

# Cost-effectiveness of injectable atypical long-acting antipsychotics for chronic schizophrenia in Poland



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## ABSTRACT

**Objective:** In order to determine the cost-effectiveness of paliperidone palmitate (PP-LAI), a long-acting injectable formulation, indicated for once-monthly injections as antipsychotic therapy, it was compared with risperidone, a long-acting, injectable (RLAI) and biweekly agent, administered for treatment of chronic schizophrenia in Poland, as perceived from the perspective of the National Health Fund (NHF).

**Methods:** We adapted a 1-year decision tree model to the Polish healthcare system with literature-derived and clinical expert inputs. The compared drugs included PP-LAI, a new treatment option of antipsychotic therapy, and RLAI, the established treatment for Polish patients. Clinical rates were derived from published trials. Model outputs included expected cost per patient, as well as the rates of hospitalization, emergency room visits, days free of symptoms and quality-adjusted life-years (QALYs). One-way sensitivity analyses were applied to major inputs. All the inputs were also simultaneously varied in probabilistic sensitivity analyses.

**Results:** Despite its higher acquisition cost, PP-LAI demonstrated a lower expected cost per treated patient. PP-LAI was associated with 0.824 QALYs, 323 days with stable disease and

44.6% hospitalization. RIS-LAI had 0.817 QALY, 317 stable days and 51.3% hospitalization. PP-LAI dominated RIS-LAI in the base case and in 55.0% of 10,000 simulations, and was cost-effective in 76.6%. However, the cost-effectiveness was sensitive, being lost with modest increases for PP-LAI or decreases for compared drugs with respect to their prices, relapse and adherence rates. Because it is injected monthly as opposed to biweekly, PP-LAI saves caregiver time as it is administered monthly, as opposed to the biweekly regimen.

**Conclusions:** From the viewpoint of the National Health Fund of Poland, when compared with RLAI, PP-LAI is a cost-effective drug with potential to reduce healthcare expenses.



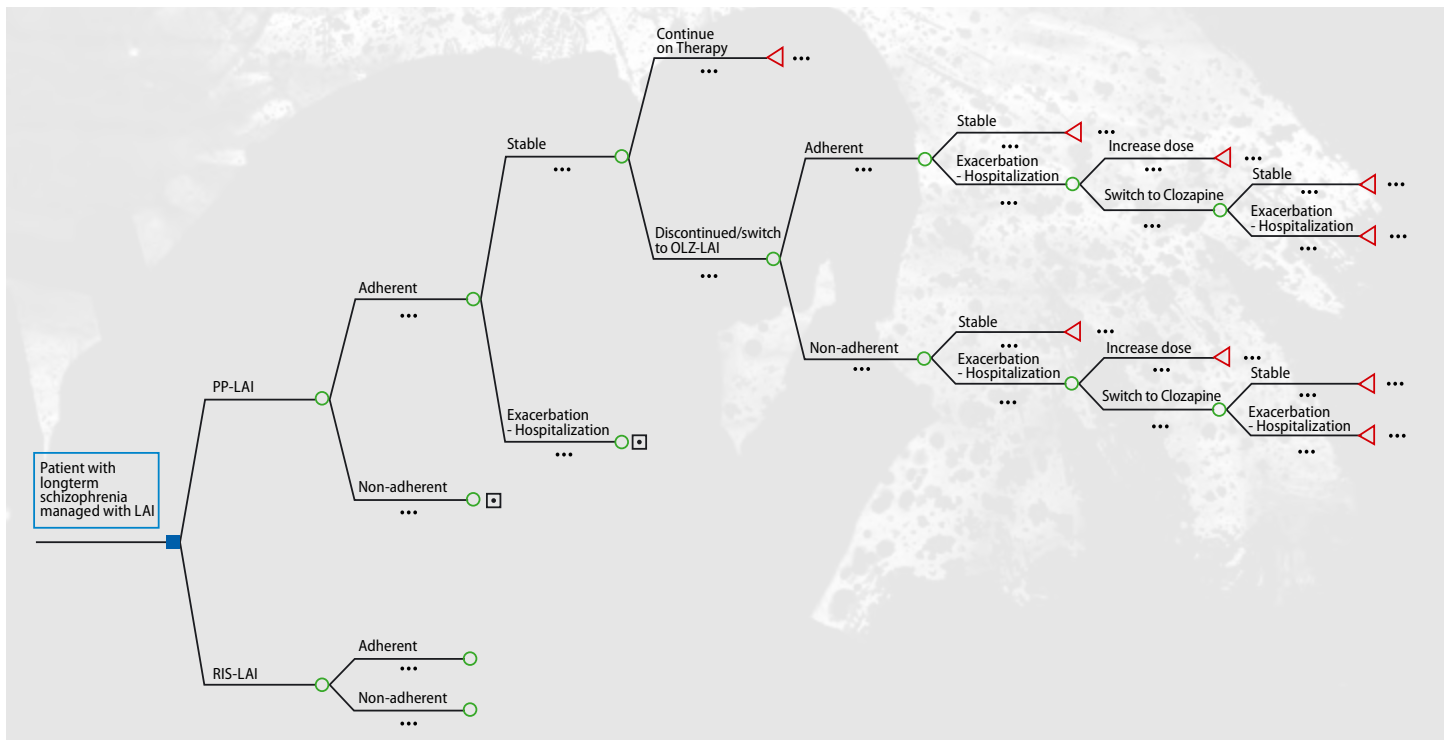


Figure 1. Decision tree used for the analysis

## INTRODUCTION

With a population of 38.4 million <sup>[1]</sup>, Poland has got a healthcare system based on national health insurance, managed by the National Health Fund (NHF). NHF, with a total annual budget of €15 billion in 2012, allocates funds for hospital and out-patient care, as well as for prescribed, reimbursed drugs <sup>[2]</sup>.

Schizophrenia is a major burden for healthcare systems, affecting about 1% of the world population <sup>[3]</sup>. The problem with schizophrenia is very serious and aggravating, due to intensive use of resources, including hospital beds and medications, where in-patient therapy represents a large cost centre <sup>[4,5]</sup>.

Hospitalization costs are related to patients' adherence to their antipsychotic medications <sup>[6]</sup>. Current innovative solutions, aimed at improving adherence rates, include the long-acting, injectable (LAI) depot formulations of drugs <sup>[7]</sup>. Although depots have been available for many years, atypical antipsychotic depots have been developed and marketed in the last decade only <sup>[8]</sup>.

Even if these new products continue their upward trend on the market, their pharmacoeconomic profiles are a largely unknown issue in many countries, including Poland. A literature search was attempted to identify studies on the costs and economic aspects of schizophrenia therapies, which are available in Poland. Medline and Embase localised merely five relevant publications, all of them drafted as abstracts for poster presentations at scientific conferences <sup>[9-13]</sup>. No full text peer-reviewed articles were identified. Consequently, a task for defined and undertaken to determine the cost-effectiveness of atypical LAIs in Poland, the evaluation to be approached from the NHF's analytic viewpoint.

## MATERIALS AND METHODS

A model, previously developed in Greece <sup>[14]</sup>, was adapted to the reality of the Polish healthcare system, see Figure 1. The introduced adaptations were based on published reports and inputs from local professionals.

Patients with chronic schizophrenia had experienced prior relapses. All of them required treatment with long-acting injectable (LAI) antipsychot-

ics. They entered the model with their disease in remission. The drugs of interest included the long-acting injectable (LAI) forms of paliperidone palmitate (PP-LAI) and risperidone LAI (RLAI).

Clinical inputs were derived from clinical trials upon which success rates were based, or from daily clinical practice (i.e., medical records). Drug regimens and doses, used for maintenance therapy and to manage relapses, were based on published sources and adapted from the previous model (see Table 1).

The clinical rates, used to populate the decision tree, are presented in Table 2. The analysis was arranged from the point of view of the NHF

and considered direct costs of care only. The direct costs included medications, hospitalization and medical care (i.e., services provided by physicians and other healthcare professionals). Drug prices were obtained from the current price list, published by the Ministry of Health [15]. The service prices were based on the NHF procedure pricing system and on opinions of professionals. The costs were provided in EURO for the 2012 exchange rate,, adjusted from other years by the Consumer Price Index for Poland [16]. The cost inputs are exhibited in Table 3.

The primary outcome was quality adjusted life years (QALYs). Their calculation was based

Table 1. Regimens used to treat patients with schizophrenia, with appropriate references

DRUG	REASON FOR ADMINISTRATION	REGIMEN	SOURCE
PP-LAI	Maintenance of stable schizophrenia	69.3 mg monthly	Average of Fleischhacker <sup>[31]</sup> Gopal <sup>[32]</sup>
	Treatment of relapse	150 mg week 1, 100 mg week 2; then 84.9 mg every 4 weeks maintenance	EMA Xeplion® product summary <sup>[33]</sup> Maintenance dose = average of Gopal <sup>[34]</sup> , Hough <sup>[35]</sup> , Nasrallah <sup>[36]</sup> , Pandina <sup>[37]</sup> , Pandina <sup>[38]</sup>
RIS-LAI	Maintenance of stable schizophrenia	40.3 mg every 2 weeks	Average of Fleischhacker <sup>[39]</sup> , Kissling <sup>[40]</sup> , Lasser <sup>[41]</sup> , Lee <sup>[42]</sup> , Olivares <sup>[43]</sup>
	Treatment of relapse	50 mg every 2 weeks	Average acute dose set to the maximum of 50 mg, pro-rated from PP-LAI ratio of acute:maintenance doses and validated by Chue <sup>[44]</sup> , Eerdeken <sup>[45]</sup> , Kane <sup>[46]</sup>

EMA, European Medicines Agency; LAI, long-acting injection;; PP, paliperidone palmitate; RIS, risperidone microspheres.

Table 2. Clinical rates used as inputs for the model

CLINICAL STATE	DRUG	ADHERENT	NON-ADHERENT
ADHERENCE	PP-LAI	0.872	0.118
	RIS-LAI	0.823	0.177
STABLE DISEASE	PP-LAI	0.803	0.148
	RIS-LAI	0.763	0.14
RELAPSED	PP-LAI	0.197	0.852
	RIS-LAI	0.237	0.86
*RATES ADOPTED FROM PREVIOUS MODEL			

Table 3. Consumed resources and their costs

RESOURCE	ITEM	COST (EURO)
HOSPITAL	ACUTE PSYCHIATRIC WARD	42.06
	EMERGENCY ROOM (2 HOURS)	26.72
	LONG TERM WARD	28.04
ADHERENCE	PSYCHIATRIC OUTPATIENT VISIT	13.17
	FOLLOW-UP VISITS	6.58
	PRIMARY CARE PHYSICIAN (HOUR)	4.66
ALLIED HEALTHCARE	PSYCHIATRIC NURSE (HOUR)	4.66
DRUGS	PP-LAI*	€9.30/DAY
	RIS-LAI	€8.46/DAY
*ESTIMATED COSTS AS NOT YET REIMBURSED		

IN ORDER TO EXAMINE THE MODEL STABILITY AND OBTAINABLE RESULTS, A SERIES OF SENSITIVITY ANALYSES WAS RUN. EACH OF THE MAJOR INPUTS (E.G., ADHERENCE RATES, HOSPITALIZATION RATES, COSTS, ETC.) WAS TESTED WITH ONE-WAY (BREAK-EVEN) ANALYSES TO DETERMINE IF OBTAINED RESULTS WOULD CHANGE WITHIN REASONABLE LIMITS.

on previously obtained utility scores, reported in the literature [17-20]. Other patient outcomes included days free of symptoms and the rates of relapse. The expected cost per treated patient was calculated for each drug. The incremental cost-effectiveness ratio (ICER) for gained QALYs was interpreted as economic outcome. Ratios below €25,000 were considered cost-effective, as per PolAHTA guidelines [21].

In order to examine the model stability and obtainable results, a series of sensitivity analyses was run. Each of the major inputs (e.g., adherence rates, hospitalization rates, costs, etc.) was tested with one-way (break-even) analyses to determine if obtained results would change within reasonable limits. Also, a probabilistic (Monte Carlo) synthesis was undertaken with 10,000

RLAI comparing iterations. The rates and costs at each decision node varied across a plausible range, using standard distributions for each variable. The proportions of iterations were also calculated, which favoured PP-LAI and comparison drugs. Two sets of outcomes were examined. In the first one, the threshold values were explored for dominance; in the second one, the threshold for cost-effectiveness was analysed, using the limits, as established by PoIAHTA.

**RESULTS**

Even with higher acquisition cost, PP-LAI would have a lower expected cost per treated patient, when the benefits are included in the estimation model (Table 4). PP-LAI was associated with 0.824 QALYS, 323 days with stable disease and 44.6% hospitalization. RIS-LAI had 0.817 QALY, 317 stable days and 51.3% hospitalization. PP-LAI dominated RIS-LAI in the base case and in 55.0% of 10,000 simulations, and was cost-effective in 76.6%. However, the cost-effectiveness was sensitive and lost with even modest increases for PP-LAI or with decreases for compared drugs with respect to drug prices, relapse and adherence rates. Because it is injected monthly as opposed to biweekly, It also saves caregiver’s time, being injected monthly, as opposed to biweekly regimens.

**DISCUSSION**

Despite its higher acquisition cost, PP-LAI demonstrated the lowest expected cost per treated patient. Because its therapeutic effect lasts a full month, having a reasonable side effect profile [22], its adherence rates are fairly high. Consequently, it exhibits higher efficacy, since adherence has been identified as the major driver of costs and patient status [23,24].

These results suggest that PP-LAI should be the atypical LAI of choice in Poland. Since more patients remain in stable condition, a broader adoption of the therapy should result in fewer hospital admissions, reducing patient loads on hospitals.

No indirect costs were taken into account in this analysis. The impact of the therapy on the number of sick leave episodes was assumed to be minimal, considering the very low employment level of schizophrenic patients; however, it is also possible that this medication could allow some of the patients to resume work or, at least, function more efficiently at home [25,26]. Other disregarded indirect costs included those, associated with the legal and justice system. It is well known that a proportion of persons with schizophrenia become violent and are frequently incarcerated, often many times [27,28]. Finally, no costs of adverse events were incorporated. At least two government agencies concluded that side effects contributed very little to the overall treatment costs [29,30]. Therefore, the results represent a conservative estimate with some underestimation of the total cost. Nonetheless, all of these aforementioned biases would be against PP-LAI.

**LIMITATIONS**

All research reveals certain limitations, either due to selected approach or the conduct of research tasks or for any other reason. A decision tree model was employed to simulate treatment and its outcomes. The results are therefore limited by the validity of inputs and the assumptions made in the modelling process. Decision trees estimate the average cost for the average patient under average conditions. The results apply therefore only to patients who meet inclusion

Table 4. Clinical and pharmacoeconomic outcomes

CLINICAL STATE	EXPECTED COST/ PATIENT (EURO)	REMISSION DAYS	HOSPITALIZATION RATE	QALYS/ PATIENT	COST (EURO)/ QALY	ECONOMIC OUTCOME
PP-LAI	PP-LAI	323.4	PP-LAI	44.60%	0.824	DOMINANT
RIS-LAI	3648	317.3	51.30%	0.817	4467	DOMINATED

criteria. They may or may not apply to related diseases, such as schizoaffective, schizophreniform, or bipolar disorder. The model was also limited to patients with chronic schizophrenia without comorbid conditions. Any extrapolations to other populations should thus be done with caution.

Inputs, specific for Poland, were used in this analysis, being, however, limited by the unavailability of certain data. In cases where some information was not available, we used data from similar environments in other countries or from multi-country trials, which may or may not have included patients from Poland. Local experts were also enquired to counsel concepts, validate assumptions and assure that inputs were appropriate and applicable.

In calculations, no co-payments were considered, assuming that they would be similar across drugs and would therefore not affect the outcomes to any great extent. The impact of that assumption is, however, not known.

## CONCLUSIONS

In this model, PP-LAI dominated the other atypical LAIs. Therefore, it is perceived as an atypical LAI of choice for patients with chronic schizophrenia. From the viewpoint of the National Health Fund of Poland, PP-LAI is a cost-effective drug with real potential to reduce healthcare expenses. ■



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