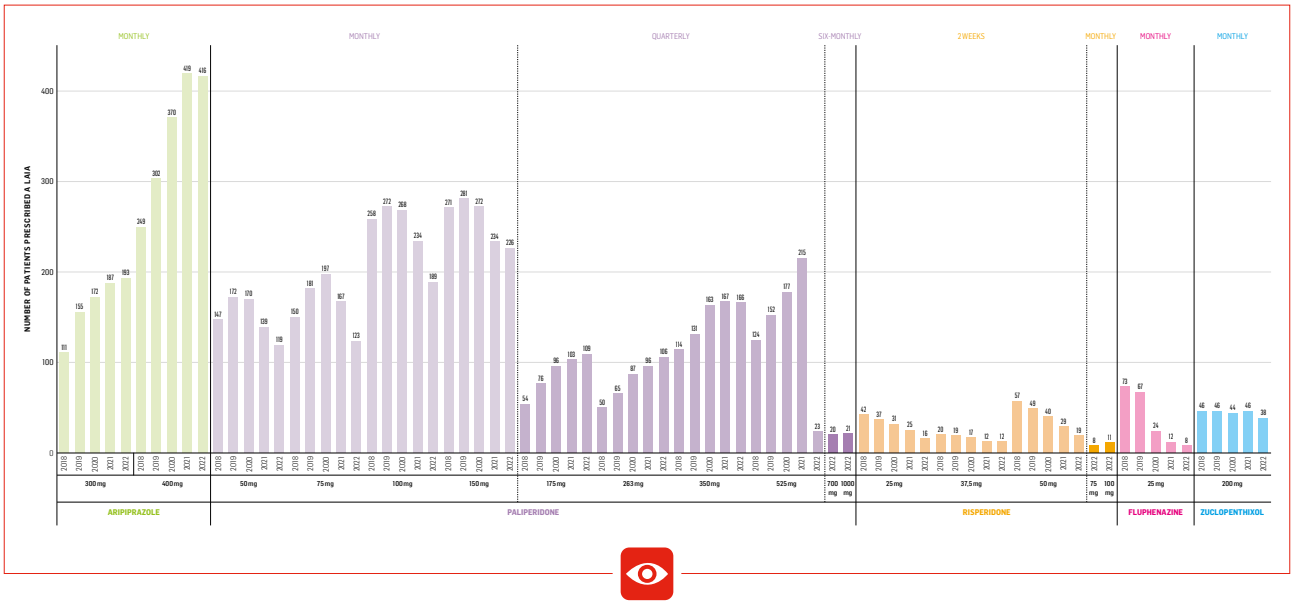


Figure 2. Number of defined daily doses (DDDs) for the LAIAs prescribed (2018–2022).

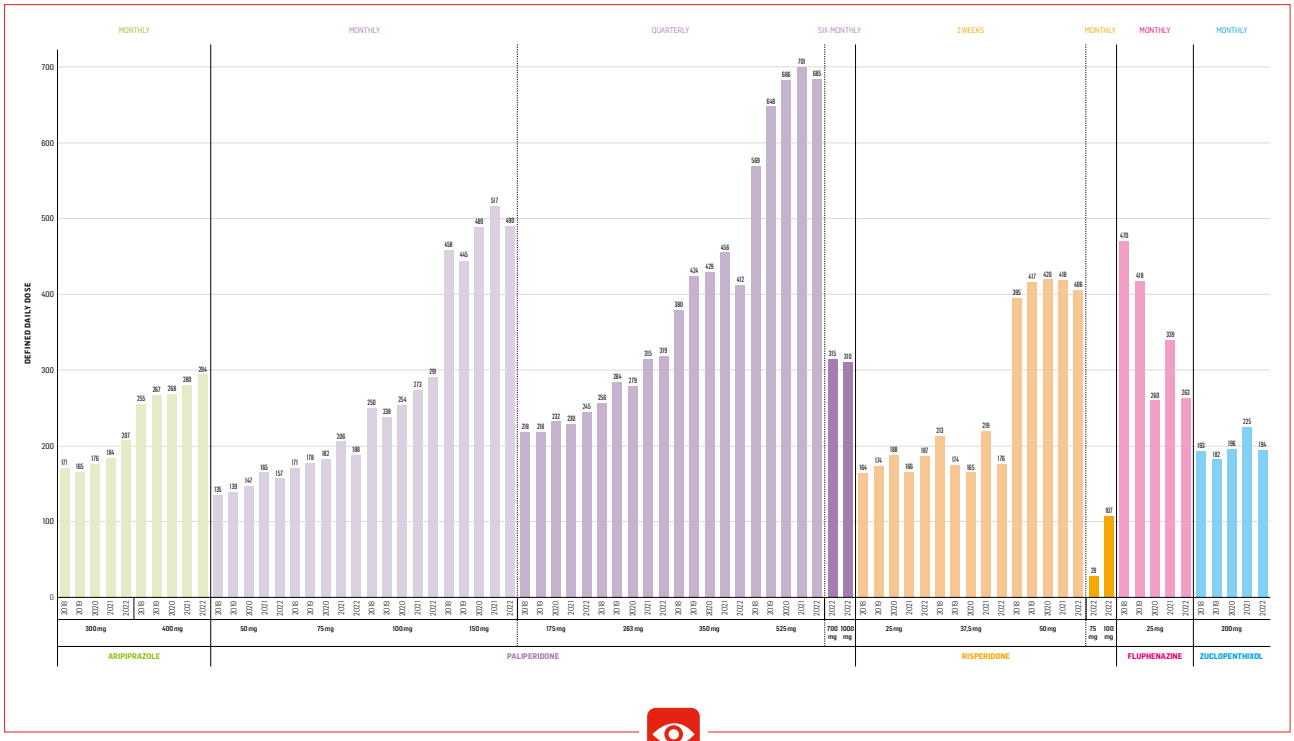
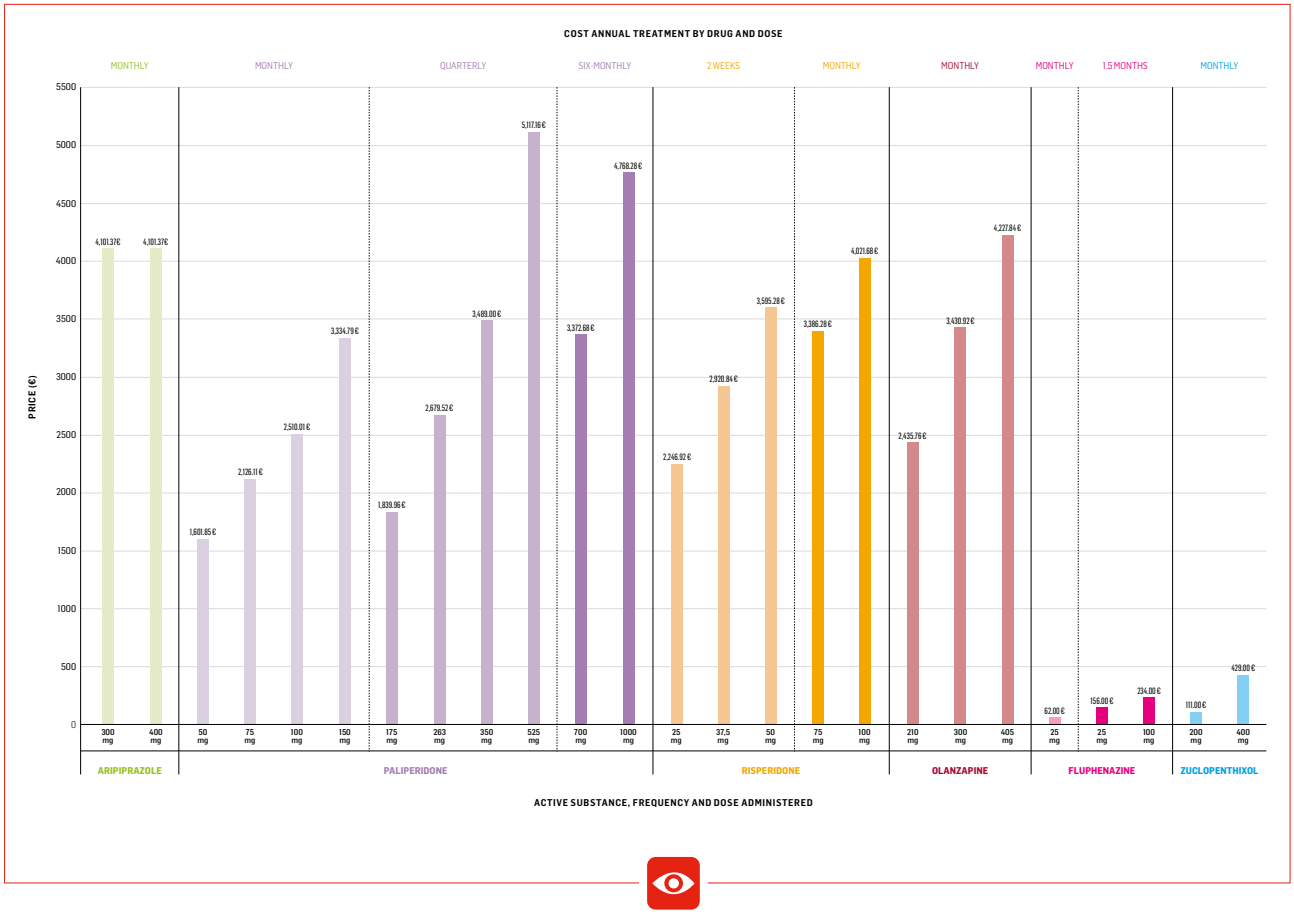


Figure 3. Annual cost of treatment with different LAIAs and doses based on manufacturer's sale price+VAT.



Conclusions

Schizophrenia patients who have presented a favorable clinical response to oral antipsychotic treatment but who have presented relapses due to non- compliance are suitable candidates for the use of LAIAs.

The quarterly and six-monthly presentations of paliperidone are indicated in patients who are clinically stable with the monthly or quarterly formulations, respectively. It should be noted that, if they appear, adverse effects will last for longer in LAIAs with a longer duration.This aspect is particularly relevant when considering pregnancy and breastfeeding plans.

The safety and efficacy of LAIAs in patients younger than 18 years and those older than 65 years has not been established.

Although LAIAs may exhibit common side effects, the differences among them emphasize the necessity of choosing the appropriate LAIA according to the patient´s profile and concurrent health conditions.

The role of monitoring therapeutic levels in LAIAs and the need to establish individual dosage regimens that ensure safety and efficacy is currently underway.

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