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Long-acting injectable antipsychotics in schizophrenia treatment: optimal duration from a cost-effectiveness standpoint

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ABSTRACT

One of the most significant challenges in schizophrenia treatment is medication non-adherence, which occurs in 50-70% of patients. Non-adherence leads to relapse, hospitalizations, and increased costs. Long-acting injectable antipsychotics (LAI-APs) are an important option for preventing relapse by improving adherence, particularly in patients with impaired insight. Meta-analyses and real-world evidence demonstrate that they are generally superior to oral antipsychotics in reducing hospitalizations.

The higher cost of LAI-APs compared to oral formulations raises questions about their cost-effectiveness. However, research indicates that by increasing treatment adherence, they reduce hospitalizations and emergency department visits. Consequently, by approximately the end of the first year, the difference in medication costs is offset within total healthcare expenditures. Cost-effectiveness varies according to countries' health policies and service costs.

A calculation based on January 2026 data from the Turkish pharmaceutical market reveals significant price differences between typical and atypical LAI-APs. The annual cost of typical LAI-APs is below €218, while that of atypical LAI-APs exceeds €780. Switching from an atypical LAI-AP to its oral form reduces costs by 3.5 to 10-fold, whereas this reduction ranges from 2 to 7-fold for typical agents. The cost of typical LAI-APs is significantly lower than that of atypical agents.

The optimal duration of LAI-AP use should be individualized based on patient characteristics. During the first 1-2 years following the acute phase and stabilization, they should be considered a "bridge treatment" to enhance insight and strengthen the therapeutic alliance. Transitioning to oral therapy should be evaluated in patients who have achieved clinical remission, developed insight, and remained stable for several years. When selecting a long-acting injectable antipsychotic, given the high cost of atypical agents, well-tolerated typical agents should be prioritized. It must be remembered that treatment success depends not only on the route of administration but also on a strong therapeutic alliance and psychosocial support.

Keywords. Long-acting injectable antipsychotics, cost-effectiveness, meta-analysis, real-world evidence, schizophrenia.

Introduction

One of the major challenges in the treatment of schizophrenia is medication non-adherence. Schizophrenia is a chronic illness characterized by a high risk of relapse, disability, and a substantial individual, social, and economic burden, and non-adherence occurs in 50-70% of patients[1-4]. Non-adherence results in relapses, emergency department visits, rehospitalizations, loss of functioning, and increased treatment costs[3,5-7]. In addition to successful psychosocial interventions aimed at improving treatment adherence[8,9], the use of long-acting injectable antipsychotics (LAI-APs) is an important option for enhancing treatment adherence and preventing relapses and hospitalizations[5,10,11]. LAI-APs provide significant ease of administration with their weekly, biweekly, monthly, and three-monthly formulations, particularly in patients with impaired insight and treatment non-adherence[12].

Meta-analyses have demonstrated that antipsychotics in depot or long-acting injectable forms are more effective than oral formulations in preventing relapse and rehospitalization, both in acute treatment and maintenance therapy, by ensuring treatment adherence[13,14]. These reviews highlight the lower side effect profile of LAI-AP formulations and the differences in side effects between molecules, recommending LAI-AP use particularly in patients with serious adherence problems, while also drawing attention to conflicting findings regarding efficacy, effectiveness, safety, quality of life, cognitive functioning, and other outcomes between LAI-APs and oral antipsychotics (OAPs), with no significant difference being noted. Similarly, a meta-analysis by Medrano et al.[15] showed no significant difference in clinical efficacy between typical and atypical LAI-APs, although differences in side effects were present. The meta-analysis by Vita et al.[16] also demonstrated no significant difference overall between LAI-APs and OAPs regarding relapse/hospitalization and acceptability, but LAI-APs were found to be superior in early-phase schizophrenia. Furthermore, a long-term real-world follow-up study showed that both typical and atypical LAI-APs were superior (20-30% lower risk) to their oral formulations in preventing rehospitalization[5]. It has also been shown that in clinically stable patients, there is no significant difference between oral and LAI administration, particularly among atypical antipsychotics, in preventing relapse[17]. LAI-APs are specifically recommended to prevent relapse/hospitalization in patients with poor treatment adherence[18].

In the initial episode or in the presence of chronic symptoms along with recurrent attacks, considering definitive or probable non-adherence to treatment, the use of long-acting injectable forms is often preferred. The choice between typical or atypical agents is made evaluating each patient individually, considering past history, risk of side effects, clinical efficacy, expectation of rapid response, etc. Sometimes, both oral and injectable forms are used together. For patients with poor insight who are unwilling to undergo treatment, in addition to intramuscular administration, the preference for orally disintegrating tablets may also be considered.

Although not recommended in treatment guidelines[18], antipsychotic polypharmacy in schizophrenia is common, occurring even in the first year of treatment (57.7%)[19]. Furthermore, the proportion of patients using both LAI-APs and oral antipsychotics is considerable, both among inpatients (40%)[20] and outpatients (38-70%)[21,22]. The practice of polypharmacy appears to be increasing over the years[23,24]. While polypharmacy may be clinically beneficial for some patients, it is generally considered a practice that increases both side effects and costs[21,24].

To What Extent are Long-Acting Injectable Antipsychotics cost-effective?

Schizophrenia imposes a high economic burden on societies due to both direct treatment costs and indirect productivity losses[2,25]. Generally, indirect costs (unemployment, inability to work, family caregiving, legal incidents, premature mortality, etc.) account for the majority of costs (50-85%)[2]. Direct costs (hospitalizations, emergency department visits, outpatient follow-ups, rehabilitation services, medication use, other medical treatments, etc.) constitute 10-50% of total costs, although this varies across countries depending on health and reimbursement policies[26]. Regardless of their proportion of total costs, medication costs themselves are a factor that must be considered in

direct cost calculations, particularly in a treatment process that may continue lifelong.

LAI formulations are more expensive than oral formulations of antipsychotics[27]. A medication that will be used for years must be both safe in terms of side effects and reasonably priced. However, finding both qualities together is often difficult on a per-patient basis. The differing side effect profiles of typical and atypical antipsychotics (primarily extrapyramidal symptoms, metabolic syndrome, etc.) and the high cost of LAI formulations, especially atypical ones, leave the selection of effective, safe, and cost-effective treatment in schizophrenia to the physician's experience and skill for each individual patient. Sometimes, treatment can be maintained for years with a very inexpensive drug without side effects or with manageable side effects, while at other times, an expensive drug may need to be used for years. Treatment options may change over time depending on patients' insight, levels of treatment adherence, and side effects.

Meta-analyses show that compared to oral antipsychotics, LAI-APs increase treatment adherence, reduce hospitalizations, emergency department visits, and total medical treatment costs, and that by the end of one year, the cost difference of LAI-APs disappears as total costs equalize between the two administration forms[28-31].

Considering the overall disease burden, it can be argued that medication costs generally do not constitute a very significant portion, and moreover, LAI-APs may be economical by preventing relapse, hospitalizations, and other healthcare expenditures[31,32]. However, it should not be forgotten that schizophrenia treatment is a long-term journey. The reduction in medication costs achieved by decreasing hospitalizations and preventing economic losses by improving patient functionality and enabling return to work can be seen as an advantage. Furthermore, hospitalization costs and productivity gains in studies generally reflect the cost structures in developed countries where such research is conducted. However, substantial differences in hospital expenses and care services can exist between high-income and low-income countries[2]. It is also known that community-based psychiatric rehabilitation services reduce hospitalization rates and length of hospital stay[33,34]. At the same time, in underdeveloped or middle- and low-income countries, psychiatric rehabilitation services are not widespread, and unemployment rates among patients are very high[35,36]. In countries where unemployment is high even among healthy individuals, the reality is that many schizophrenia patients capable of working remain unemployed. From this perspective, the long-term use of high-cost LAI-APs[31] warrants pharmacoeconomic scrutiny.

Studies comparing the costs of typical and atypical LAI-APs are scarce. In a multicenter study by Rosenheck et al.[37], paliperidone palmitate (PP) and haloperidol decanoate (HD) LAI-APs were compared. Over 15 months of follow-up, both drugs were found to be clinically effective, with no difference in treatment adherence; however, HD was more cost-effective than PP. From a pharmacoeconomic standpoint, the authors suggested that PP use is appropriate for patients who do not benefit from or cannot tolerate the side effects of an HD trial.

Long-acting injectable antipsychotics should undoubtedly be a leading choice for symptom control and clinical stabilization in the patient group with impaired insight and treatment adherence problems. However, the question of which LAI-AP to choose from a pharmacoeconomic perspective requires careful consideration. Despite the lack of difference in clinical efficacy between them[15,38], the fact that most preferences lean toward atypical agents should also be questioned. At the same time, treatment adherence should not be reduced merely to the act of receiving an injection. It must be remembered that adherence has other dimensions, including psychosocial factors, the therapeutic relationship, and side effect management. More real-world studies comparing typical and atypical LAI-APs are needed to clarify this issue. Health policies and reimbursement conditions differ in every country or region. The fact that a practice is cost-effective in one country should not be interpreted as meaning it will yield the same result in others.

A Calculation from the Turkish Pharmaceutical Market

As of January 2026, Table 1 presents the box prices and annual costs of long-acting injectable

antipsychotic drugs available in the Turkish pharmaceutical market at their maintenance doses, compared with the oral forms (OAPs) of the same molecules. Undoubtedly, patients are expected to achieve clinical remission with the ideal doses shown in the table; however, this is not the case for most patients, and higher doses are occasionally required. At the same time, most patients use other APs and other psychotropic drugs in addition to the primary medication, rather than a single AP. Therefore, this section aims to provide a price comparison of LAI-APs rather than calculating a comprehensive annual medication cost.

Table 1. Average annual costs of long-acting antipsychotic drugs and their oral forms available in the Turkish pharmaceutical market in maintenance treatment (January 2026, in EUR)

Molecule	Preparation *	Price (EUR)**	Application	Annual Cost (EUR)***
Risperidone	Risperdal tablet 4 (20)	6.17	Daily	112.60
	Risperdal Consta 37.5	45.70	2-weekly	1,188.20
Paliperidone palmitate	Invega tablet 6 (28)	17.22	Daily	224.38
	Xeplion LAI 75	65.70	Monthly	788.40
	Trevicta LAI 263	195.03	3-monthly	780.12
	Byannli LAI 700	467.17	6-monthly	934.34
Aripiprazole	Abilify tablet 10 (28)	14.87	Daily	193.76
	Abilify maintena LAI 400	119.00	Monthly	1,428.00
Haloperidol	Norodol tablet 5 (50)	2.57	Daily	18.76
	Norodol decanoate 50	4.01	Monthly	48.12
Zuclopenthixol	Clopixol tablet 10 (100)	8.93	Daily	30.59
	Clopixol depot 200	8.38	2-weekly	217.88
Flupentixol	Fluanxol tablet 3 (50)	9.73	Daily	71.03
	Fluanxol depot 20	2.55	2-weekly	66.30
Fluphenazine	Prolixin decanoate 25	3.70	2-weekly	96.20

*Preparation available in the Turkish Pharmaceutical Market, taken as mg. The figure in parentheses is the number of tablets in the box; injections are taken as single boxes. **Box price in EUR. LAI: Long-Acting Injectable. ***Current price as of January 27, 2026: 1 EUR = 51.64 TRY

Table 2. Price ranges of LAI-APs and their oral forms based on the annual cost at maintenance treatment doses (January 2026)

< 50€	50-150€	150-300€	750-€1,200	>€1,300
Haloperidol tab Zuclopenthixol tab Haloperidol LAI	Flupentixol LAI Flupentixol tab Fluphenazine LAI Risperidone tab	Aripiprazole tab Zuclopenthixol LAI Paliperidone tab	Paliperidone LAI Risperidone LAI	Aripiprazole LAI

The price range distribution shown in Table 2 is consistent with the evaluation conducted in 2022 with the drugs available in the Turkish pharmaceutical market at that time[27].

Cost Change When Switching from Long-Acting Form to Oral Form

As shown in Tables 1 and 2, both the oral and intramuscular forms of typical APs have considerably lower costs compared to atypical ones. In patients stabilized with a typical agent, for example, the annual cost of monthly haloperidol decanoate 50 mg is €48, while switching to daily haloperidol tablet 5 mg reduces the annual cost by half, to €19. Similarly, the annual cost of zuclopenthixol depot 200 mg every two weeks is €218, whereas switching to daily oral zuclopenthixol 10 mg reduces the annual cost sevenfold, to €31.

The economic benefit is particularly substantial when switching from atypical LAI-APs to their oral formulations. Switching from risperidone LAI (€1,188 annually) to oral risperidone (€113 annually) results in a 10-fold cost reduction. Switching from

paliperidone palmitate LAI (€788 annually) to oral paliperidone (€224 annually) reduces cost by 3.5-fold. Switching from aripiprazole LAI (€1,428 annually) to oral aripiprazole (€194 annually) yields a 7.4-fold reduction.

When comparing typical and atypical APs in terms of annual cost, a significant difference emerges. The annual cost of oral typicals is below €72, while atypicals are nearly double, starting above €113. The annual cost of intramuscular form of typicals is below €218, whereas those of atypicals exceed €780, a more than threefold increase. This price disparity between typical and atypical APs is also evident in European study[39]. According to this study, the cost of typical APs in outpatients is five times lower than that of atypicals. It should also be noted that drug prices vary across European Union countries; for example, the price of a 5 mg olanzapine tablet is €64.53 in Bulgaria but €37.26 in Belgium[40].

The calculations presented here are based on an ideal scenario in which patients are in the maintenance phase and experience no relapses throughout the year. However, patients' clinical conditions are not always stable, and exacerbations can occur. Doses twice as high as, or even higher than those listed in the table may also be necessary. Moreover, medications used to manage side effects and additional antipsychotics can further increase costs, making it clear that careful consideration is required when selecting LAI-APs to ensure cost-effectiveness. Multiple antipsychotic use increases costs in various ways[41]. Therefore, without falling into the misconception that LAI treatment must be lifetime, it is important to discontinue the LAI and switch to oral therapy at the earliest possible opportunity.

What Should Be the Optimal Duration of Long-Acting Injectable Antipsychotic Use?

After symptom remission is achieved through intramuscular administration, the goal is to maintain remission. Efforts should be made to improve functionality and enable patients to return to their social roles, even if mild or moderate residual symptoms persist. Functionality sustained for 2 years with clinical stability without relapse is considered recovery[42]. How long should LAI-AP treatment be continued in a patient who has recovered or is on the path to recovery?

In most patients, annual dose reduction (typically by 10-20%) is implemented alongside clinical remission. Long-term antipsychotic treatment at the lowest effective dose is recommended by guidelines[18]. For example, the daily dose of a patient stabilized on 20 mg/day olanzapine can be reduced to 5 mg, and that of a patient stabilized on 8 mg/day risperidone can be reduced to 3 mg at the maintenance therapy. The critical point here is that patients must be closely monitored during dose reductions, and if any risk of exacerbation is detected, the previous dose should be resumed immediately. The dose that caused exacerbation can be identified as a dose not to be tried again for that specific patient. The ease of dose reduction and monitoring applicable to oral medications also extends to LAI-APs. For instance, reductions may be possible from 75 mg to 25 mg for Risperdal Consta (biweekly administration), from 150 mg to 100 mg for Xeplion (monthly), from 575 mg to 172 mg for Trevicta (3-monthly), from 800 mg to 200 mg for zuclopenthixol (monthly), and from 150 mg to 50 mg for haloperidol (monthly) at the maintenance therapy.

In LAI-AP treatment, the goal in the short term (approximately 1 year) should be to stabilize the patient's clinical condition by ensuring treatment adherence. In the medium term (lasting 1-2 years), the aim is for the patient to maintain functionality with treatment adherence without experiencing relapse. Treatment extending beyond 3 years should only be implemented in chronic patients with severe insight and rehospitalization problems. For these patients, is it more cost-effective to use atypical or typical LAI-APs? The choice should be made by assessing the patient's risk of side effects and its' effect on treatment adherence. When typical antipsychotics are given at appropriate doses, treatment can be maintained with no or minimal side effects. If the dose of a typical antipsychotic needs to be increased or if side effects become intolerable, a switch to an atypical agent should be considered with close monitoring for side effects. It should also be remembered that a significant proportion of chronic patients can maintain oral treatment. Nevertheless, long-term LAI-AP use may remain a suitable option for a small group of

patients whose functionality has improved but who still have a risk of medication non-adherence.

The decision to continue or discontinue LAI-AP treatment should be made on a patient-by-patient basis. Transitioning from injectable to oral administration should be considered for patients who are in clinical remission, have good functionality sustained for at least 2 years, and have developed insight. Some patients experience limited improvement in functionality, and most cannot participate in working life. However, if clinical stabilization is accompanied by improved insight and social support is adequate, there is no justifiable reason beyond mechanical adherence to continue LAI-APs further in these patients.

Conclusion

Although LAI-APs have higher acquisition costs, they reduce total costs in the long term by decreasing relapse and hospitalizations. Cost-effectiveness analyses should be conducted on a country-specific basis. The finding that using very expensive LAI-APs is cost-effective for a developed country may not yield the same result for a developing country. The choice between typical and atypical LAI-APs should be made on a patient-by-patient basis. The higher cost of atypical agents compared to typical ones must be considered. If no significant side effects occur, selecting typical agents should take precedence from a cost perspective. Long-acting injectable antipsychotic use should be considered a "bridge treatment" for the first 1-2 years following the acute phase and stabilization. The goals during this period should be to improve insight, strengthen the therapeutic alliance, and establish the habit of daily oral treatment.

Treatment adherence should not be viewed solely as LAI administration. Long-term patient follow-up should ideally be conducted at the same center and by the same personnel whenever possible, and adherence should be enhanced by providing psychoeducation to the patients and their family members. The optimal duration of LAI-AP treatment should be tailored to the individual characteristics of the patient. Transitioning from intramuscular administration to the oral form of the same medication should be considered for patients with developed insight, who are clinically stable, and have adequate social support. It should not be overlooked that the "long-term use for everyone" approach, which is increasingly seen in clinical practice as the indications for LAI-APs are broadened, contradicts the principle of personalized medicine. Particularly in developing countries, LAI-APs should be reserved for non-adherent or resistant cases, those with frequent relapses, and patients generating high costs. Resources saved by preventing unnecessary use should be directed towards psychosocial interventions and strengthening community-based care. Without a strong therapeutic alliance between the patient and the physician or treatment team, the administration of LAI-APs or oral antipsychotics becomes inconsequential. Administering LAI-APs does not guarantee treatment success. Medication administration must contribute to pharmacoeconomic outcomes not only through its scientific aspects but also through its artistic aspects.

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