Cost-utility analysis of long-acting paliperidone in comparison with oral risperidone, oral paliperidone and long-acting risperidone in the maintenance treatment of schizophrenia in the Czech Republic

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Abstract

Objectives. Lifetime prevalence of schizophrenia ranges from 1 to 1.5%. The number of patients in the Czech Republic amounts annually to approximately 126,000. Schizophrenia causes significant increases in mortality, shortening life expectancy by 25 years compared to the general population. Patients on long-acting paliperidone treatment remain in remission longer and thus experience higher quality of life.

Methods. Cost-utility analysis was performed using a Markov model. The primary outcome was ICER/QALY. Oral risperidone, oral paliperidone and long-acting risperidone were selected as comparators. The basic components of the model include probabilities of relapse, individual hazard ratios for non-compliance by medication type and switch of treatment probabilities. Specific utilities for each health state were considered. Among relevant costs, reflecting payer's perspective, drug acquisition costs, monitoring costs, costs of relapses, follow-up care and adverse events were considered.

Results. Long-acting paliperidone reached ICER of EUR 16,233/QALY compared to oral risperidone, EUR 15,058/QALY to oral paliperidone and EUR 335/QALY to long-acting risperidone. The robustness of the model was supported by one-way deterministic analysis and probabilistic sensitivity analysis, which gave stable results. Long-acting paliperidone was cost effective in 97% of the simulations compared to oral risperidone. Long-acting paliperidone treatment gained incremental 0.903 QALYs on average compared to oral risperidone.

Conclusions. The treatment of schizophrenia using long-acting paliperidone is associated with increased QALYs. It reduces incidence of adverse events, results in better prevention of relapses and can be considered as a cost-effective treatment in the Czech Republic.

Keywords. Cost Utility Analysis, Schizophrenia, Paliperidone, Risperidone.

Objectives

The aim of the pharmaco-economic evaluation was to assess costs and benefits of maintenance treatment of schizophrenia with paliperidone long-acting injection (LAI) (paliperidone palmitate LAI or depot paliperidone) compared to maintenance therapy with oral risperidone, oral paliperidone or risperidone long-acting injection (LAI) in patients who: a) were stabilised on oral risperidone or paliperidone; b) have mild to moderate psychotic symptoms and have confirmed previous sensitivity to oral paliperidone or risperidone.

The analysis is based on the assumption that the treatment with paliperidone LAI is a cost-effective therapy compared to the above mentioned comparators due to the increased patient adherence to treatment, which generally leads to fewer relapses requiring or not requiring hospitalisation even with higher drug acquisition costs of paliperidone LAI. The reduction of the number of relapses is then positively reflected in lower monitoring costs and in a higher number of generated QALYs, because patients on treatment with paliperidone LAI remain in remission longer, which is associated with a higher quality of life.

The pharmaco-economic evaluation was performed from the perspective of the public healthcare payer and only the costs that affect the utilisation of public health insurance resources were included.

Target population

Schizophrenia is one of the severe diseases. It is a disorder of information processing and is characterised by significant malfunctions in thinking (formal and substantive) and the perception of emotional, behavioural and cognitive functions. It is a disease with a multiform picture of psychopathology, clinical process and outcomes, uncertain therapeutic response and probably inconsistent etiopathogenesis, which, however, is primarily neurobiological (1).

The disease affects men and women equally. The typical age of disease onset is during adolescence and young adulthood.

Results of epidemiological studies indicate a lifetime prevalence of the disease between 1-1.5% (2). A Europe-wide survey examining the prevalence and severity of psychiatric illness and other brain diseases in Europe showed that schizophrenia affects approximately 5 million Europeans, with the prevalence of 1.2% (2). At this given rate of prevalence the number of patients in the Czech Republic reaches approximately 126,000.

Recurring chronic courses of the disease can lead to severe functional impairment, personality changes, deterioration in quality of life with a high degree of incapacity and permanent disability. Negative consequences have an impact not only on patients but also on their families and society.

The Health Statistics from 2011 (3) stated that the Czech Republic recorded 6,562 hospital admissions for schizophrenia, which had an average treatment duration of 143.3 days. After being released from a psychiatric facility, the majority of patients needed outpatient care, either permanent (47%) or temporary (32%). In 9% of cases, further inpatient treatment was required, and only 5% of hospitalised patients did not require any care after discharge from psychiatric facilities. Permanent outpatient care after discharge was needed in 65% of the total number of patients who were treated for schizophrenia, schizotypal and delusional disorders.

Schizophrenia increases mortality significantly. The life expectancy of patients with schizophrenia in comparison with the general population is reduced by up to 25 years (4). The lifetime risk for suicide is nearly 5%, especially in the early disease (5).

The treatment of schizophrenia can be divided into the acute phase, to reduce psychotic symptoms, the stabilisation phase to restore the normal functioning, and the long-term (maintenance) treatment aiming at achievement and maintenance of remission and prevention of relapses. The fundamental pharmacological treatment of schizophrenia is antipsychotic treatment (6). Early initiation of antipsychotic treatment not only reduces the risks associated with acute psychotic symptoms, but also reduces the risk of chronic course. When selecting a specific drug, the doctor checks the predominant symptomatology, previous drug history, occurrence of side effects, overall tolerability, possible drug interactions and contraindications for individual patients.

The decision on the dosage form and route of administration (oral, parenteral) is influenced by the degree of patient cooperation and the terms of payment, according to which a given therapy is covered by public health insurance. Treatment of psychotic disorders is not limited to the acute phase of the disease but can include a new disease, new episode or relapse with the duration of a few weeks. The treatment is particularly aimed at symptom control, but more often it comprises of long-term treatment (maintenance). Apart from the symptoms the goal of long-term therapy is also to reduce the risk of relapse, occurrence of side effects and to maintain or improve the patient life quality.

The treatment of schizophrenia is associated with a high rate of non-adherence. Approximately 40-60% of patients are not adherent (7).

For patients with a low adherence rate the use of depot antipsychotics is preferred according to current treatment guidelines (8).

Methods

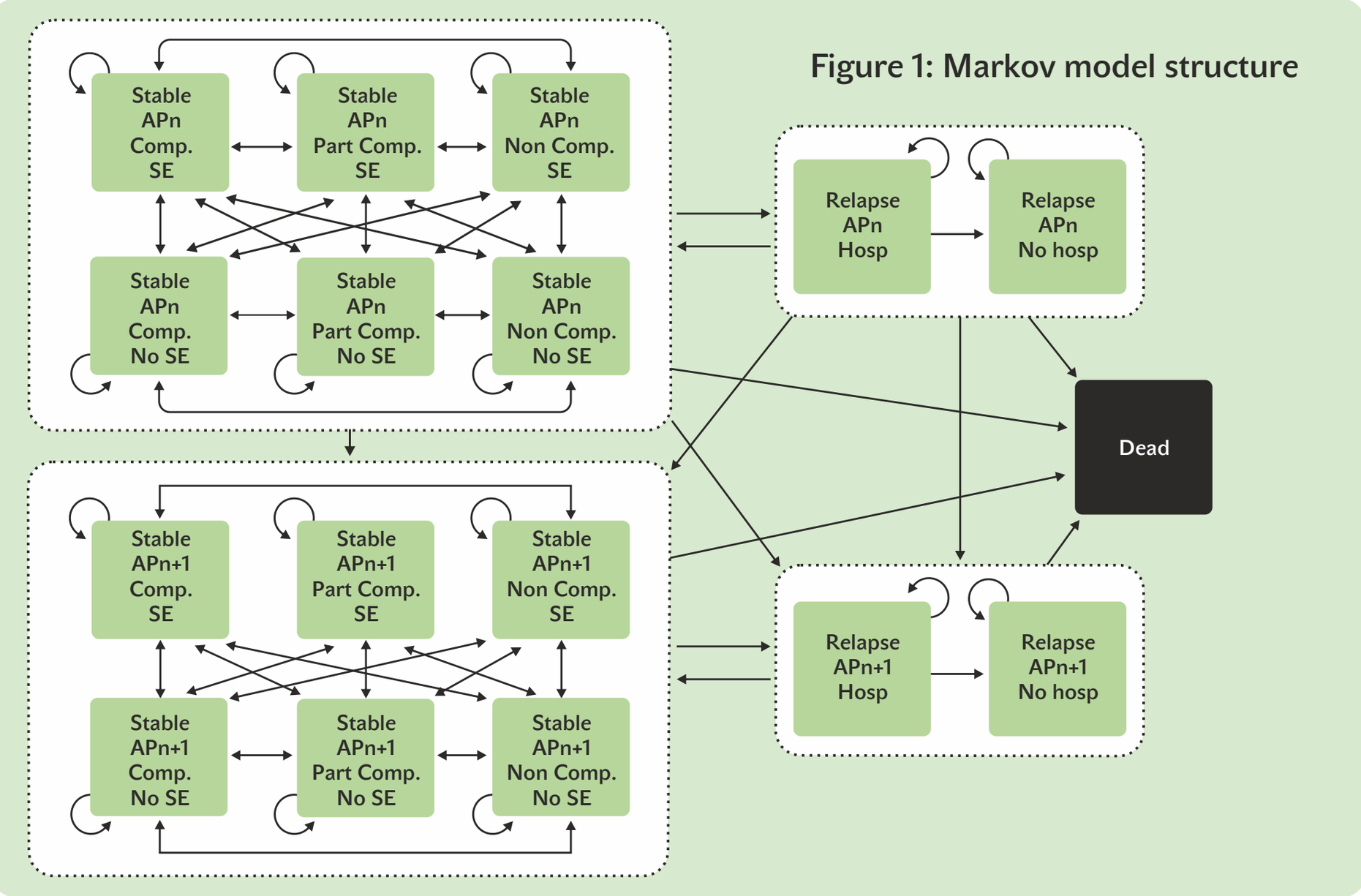
Health-economic model

In the baseline scenario, a time horizon of 10 years and a discount rate for benefits and costs of 3% were chosen. The time horizon was considered to be optimal with regard to the trial population aged 35-39 years and the fact that after ten years 19.4% of patients remain on treatment with paliperidone LAI (based on the model calculation according to the probability of a change in medication and death). A longer time period related to the real clinical use was not considered, since the number of treated patients in the longer time horizon remains low. A shorter time horizon was used as a separate scenario to eliminate the methodological uncertainty.

Health-economic analysis was performed using a Markov model built in MS Excel. The analysis was conducted from the perspective of the public healthcare payer as Cost-Utility Analysis (CUA). The result is ICER expressed as incremental costs per incremental QALY. ICER per one prevented relapse was computed as a secondary outcome.

The model compared the effects and costs of paliperidone LAI with oral risperidone, oral paliperidone and risperidone LAI treatments. The structure of the model is captured in the diagram in Figure 1.

Figure 1: Markov model structure



In the model health states comprising combinations of the following conditions were considered: patient on first antipsychotic treatment (Apn), patient on changed antipsychotic treatment (APn+1), compliant, partially compliant and fully compliant patient on treatment, and finally patient with/without side effects (SE / No SE). Relapsed patients can be on treatment with first or changed (subsequent) antipsychotics, hospitalised or not hospitalised as a relapse consequence. The terminal state represents death. Patients can move from each state to all others (except for moving from changed AP to first AP and from death). Patients can remain in the same state for more cycles.

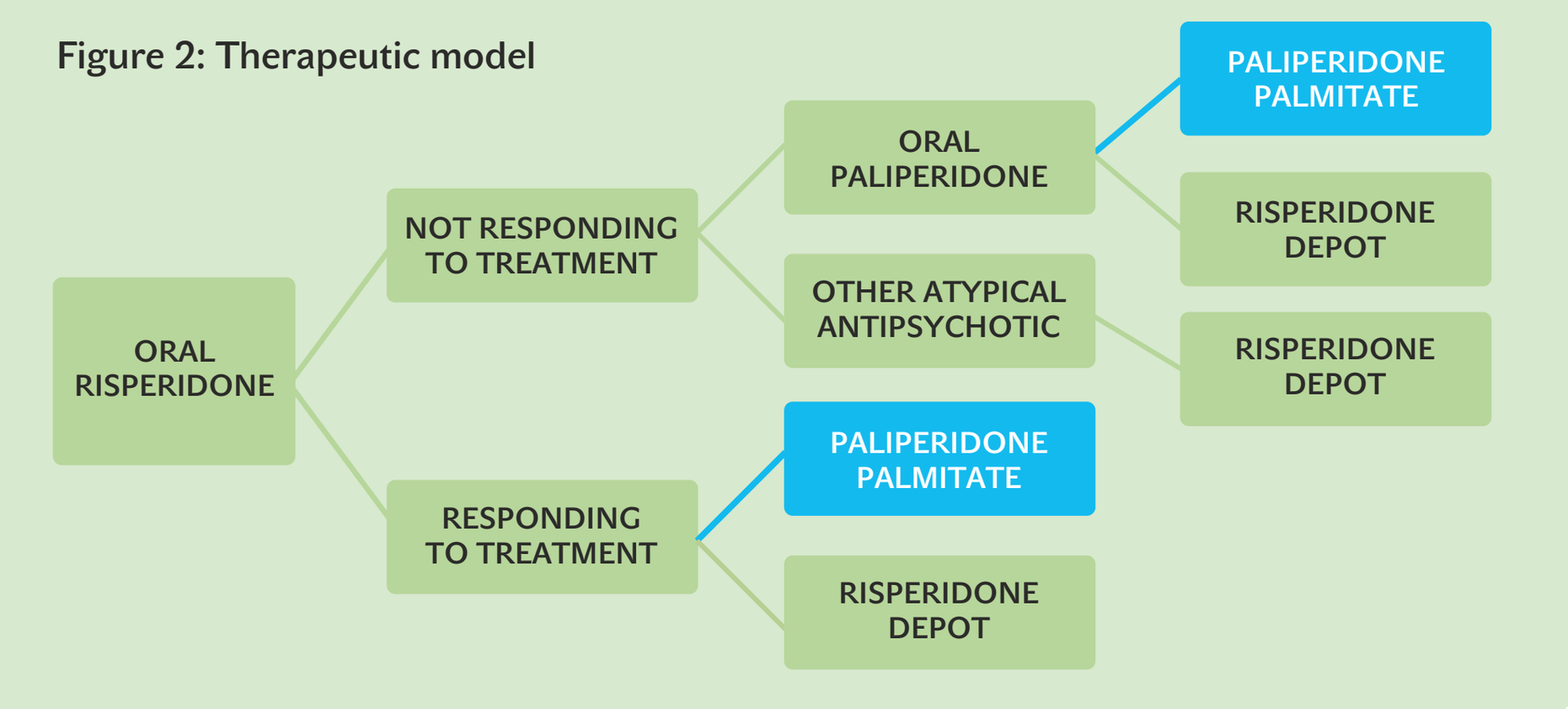
Transition probabilities between health states were determined by the probability of relapse (with hospitalisation or without hospitalisation), the probability of occurrence of adverse events, specific mortality for schizophrenic patients and the probability of adherence to treatment. The patient may change antipsychotics due to the following reasons: inefficiency, adverse events, lack of adherence, patient's request.

Other inputs into the model were utility values for each health state, monitoring costs and administration costs.

Comparators

Medicines that are used and reimbursed in the Czech Republic for patients who were stabilised on oral risperidone or paliperidone or have mild to moderate psychotic symptoms and confirmed previous sensitivity to oral paliperidone or risperidone were chosen as comparators. These are oral risperidone, oral paliperidone and risperidone LAI. For each comparator a separate cost effectiveness scenario was calculated. Based on the actual reimbursed indications in the Czech Republic the model strategy is as follows (Figure 2).

Figure 2: Therapeutic model



Oral risperidone is used prior to all other antipsychotic drugs. If a patient is sensitive to oral risperidone (evaluated as strategy 1) a change to paliperidone LAI (strategy 2) or risperidone LAI (strategy 4) can occur. If the patient is not sensitive to oral risperidone the change to oral paliperidone (strategy 3) or other antipsychotic drugs take place. If a patient is sensitive to oral paliperidone the change to paliperidone LAI can occur.

Probabilities

In the model probabilities of occurrence of relapse, adverse events, adherence, switch and specific mortality were used. Probability of relapse (defined by clinically significant worsening of symptomatic exacerbations syndromes such as deterioration on the PANSS scale, BPRS scale, CGI scale and/or hospitalisation is needed) was specific for patients that need hospitalisation and for patients that do not need hospitalisation. The occurrence of relapse requiring hospitalisation was expressed as a percentage of total relapses.

The probability of relapse depends on the type of treatment and the level of compliance and was calculated based on the following variables:

- the probability of relapse of patients on placebo (P_0) (reference probability);
- the ratio of risk of relapse of patients on treatment with certain AP and the risk of relapse on placebo (treatment effect, α_T);
- the ratio of the risk of relapse among patients with different levels of adherence (adherent, non-adherent and partially adherent patients) and reference adherence level (the effect of adherence = β_C). The equation used for calculation of probability of relapse is as follows: $P\,(Relapse \mid Treatment = T, Compliance = C) = \alpha_T . \beta_C . P_0$

The baseline annual probability of relapse in patients on placebo is 43.6% (based on the analysis listed on page 148 in the 2009 NICE Guidance (9)).

Each AP has different risk of relapse (depending on type of administration), which is expressed as a relative risk to the reference value (placebo) equal to 1. A summary of risk ratios is shown in Table 1 (9), (10), (11), (12).

Table 1: Relative risk of relapse

active substance	relative risk of relapse	source
Paliperidone oral	0.37	[9]
Paliperidone palmitate	0.33	*
Quetiapine	0.76	[10]
Risperidone depot	0.33	[9], [10]
Oral olanzapine	0.46	[9]
Oral risperidone	0.63	[9]
Conventional depot	0.6	[11]
Olanzapine LAI	0.46	[12]
Oral typical	0.76	[9]
Oral atypical (ref)	0.49	**
Clozapine	0.76	[10]
Placebo	1.00 (ref)	[9]

* Assumed equal to Risperdal Consta
** Average of paliperidone oral, oral olanzapine, oral risperidone

The pharmacological treatment of schizophrenia is associated with the occurrence of adverse events that is different for each AP. The following adverse events (AEs) were considered in the model: extrapyramidal symptoms (EPS), weight gain and diabetes. The probabilities of occurrence of these AEs for each AP are listed in Table 2 (9), (12), (13), (14), (15).

Table 2: Occurrence of adverse events

Proportion of stable patients with extrapyramidal symptoms by treatment, over 12 months		
Active substance	**Occurance rate**	**Source**
Paliperidone oral	11.4%	[13]
Paliperidone palmitate	9.3%	[13]
Quetiapine	9.1%	[13]
Risperidone depot	12.6%	[13]
Oral olanzapine	7.6%	[13]
Oral risperidone	18.2%	[13]
Conventional depot	26.4%	[13]
Olanzapine LAI	7.6%	*
Oral typical	19.7%	[13]
Oral atypical (ref)	1.4%	**
Clozapine	8.8%	[13]

Proportion of stable patients with tardive dyskinesia by treatment, over 12 months		
Active substance	**Occurance rate**	
Paliperidone oral	4.1%	[13]
Paliperidone palmitate	0.3%	[13]
Quetiapine	4.0%	[13]
Risperidone depot	1.2%	[14]
Oral olanzapine	3.0%	[13]
Oral risperidone	4.1%	[13]
Conventional depot	7.3%	[13]
Olanzapine LAI	3.0%	[13]
Oral typical	5.2%	[13]
Oral atypical (ref)	2.4%	**
Clozapine	3.1%	[13]

Proportion of stable patients with weight gain by treatment, over 12 months		
Active substance	**Occurance rate**	
Paliperidone oral	11.7%	[13]
Paliperidone palmitate	6.0%	[15]
Quetiapine	7.9%	[13]
Risperidone depot	9.1%	[13]
Oral olanzapine	16.3%	[13]
Oral risperidone	12.0%	[13]
Conventional depot	12.6%	[13]
Olanzapine LAI	16.0%	[12]
Oral typical	9.5%	[13]
Oral atypical (ref)	13.4%	**
Clozapine	12.6%	[13]

Proportion of stable patients with diabetes by treatment, over 12 months		
Active substance	**Occurance rate**	
Paliperidone oral	2.1%	[9]
Paliperidone palmitate	1.6%	***
Quetiapine	1.5%	***
Risperidone depot	1.7%	***
Oral olanzapine	4.2%	[9]
Oral risperidone	2.1%	[9]
Conventional depot	2.0%	[9]
Olanzapine LAI	4.2%	*
Oral typical	2.0%	[9]
Oral atypical (ref)	2.8%	**
Clozapine	2.4%	***

* Equal to oral olanzapine (no significant differences)
** Average of paliperidone oral, oral olanzapine, oral risperidone
** Average of (NICE diabetes/weight gain) ratios of pali oral, oral risp, oral olz, CD * weight PP

The level of adherence is defined according to the patient's intake of medications. Annual patient adherence was measured on an ordinal scale derived from the cumulative proportion of real treatment dosage and optimal treatment dosage. Levels of adherence were then defined by the above mentioned proportions that are as follows: adherent patients (compliant) 0.8 to 1.1, partially adherent patients 0.5 to 0.79 or greater than 1.1 and non-adherent patients less than 0.5. Based on Gilmer (16), 41% of patients with schizophrenia are compliant, 35% of patients are partially compliant and 24% of patients are non-compliant. These values were considered as references. The proportions of patients having different levels of adherence were considered stable over time (17).

Patient adherence varies across the medications used. Differences in adherence for each medicine were captured by the relative risk to the reference values. Relative risks were obtained from clinical data. Individual hazard ratios for compliance rates are shown in Table 3 (13), (16).

Table 3: Compliance levels by treatment arm for the general schizophrenia cohort

compliance category	Compliant		Partially compliant		Non-compliant		Source
active substance	**Probability**	**Risk ratio**	**1-(Comp+ Non Comp)**	**Risk ratio**	**Probability**	**Risk ratio**	
Paliperidone oral	41.0%	1.00	27.5%	0.79	31.4%	1.31	[13], [16]
Paliperidone palmitate	54.9%	1.34	42.2%	1.21	2.9%	0.12	[13]
Quetiapine	41.0%	1.00	9.1%	0.26	49.9%	2.08	[13], [16]
Risperidone depot	52.9%	1.29	43.1%	1.23	4.0%	0.17	[18]
Oral olanzapine	40.9%	1.00	35.2%	1.01	23.9%	1.00	[13], [16]
Oral risperidone	41.0%	1.00	27.6%	0.79	31.4%	1.31	[13], [16]
Conventional depot	48.0%	1.17	30.8%	0.88	21.3%	0.89	[13]
Olanzapine LAI	50.8%	1.24	43.9%	1.26	5.2%	0.22	*
Oral typical	37.2%	0.91	24.9%	0.71	37.9%	1.58	[13], [16]
Oral atypical	40.9%	1.00	24.0%	0.69	35.2%	1.47	[13], [16]
Clozapine	60.1%	1.47	17.9%	0.51	22.0%	0.92	[13], [16]
Reference	41.0%	1.00	35.0%	1.00	24.0%	1.00	[16]

* Assumes 3hr post-injection monitoring reduces compliance by 5%

Different degrees of adherence to treatment are also associated with different probabilities of relapse expressed as a relative risk to the baseline risk of relapse (reference) (16): compliant patients have a reference relative risk of relapse equal to 1, partially compliant patients have a risk ratio of 1.81, and non-compliant patients have a risk ratio of 2.59.

The probability of treatment switch depends on the type of treatment and the patient's condition. The following four reasons were considered as the cause of change of treatment: inefficiency, adverse events, lack of adherence and patient request.

The probability of switch due to lack of efficacy was considered only in patients with relapse. Therefore, the probability of switch due to a lack of efficacy was calculated as the ratio of the probability of switch due to a lack of efficacy and the probability of relapse in each cycle.

Similarly, the probability of switch due to adverse events was assigned only to patients with AE, and thus it was divided by the probability of AE occurrence. The probability of switch due to non-adherence was split between partially adherent and non-adherent patients only.
In contrast, the probability of switch due to patient request was considered the same for all patients.

The following assumptions were considered in the model:

- patients with relapse may change treatment because of lack of efficacy or their own request
- partially adherent or non-adherent stable patients with adverse events may change treatment due to insufficient adherence, AEs, or their own request
- partially adherent or non-adherent stable patients without adverse events may change treatment because of lack of adherence or their own request
- adherent patients with adverse events may change treatment due to AEs or their own request
- adherent patients without adverse events may switch due to their own request.

It was assumed that the reasons for the changes are independent. Based on these assumptions, the probability of switching was calculated for different health states as the product of probabilities of all possible switching options in each health state. For example, the probability of switch for partially adherent patients with adverse events was calculated as follows:

$$P\,(Switch \mid PartComp, SE) = 1-(1-P_{LackOfComp})(1-P_{SE})(1-P_{PatientRequest})$$

Probabilities of switching to another medication for each AP are stated in Table 4 (13), (18).

Table 4: Causes of changing medications within 12 months

active substance	lack of efficacy	side effects	lack of compliance	patient request	source
Paliperidone oral	8,2%	3,5%	4,3%	4,3%	[13]
Paliperidone palmitate	7,3%	1,4%	0,7%	3,3%	[13]
Quetiapine	19,7%	5,0%	6,3%	6,2%	[13]
Risperidone depot	7,3%	2,0%	0,9%	3,3%	[18]
Oral olanzapine	6,6%	2,2%	3,1%	4,0%	[13]
Oral risperidone	8,2%	3,5%	4,3%	4,3%	[13]
Conventional depot	11,8%	3,2%	3,4%	5,4%	[13]
Olanzapine LAI	6,6%	2,2%	0,7%	4,0%	[13]
Oral typical	12,8%	4,6%	4,5%	6,0%	[13]
Oral atypical (ref)	11,0%	3,8%	4,8%	4,8%	*
Clozapine	6,3%	2,5%	3,1%	2,1%	[13]

* Average of paliperidone oral, oral olanzapine, oral risperidone

Table 5 shows the proportions of patients who switched to other medication during treatment for each AP (based on the above calculated probabilities).

Table 5: Proportions of patients changing medications within 12 months

active substance	stable compliant		stable partial/non-c.		relapse requiring hospitalization	relapse not requiring hospitalization
	without side effects	**with side effects**	**without side effects**	**with side effects**		
Paliperidone oral	0.37%	12.00%	0.98%	12.55%	10.76%	10.76%
Paliperidone palmitate	0.28%	7.17%	0.41%	7.29%	13.61%	13.61%
Quetiapine	0.53%	22.54%	1.44%	23.25%	11.85%	11.85%
Risperidone depot	0.28%	8.13%	0.44%	8.27%	13.32%	13.32%
Oral olanzapine	0.34%	7.07%	0.78%	7.49%	6.97%	6.97%
Oral risperidone	0.36%	9.52%	0.98%	10.09%	6.18%	6.18%
Conventional depot	0.46%	6.55%	1.01%	7.07%	10.42%	10.42%
Olanzapine LAI	0.34%	7.07%	0.45%	7.18%	8.11%	8.11%
Oral typical	0.52%	12.74%	1.12%	13.27%	7.82%	7.82%
Oral atypical (ref)	0.41%	12.42%	1.10%	13.03%	10.77%	10.77%
Clozapine	0.18%	9.07%	0.83%	9.67%	4.38%	4.38%

Specific mortality for patients with schizophrenia was calculated from general mortality data from the Czech Republic, which was age and gender specific. The specific mortality was obtained using the relative risk of mortality of patients with schizophrenia from published literature (19). It is 2.80 for males and 2.40 for females where 1.00 is the reference mortality rate for the general population.

Utilities

Utility values were assigned for each health state. The following basic health states were considered: stable state, relapse not requiring hospitalisation, relapse requiring hospitalisation and death.

In the case of relapse not requiring hospitalisation it was assumed that the utility value is equal to the midpoint of the stable state and relapse requiring hospitalisation utility values. It was also assumed that adverse events have a negative impact on the quality of life expressed as utility decrements. The utility of a particular state where adverse events occur was decreased by the utility decrement of the particular adverse event. The values of utilities and their decrements are based on clinical trials. The values of individual utilities are as follows (20): stable patients 0.919, relapsed patients not requiring hospitalisation 0.762, relapsed patients requiring hospitalisation 0.604, death 0.00, utility decrements for acute EPS and tardive dyskinesia 0.197, weight gain 0.094 diabetes 0.150.

Costing

Among relevant costs (from the payer's perspective) drug acquisition costs, monitoring costs, costs of relapses, aftercare costs and costs of treatment of adverse events were considered. The cost analysis was based on the current list of reimbursed drugs and medical examinations in the Czech Republic (24) (25).

When calculating drug acquisition costs, costs of daily drug dosage were calculated according to the recommended daily doses valid in the Czech Republic. Ddrug administration costs were considered as additional treatment related costs. These relevant medical procedures were obtained from an expert panel in the Czech Republic (23).

Monitoring costs include costs of one complex medical examination performed once per year, one specific examination per year and three regular check-up examinations per year for stable patients without adverse events. In case of relapsed patients not requiring hospitalisation the number of regular check-up examinations increases to 24 annually, where patients are controlled every two weeks. The frequency of these medical performances and the exact content of each type of examination were determined by expert panel.

Costs of relapses and aftercare costs include hospitalisation costs due to relapse. Generally 63% of patients with schizophrenia having relapse are hospitalised (21). After hospitalisation 60% of these hospitalised patients can go home but still show signs of relapse, 20% continue with long-term psychiatric care and 20% return home in a stable state (22). The average duration of hospitalisation is 30 days, long-term psychiatric care lasts on average 90 days and patients who could return home but still show signs of relapse stay in this condition for 30 days on average (23).

Within the elimination of methodological uncertainty a scenario based on different sources of data (3) was developed. The data show that patients are hospitalised for 143 days on average, 79% of patients leave for home, but still have signs of relapse, 9% of patients continue with long-term treatment and 12% are stabilised after hospitalisation. The total duration of relapse not requiring hospitalisation lasts 38 days on average (3).

Costs of AE treatment are associated with certain procedures and examinations that are performed: laboratory tests for cholesterol in case of weight gain and tests for glycaemia in case of diabetes. The dosage of AP is then adjusted or the medication is switched.

Results

The model worked with the evaluation of interventions and all comparators simultaneously providing the option of mutual comparison of all outputs. The costs for each comparator are listed in Table 6.

Patients on paliperidone LAI treatment gained the most QALYs (5.42 discounted QALYs) among all compared medications. Paliperidone LAI also prevented the most relapses. The discounted number of relapses reached 2.39. However, paliperidone LAI generated the highest overall costs. Calculations in EUR were based on yearly average exchange rates of the Czech National Bank for 2013 (26). Table 6 shows the ICERs of compared medications.

Table 6: Treatment costs and ICER/QALY

Average costs per patient		Strategy 1	Strategy 2	Strategy 3	Strategy 4	Strategy 5
Antipsychotic acquisition costs		EUR 1533.56	EUR 19369.33	EUR 9344.74	EUR 19137.34	EUR 19137.34
Schizophrenia-related ambulatory care	**Stable**	EUR 574.59	EUR 599.96	EUR 589.87	EUR 599.06	EUR 599.06
	Relapse	EUR 139.39	EUR 81.23	EUR 104.34	EUR 83.28	EUR 83.28
Side Effects Costs		EUR 69.78	EUR 45.62	EUR 69.46	EUR 58.19	EUR 58.19
Hospitalisation Costs		EUR 4154.57	EUR 2429.02	EUR 3116.73	EUR 2490.31	EUR 2490.31
TOTAL		EUR 6471.90	EUR 22525.15	EUR 13225.14	EUR 22368.19	EUR 22368.19
Discounted TOTAL		**EUR 5726.71**	**EUR 20388.36**	**EUR 11985.06**	**EUR 20267.24**	**EUR 20267.24**
QALYs, per patient		4.94	6.00	5.35	5.58	5.58
DisDiscounted QALYs		**4.51**	**5.42**	**4.86**	**5.05**	**5.05**
Relapses, per patient		4.67	2.74	3.51	2.81	2.81
Relapses, discounted		**4.15**	**2.39**	**3.07**	**2.45**	**2.45**

ICER	Strategy 1	Strategy 2	Strategy 3	Strategy 4	Strategy 5
vs. Strategy 1		EUR 16233.09	EUR 18132.77	EUR 26863.83	EUR 26863.83
vs. Strategy 2	EUR 16233.09		EUR 15058.20	EUR 334.65	EUR 334.65
vs. Strategy 3	EUR 18132.77	EUR 15058.20		EUR 42228.53	EUR 42228.53
vs. Strategy 4	EUR 26863.83	EUR 334.65	EUR 42228.53		-
vs. Strategy 5	EUR 26863.83	EUR 334.65	EUR 42228.53	-	

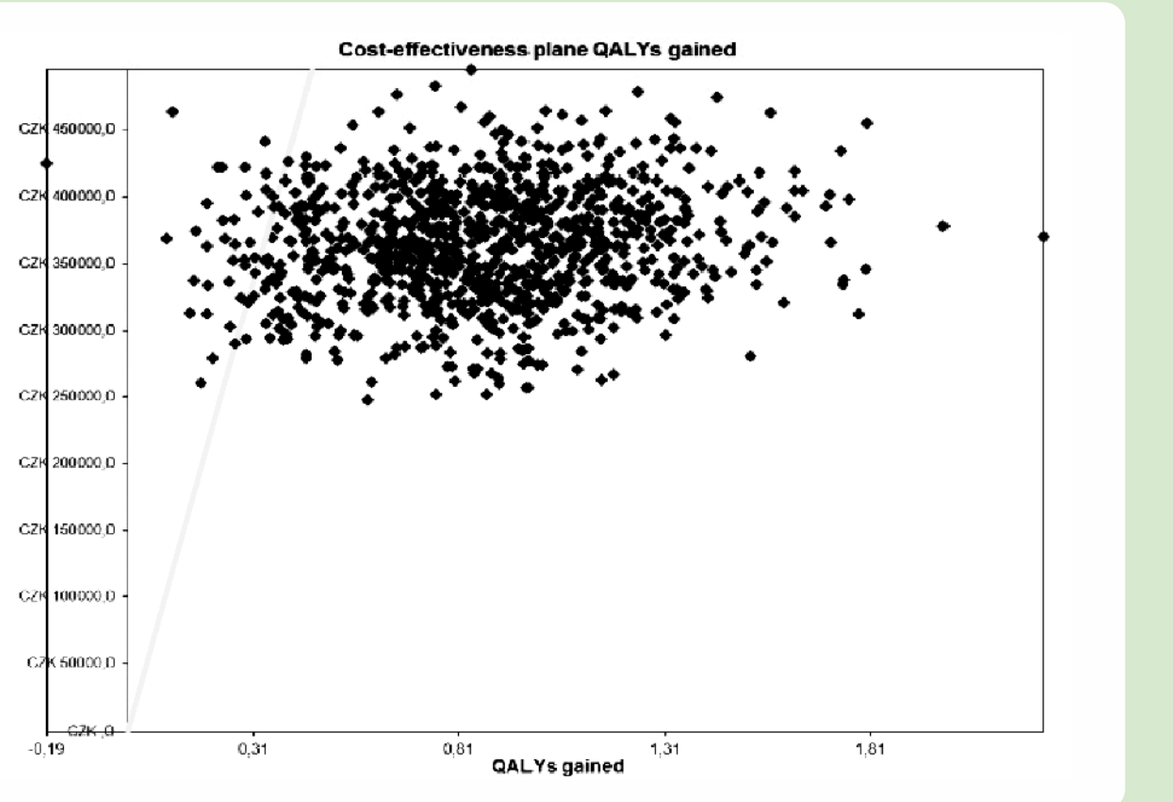
Paliperidone LAI reached ICER of EUR 16,233/QALY compared to oral risperidone, EUR 15,058 to oral paliperidone, and EUR 335 to risperidone LAI.

Sensitivity analyses

One-way deterministic analysis (DSA) was carried out as a set of separate scenarios, where parameters with possible methodological bias impacting ICER or parameters having significant impact on ICER were varied separately. The parameters varied in deterministic sensitivity analysis were as follows: length of time horizon (5 and 8 years), adherence to treatment, occurrence of relapses, occurrence of adverse events, proportion of relapses requiring hospitalisation, duration of relapses, proportion of patients in each regime after hospitalisation (long-term psychiatric care, leaving for home with signs of relapse, stable patients), rates of switching to another medication, relative mortality in patients with schizophrenia (19), utility (20) and change of reimbursement level of each medication ± 20%. The model showed stable results within all these different settings.

The robustness of the model was also supported by probabilistic sensitivity analysis (PSA), which simulated 1,000 randomly changed combinations of selected input parameters (impacting ICER) defined by statistical distributions. The outcome of PSA comparing paliperidone to oral risperidone as the base case of the model is presented as a cost effectiveness plane, where incremental cost is plotted on the vertical axis and QALYs gained plotted on the horizontal axis for each simulation.

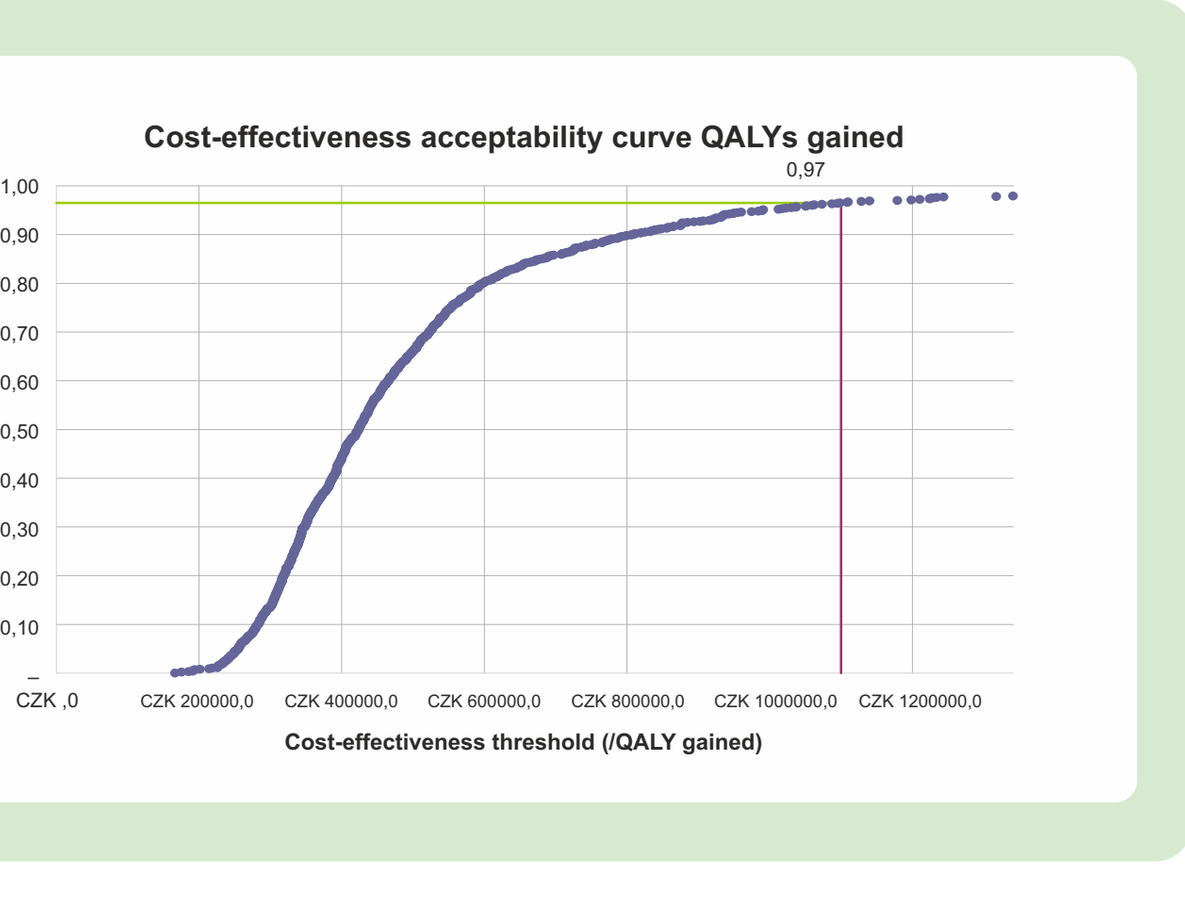
Figure 3: Cost effectiveness plane



The line represents the willingness to pay, which currently in the Czech Republic is considered to be CZK 1,097,000 (EUR 42,235) per QALY gained (used by the SUKL regulatory body in the Czech Republic).

The comprehensive overview of the resulting ICERs is seen in the CEAC (Cost-effectiveness Acceptability Curve). It shows what percentage of simulated samples at a given threshold of willingness to pay is cost-effective. The results show that treatment with paliperidone LAI compared to oral risperidone was cost effective in 97% of the simulations according to the above considered willingness to pay.

Figure 4: CAEC



Conclusions

The health economic model calculated the costs and benefits of paliperidone LAI treatment of schizophrenia in the base case for a time horizon of 10 years. Long-term clinical data are available thus validation of the model outputs was performed. The clinical data obtained in published trials were compared to the model outputs. Validated outputs were as follows: proportion of patients continuing treatment, proportion of stable patients, QALYs, occurrence of relapses and hospitalisations. Based on clinical trials (18) the proportion of patients on treatment after 12 months was 86.1% and the model calculated this proportion as 87.9% for paliperidone LAI and 87.4% for risperidone LAI. The proportion of stable patients from the trial after 2 years was 82.7% (25) and the model showed 80% (risperidone LAI). From clinical trials the average number of relapses during 5 years was 4.08 (27), (28). The model calculated 3.69 relapses.

The model demonstrated compliance with observational data in all the validated parameters or the differences were explained. The model can thus be considered as validated. The model was also subjected to detailed analyses of sensitivity (DSA and PSA), which eliminated both parametric and methodological uncertainty.

Cost-utility analysis was performed from the payer's perspective. Patients treated with paliperidone LAI gained in average 0.903 quality adjusted life years compared to treatment with oral risperidone, which corresponds to the ICER of EUR 16,233/QALY.

Patients treated with paliperidone LAI also achieved greater adherence to treatment, thus the occurrence of relapse was lower. Administration of paliperidone LAI is, however, associated with higher treatment costs. On the other hand cost savings in hospitalisation of patients compared to risperidone amount to approximately CZK 56,000 (EUR 2,156) per patient due to a lower risk of relapse.

Paliperidone LAI enables patients suffering from schizophrenia to reduce the occurrence of adverse events and lower the risk of relapse thanks to higher adherence to treatment. This benefit is associated with significantly higher quality of life. The base case ICER or lower value of ICER was achieved in 48% of simulations in PSA and the ICER value did not exceed the willingness to pay in 97% of simulations when comparing paliperidone LAI to oral risperidone. Based on these conclusions, treatment with paliperidone LAI is considered as cost-effective from the payer's perspective.

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