(LAIs). They have become a mainstay in treatment because of their prolonged effect and consequent prevention of much of the intentional and non-intentional non-adherence that results in treatment failures and hospitalizations [3]. The clinically meaningful superiority of depot medication compared to oral antipsychotic drugs in outpatients with schizophrenia has also been confirmed by the findings of a recent meta-analysis which demonstrated that depot formulations significantly reduced relapses from an average of 33.2% to 21.5% [5].

A further advance has been the development of atypical antipsychotics. They have advantages over the traditional drugs in that they improve both the positive and negative symptoms of the disease [6]. A depot form of atypical antipsychotic was not available until 2002, the first of which was risperidone (RIS-LAI) [7,8]. In a review of the clinical research, Möller concluded that RIS-LAI displayed clinical efficacy and a reasonable degree of tolerability [8]. Moreover, based on the results of a recent multi-centre cohort study across 15 French regions that accounted for 77.6% of the French population in 2005, RIS-LAI use compared to all other LAIs and first or second generation per os antipsychotics was associated with a 34% reduced rate of hospitalization [9]. A clinical disadvantage is that, although clinically effective, it must be administered every two weeks, usually by a specially trained psychiatric nurse or physician [10].

More recently, paliperidone palmitate (PP-LAI) has been developed and approved by the European Medicines Agency [11]. Among the other advantages that it shares with existing drugs, this new product has an added advantage in that it may be administered monthly [12]. PP-LAI is already marketed in several European markets, most often at a higher acquisition price than RIS-LAI.

Although the clinical use of PP-LAI has been investigated in a number of randomized controlled trials [13-17], few economic evaluations have yet been conducted. A search of the international peer reviewed literature revealed one study from the USA that included PP-LAI [18]. However, that study did not use data inputs generated by PP-LAI, but rather they used data from RIS-LAI studies and assumed the two drugs to be exactly equal. Considering differences in dosing regimens, such assumptions and associated cost outcomes may not be valid. Several pharmacoeconomic studies have compared RIS-LAI with other drugs, mainly oral atypicals and traditional depots. In his review of those studies, Haycox found that RIS-LAI was the dominant strategy in all eight different countries, using different analytical models [19].

In Greece, a single pharmacoeconomic study by Geitona and associates [20] was published which focused on paliperidone extended release oral tablets. That study demonstrated that paliperidone was cost-effective over all other oral drugs tested, including risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole. Paliperidone had the lowest overall cost and the highest number of days with stable disease. No other similar studies from Greece could be located.

Given that PP-LAI has a higher acquisition price than RIS-LAI and taking into consideration the scarcity of resources health care systems are faced with, economic evaluation of new technologies is important for decision making purposes. The aim of this paper is to compare costs and outcomes of PP-LAI versus RIS-LAI for the treatment of persons with chronic schizophrenia in Greece.

Methods

Patient population

Unlike a clinical trial, patients are not recruited into this research. Rather, a decision model was used to represent the average patient being treated using standard approaches.

Therefore, it is necessary to define the population to whom results would apply. The population of interest consisted of patients having chronic schizophrenia with multiple relapses, frequent hospitalizations, and problems with adherence to prescribed medications. At initiation of the analysis, all patients were stable and treated as outpatients with maintenance doses of their LAIs. For the purposes of this analysis, comorbidities were not considered even though they are common in this population [21].

Drugs of interest

The primary drug of interest was PP-LAI, which was compared against RIS-LAI. Long term use of PP-LAI has been investigated in a number of randomized controlled trials [13-17]; one of these trials involved a comparison with RIS-LAI [15]. As previously mentioned, the European Medicines Agency has approved PP-LAI for monthly dosing [12], while RIS-LAI is administered every two weeks [10]. It should be noted that at the time of this analysis PP-LAI was not marketed in Greece and there was no local clinical experience.

Model and base case

Data were modelled for one year using a previously validated decision tree [22], which appears in Figure 1, adapted for use in Greece. An expert panel was recruited and interviewed to provide clinical input describing patterns of patient management in this country. To enter the model, an average patient with chronic relapsing schizophrenia must be an outpatient with stable disease treated with either PP-LAI or RIS-LAI. The patient can be either adherent or non-adherent, according to published rates and expert opinion. Patients can remain stable or can relapse, with treatment either in the

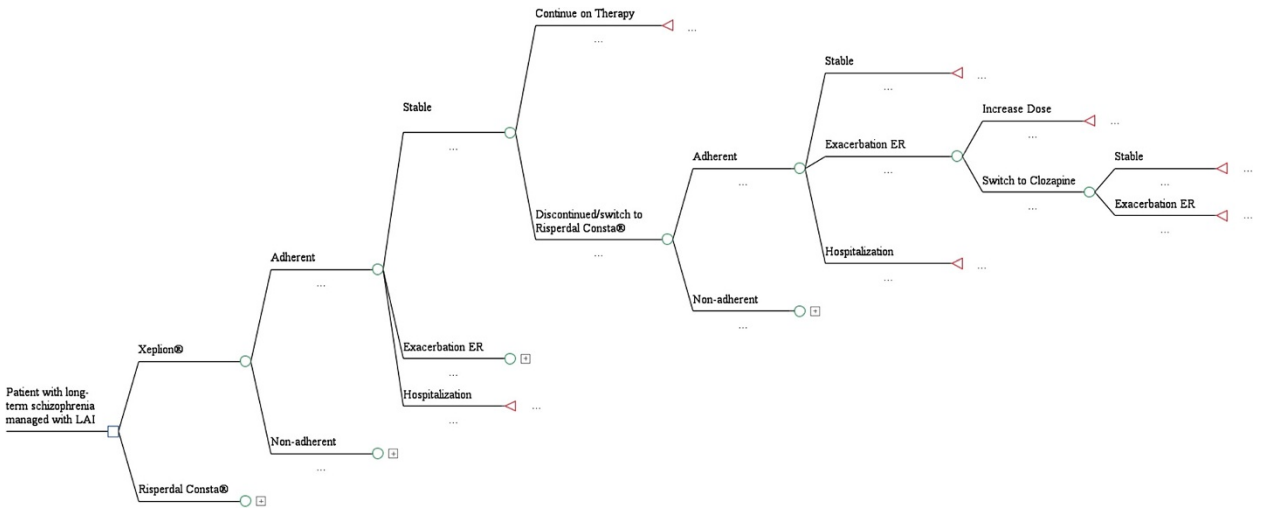

Figure 1 Decision tree model used for the pharmacoeconomic analysis.

emergency room or in hospital for severe cases. Those who cannot tolerate the primary drug or refuse to take it are switched to olanzapine oral tablets. In the event of a subsequent failure on that drug, clozapine oral tablets are prescribed [23,24].

Clinical inputs

Given the challenge of collecting valid local data for populating the model, which has also been identified in the relevant literature [25], data on resource utilisation, frequency and duration of relapses were mainly

Table 1 Clinical inputs into the model and sources of information

Rate	RIS-LAI	Source	PP-LAI	Source
Probabilities				
Adherence	0.823	Olivares [26]	0.872	RIS rate adjusted via Mehnert [27]
Adherent, stable disease	0.763	Calculation [1 - (ER exacerbation rate + hospitalization rate)]	0.803	Calculation [1 - (ER exacerbation rate + hospitalization rate)]
Adherent, exacerbation requiring ER visit	0.071	Ratio of ER vists: hospitalizations Ascher-Svanum [28]	0.059	Ratio of ER vists: hospitalizations Ascher-Svanum [28]
Adherent, hospitalized	0.166	Olivares [29]	0.138	Gopal [14], Hough [13]
Non-adherent, stable	0.140	Kane [30]	0.148	Hough [13]
Non-adherent, exacerbation	0.274	Calculation [1 - (Stable rate + hospitalization rate)]	0.299	Calculation [1 - (Stable rate + hospitalization rate)]
Non-adherent, hospitalized	0.586	Assumption; PP rate adjusted based on calculations by Mehnert & Diels [27]	0.553	Morken [31]
Dosing				
Maintenance dose	40.3 mg biweekly	Fleischhacker [15], Kissling [32], Lee [33], Lindenmayer [34], Olivares [29]	69.3 mg monthly	Gopal[14], Fleischhacker [15]
Dose after relapse	50 mg biweekly*	Risperdal Consta® Approved Summary of Product Characteristics [10] maximum dose	84.9 mg monthly	Gopal [35], Pandina [36], Hough [16], Nasrallah [37], Pandina [38]
Dose after discontinuation	50 mg biweekly*	Risperdal Consta® Approved Summary of Product Characteristics [10] maximum dose	150 mg week 1, 100 mg week 2, then 84.9 mg every 4 weeks	Xeplion® Product monograph [12], Hough [13]
Clozapine maintenance after failing both drugs	450 mg daily	Simonsen[23], Wahlbeck [24]		
Clozapine maximum dose	750 mg daily	Simonsen[23], Wahlbeck [24]		

ER emergency room, *PP-LAI* paliperidone palmitate long-acting injection (Xeplion®); *RIS-LAI* risperidone microspheres long-acting injection (Risperdal Consta®)
*A slightly higher average dose of 58.2 mg biweekly was used in clinical trials in patients with acute eacerbations of schizophrenia by Kane [5], Chue [35], and Eerdekens[36]; however, they used a dose of 75 mg mg in some patients, which is not commercially available and which exceeds the now-recommended maximum.

Table 2 Cost inputs into the economic model (2011€)

Resource	Item	Unit	Cost	Source
Drugs	paliperidone palmitate	mg	€ 2.90	calculation*
	risperidone microspheres	mg	€ 2.52	calculation†
	olanzapine tablets	mg	€ 0.27	calculation†
	clozapine tablets	mg	€ 0.0023	calculation†
Medical	visit/injection	1 visit	€ 10.12	Geitona [20], Urdahl [42]
Hospital	emergency room	1 visit	€ 50.00	Syriopoulou [43]
	hospital bed acute care	21 days	€ 146 for the first 21 days	DRG tariffs‡
	hospital bed acute care	1 day	€ 45.00/day after 21 days	DRG tariffs‡
	day hospital	1 day	€ 36.86	Geitona [20], Urdahl [42]

*Based on available EU prices in the 22 countries used for reference pricing in Greece at the end of September 2011.
†Based on hospital prices published in Price Bulletin 4/8/2011 and IMS Greece market shares July 2011.
‡Calculation based on officially published Ministry of Health Diagnosis Related Group (DRG) tariffs, Government Gazette B 1702/1-8-2011.

extracted from an expert panel consisting of hospital psychiatrists. Other clinical rates and associated data inputs were determined from the literature (Table 1) [10,12-16,23,24,26-40]. The doses of drugs actually administered in long term trials of these drugs were used, rather than the Daily Defined Doses (DDDs) as published by the World Health Organization. DDDs represent the average dose for the drug when used in its most common indication, which does not represent our target population [41]. In the present analysis, the research hypothesis is focused on frequently relapsing patients, necessitating hospitalization and intensive intervention. Therefore, DDDs may underestimate the doses used in the real world when treating these patients, whereas doses from the clinical trials could be considered as better proxy for real world dosing.

Cost inputs

Costs were considered from the perspective of the National Health Service of Greece. We included only direct costs of care while indirect costs, such as time lost from work, were excluded (Table 2) [20,42,43]. We did not apply discounting because the analysis had a time horizon of one year. Prices were taken from official bulletins or from the literature, then inflated to 2011 Euros using the Consumer Price Index for Greece [44].

Analysis and outputs

For each drug, we calculated the average cost per patient treated. Patient outcomes analyzed included average days with stable disease, numbers of hospitalizations, emergency room visits, and quality-adjusted life-years (QALYs). To derive utilities (i.e., the quality weights) for this quality adjustment, preference based estimates were obtained from the literature [45-49]. Each of the three primary health states (i.e., stable disease, exacerbation requiring emergency room treatment, and hospitalization) were weighted using the average of the reported utility scores. QALYs were then estimated for each drug by multiplying the amount of time in each health state by the quality value assigned to that health state. Therefore, a cost-utility analysis was conducted, which involves calculating the incremental treatment cost per QALY as the pharmacoeconomic outcome. In addition, a cost-effectiveness analysis was performed in order to assess other important clinical outcomes, such as the number of stable and relapse days as well as rates of hospitalisation and emergency room visits.

Several sensitivity analyses were performed to determine if alterations in clinical or cost inputs would influence outputs. One-way sensitivity analyses were done to identify break-even points, that is, what the values would have to be in order for PP-LAI to cost more than RIS-LAI. We conducted one-way sensitivity analyses on important parameters such as rates of adherence, hospitalization, and emergency room visits as well as drug acquisition costs. Finally, all variables were varied over plausible ranges in a probabilistic sensitivity analysis (also called a Monte Carlo simulation) with 10,000 iterations. That analysis reproduces results for a large group of patients and gives a projection of what average costs and outcomes would be.

Results

Cost analysis

The total direct cost to treat one patient over the year was calculated for each drug, as presented in Table 3. Included in those calculations were drugs, medical care (visits) and hospital care, based on the units presented in Table 2. The overall cost to treat patients with PP-LAI was lower than with RIS-LAI by €166, despite having a higher acquisition cost. In the case of PP-LAI, drugs accounted for the largest proportion of the total costs (61%), while hospitalization comprised 30% and medical care the remaining 9%. Costs for RIS-LAI had a similar