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Original article

Cost effectiveness of paliperidone palmitate versus risperidone long-acting injectable and olanzapine pamoate for the treatment of patients with schizophrenia in Sweden

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Abstract

Objective:
To model the cost effectiveness of paliperidone palmitate (paliperidone long-acting injectable; PLAI), a new once-monthly long-acting antipsychotic therapy, compared with risperidone long-acting injectable (RLAI) and olanzapine pamoate (OLAI), in multi-episode patients (two or more relapses) with schizophrenia in Sweden.

Methods:
A Markov decision analytic model was developed to simulate the history of a cohort of multi-episode patients transitioning through different health states on a monthly basis over a 5-year time horizon from the perspective of the Swedish healthcare system. Therapeutic strategies consisted of starting treatment with RLAI (mean dose 37.5 mg every 2 weeks), PLAI (mean dose 75 mg equivalent (eq.) every month) or OLAI (150 mg every 2 weeks or 300 mg every 4 weeks). Probability of relapse, level of adherence, side-effects (extrapyramidal symptoms, tardive dyskinesia, weight gain and diabetes) and treatment discontinuation (switch) were derived from long-term observational data when feasible. Incremental cost-effectiveness outcomes, discounted at 3% annually, included cost per quality-adjusted life-year (QALY) and cost per relapse avoided (expressed in 2009 Swedish Krona SEK).

Results:
Relative to RLAI and OLAI, PLAI is economically dominant: more effective (additional QALYs, less relapses) and less costly treatment option over a 5-year time horizon. The results were robust when tested in sensitivity analysis.

Limitations:
The impact of once-monthly treatment on adherence levels is not yet known, and not all variables that could impact on real-world outcomes and costs were included in this model.

Conclusion:
PLAI was cost saving from a Swedish payer perspective compared with RLAI and OLAI in the long-term treatment of multi-episode (two or more relapses) schizophrenia patients.

Introduction

Schizophrenia is a chronic and debilitating psychiatric illness with a median age of onset in the early to mid-20s for men and in the late 20s for women[1].

Treatment with antipsychotic medication is recognized as an important element of relapse prevention in the management of schizophrenia[1,2].

Although the illness has a prevalence of around seven per 1000 persons worldwide[3], the treatment of schizophrenia is costly, accounting for approximately 1.5–3% of total national healthcare expenditures[4]. Relapse, especially the associated inpatient care, accounts for a significant proportion (>60%) of the direct medical costs of care[5,6]. Moreover, frequent relapse substantially increases the costs of care. Patients with prior relapse in the previous 6 months were found to have approximately three times the costs of patients without prior relapse[7]. The higher costs of relapse for these patients were associated with a greater number of hospitalizations, a longer length of stay and higher costs of outpatient services and medications[7]. Furthermore, the increased costs associated with relapse across healthcare service use may also persist at least over the subsequent 12 months[8], identifying an important long-term consequence of relapse.

It is widely accepted that not all patients take their prescribed medication all of the time. It is also recognized that the definitions of partial and non-adherence vary between studies[9]. However, in spite of this varied consensus, it has been documented that poor adherence to antipsychotic medications is widespread, and is found in approximately half of the patient population with schizophrenia[9,10]. Less favorable outcomes, including increased rates of relapse, hospitalizations and costs[11], have been consistently associated with poor adherence in patients with schizophrenia, including patients with recent-onset schizophrenia[12].

Long-acting injectables (LAIs) have been developed as an alternative to oral antipsychotics that require daily adherence for treatment efficacy. In an international, long-term, prospective, observational study of patients with schizophrenia (electronic Schizophrenia Treatment Adherence Registry [e-STAR]), 1345 patients in Spain prescribed risperidone long-acting injectable (RLAI) had improved long-term outcomes including better treatment retention (81.8% versus 63.4% on oral antipsychotics; $p<0.0001$) and greater reductions in hospitalizations (0.37 less stays per patient versus 0.2; $p<0.05$) over 24 months than patients receiving oral antipsychotics[13]. Similar outcomes with RLAI were found in 1659 patients in a combined analysis from six European countries (including Belgium, the Czech Republic, The Netherlands, Sweden, Slovakia and Spain). A total of 85% of patients remained on RLAI after 24 months of initiating therapy and greater reductions in hospitalization were found in those who remained on RLAI compared with the pre-RLAI initiation period (66.2% reduction vs. 29.2% at 12 months post-initiation)[14]. Recently, two other long-acting atypical antipsychotic therapies were approved for treatment of schizophrenia: olanzapine pamoate (olanzapine long-acting injectable [OLAI]), which is a biweekly or 4-weekly injection, and paliperidone palmitate (paliperidone long-acting injectable [PLAI]), a new once-monthly LAI antipsychotic.

First-generation antipsychotic depot formulations have been shown to be more cost effective than traditional oral neuroleptics[15]. In addition, and in line with long-term observational data, pharmacoeconomic evaluations have also demonstrated the economic benefits of RLAI versus oral atypicals or conventional depots across healthcare settings including Germany, the Netherlands, Portugal, Italy, Belgium, France, Australia, USA and New Zealand[16]. However, little is known about the relative costs and effects of newer LAI antipsychotics when compared with each other. Therefore, this study will focus on determining the cost effectiveness of the three LAI therapies available in Sweden (PLAI, RLAI and OLAI) in multi-episode patients (two or more relapses) with schizophrenia, from the perspective of the Swedish healthcare system.

Materials and methods

Model structure and design

A Markov decision analytic model was developed to simulate the history of a cohort of multi-episode patients (two or more relapses) with schizophrenia transitioning between different health states on a monthly basis over a 5-year time horizon (Figure 1). The model did not include a half-cycle correction due to the short cycle length. As Figure 1 shows, the model has eight states for every line of treatment: six stable health states with different levels of adherence and presence/absence of adverse events (AEs) (enclosed in big box) and two relapse health states, requiring or not requiring hospitalization (enclosed in smaller box). With a maximum of four treatment lines, this means that there are up to 32 states. The arrows indicate directions of transitions between health states and treatment lines. Finally, death is a terminal model state.

The Markov model provided a simple and transparent framework of the clinical course of a complex chronic disorder such as schizophrenia from which to calculate accumulated outcomes. A Markov model was deemed appropriate after review of the published models, which included both discrete event simulation (DES) and Markov models. As it was important that the model be accessible to other users a Microsoft Excel-based Markov model was selected (also see Discussion). Patients entered into the model had previously experienced at least two relapses and had received prior oral treatment from which they are able to change to a new treatment. A time-horizon of 5 years was used in the base case as it was considered to capture both longer-term benefits (>1 year) of therapy in a chronic illness while taking into

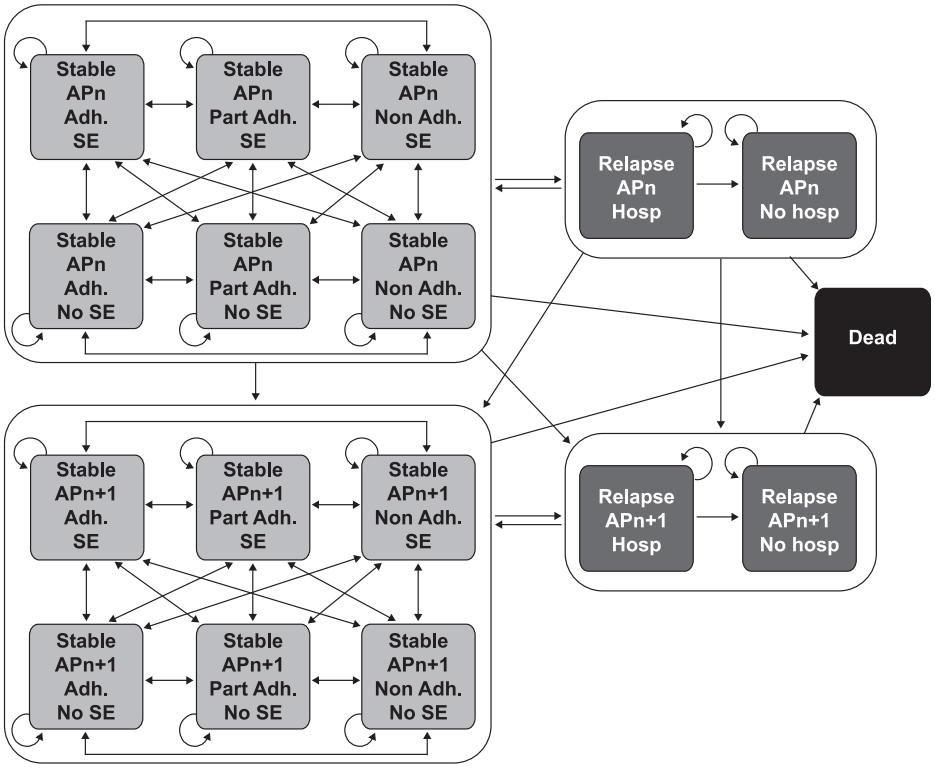

Figure 1. Markov decision analytic model simulating the history of a cohort of multi-episode (two or more relapses) with schizophrenia. The Figure depicts the first two (of a maximum of four) treatment lines. APn, initial antipsychotic; APn+1, treatment switch; Adh., adherent; Part Adh., partial adherent; Non Adh., non-adherent; Hosp, hospitalization; No Hosp, no hospitalization; SE, side-effect.

account the high switch rates observed in the treatment of schizophrenia. The model was carried out from the perspective of the Swedish healthcare system from the direct medical payer perspective. The model was programmed in Microsoft Excel 2007 supplemented by Visual Basic Application programming.

Treatment strategies

The model can accommodate up to four subsequent treatment lines, with eight possible health states for every line of treatment. The second- and third-line treatments include 15 options with which patients can be treated (split between treatments to add up to 100%). As the purpose of the model is to evaluate the cost and effects of using PLAI, RLAI or OLAI as starting treatment, the later-line treatments should be as similar as possible between arms in order to minimize confounding through costs and outcome effects that are due to differences in later-line treatment options. Based on Swedish Expert advice elicited in a Delphi panel, the second-line treatments in the model consisted of a mix of antipsychotic treatments, which were dependent upon the first-line treatment given (see Figure 2), while clozapine is the third and last line of treatment in the model. Second- and third-line treatments following OLAI were assumed to be the same as for RLAI, except that for OLAI patients, RLAI replaced OLAI in the second-line treatment (Figure 2). For the second- and third-line treatments, the model uses averages of the different treatment options and allows a split between the various second- and third-line treatment options. This split is used to calculate the weighted average of the efficacy and other parameters for the model.

Transition probabilities

The following parameters were considered to be influenced by treatment and were included in the model: probability of relapse, level of adherence, side-effects (extrapyramidal symptoms [EPS], tardive dyskinesia [TD], weight gain and diabetes) and treatment discontinuation (switch).

The probability of relapse was calculated as a product of the probability of relapse on placebo (untreated risk of relapse in the schizophrenia patient population) (P_0), treatment effect (risk ratio of relapse on the considered treatment and placebo) (α_T), and the effect of adherence level (relapse risk ratio of non- or partial adherence to full adherence) (β_C); with full adherence as the reference (β_C

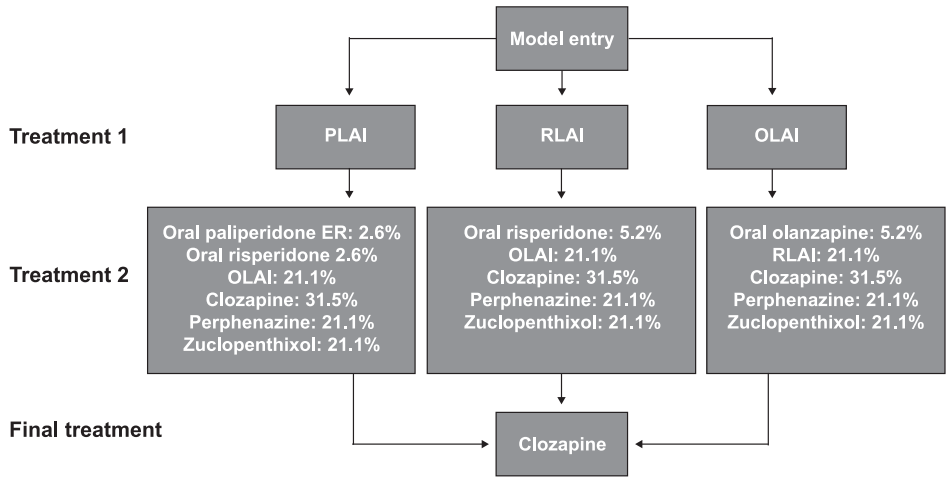

Figure 2. Treatment sequence. PLAI, paliperidone palmitate; RLAI, risperidone long-acting injectable; OLAI, olanzapine pamoate; ER, extended release.

(full adherence) = 1.00). A probability of relapse >1 was not possible in the model.

$$P(Relapse|Treatment = T, Compliance = C) = \alpha_T.\beta_C.P_0$$

The untreated risk of relapse in the schizophrenia patient population (P_0) was derived using a health technology assessment (HTA), National Institute of Health and Clinical Excellence (NICE) mixed treatment comparison (MTC), which is included in the recently updated national UK treatment and management guidelines on schizophrenia (CG82), and calculates the probability of relapse in patients with schizophrenia on placebo treatment over 52 weeks (43.6%)[2].

To ensure rates reflected true treatment efficacy (i.e., assuming full compliance), only clinical trial data were used as source. Where data were available, treatment probabilities versus placebo (α_T) were calculated based on the NICE MTC, which is based on randomized clinical studies. For products not included in the NICE MTC, calculations were based on several recently published studies[17–20], (described in Table 1). In the absence of relapse-prevention studies comparing RLAI and the common comparator (placebo), the treatment effect for RLAI versus placebo in clinical trial settings was calculated based on the Risperdal Consta Trial of Relapse Prevention and Effectiveness (ConstaTRE), a 2-year study comparing relapse rates with RLAI versus quetiapine[21]. While quetiapine was not included in the NICE MTC, a recent meta-analysis included a large unpublished study ($n = 301$), which found no difference between quetiapine and haloperidol with regard to relapse (Food and Drug Association [FDA] evaluation for quetiapine). To link the RLAI value to the NICE MTC values of the other comparators, the annualized RLAI/quetiapine ratio from ConstaTRE was multiplied by the NICE MTC annual relapse ratio versus placebo of haloperidol, applying the principle of indirect comparison[22] (see detailed formula in Table 1).

The clinical trial treatment effect for PLAI was assumed equivalent to RLAI based on non-inferiority results from a 13-week randomized, double-blind comparative study of flexible doses of PLAI and RLAI[23]. A 24-week, randomized, double-blind trial found that OLAI was efficacious in maintenance treatment of schizophrenia for up to 24 weeks, with a safety profile similar to oral olanzapine except for injection-related AEs[18].

The effect of adherence on risk of relapse (β_C) was based on a study by Gilmer *et al.*, a retrospective analysis of US pharmacy claims data that evaluated the relationship between adherence to medication and hospitalizations[10]. In the study, a person-year's adherence was categorized based on the cumulative medication possession ratio using the following designations: non-adherent (ratio = 0.00–0.49), partially adherent (ratio = 0.50–0.79), adherent (ratio = 0.80–1.10), and excess medication fillers (ratio >1.10). The relapse risk ratio by level of adherence (β_C) was calculated as the ratio of the annual hospitalization rates by adherence category (34.9% in non-adherent patients, 24.1% in partially adherent, 24.8% in excess fillers and 13.5% in adherent patients)[10]. Excess fillers and partially adherent patients were grouped in the model, as they both represented partial adherence to the appropriate prescription and have a similar risk of psychiatric hospitalization (Table 1). In the model, the concept of partial adherence with an LAI would indicate that a patient failed to attend an injection visit at the appropriate dosing schedule, e.g. there was a delay beyond flexible dosing windows as clinically recommended.

The baseline proportion of adherent (41%), partially adherent (16% + 19% = 35%) and non-adherent (24%)

Table 1. Clinical input values.

Parameters	Value	Data/comment
Risk ratio of relapse versus placebo (1 year)		
PLAI	0.33	Assumed non-inferior to RLAI (PSY-3006)[23]
RLAI	0.33	RLAI/quet (ConstaTRE)[17] *oral typical[2]; quet=haloperidol (relapse)[26] $\left(1-\left(1-\frac{54}{327}\right)^{\frac{364}{483.76}}\right)\Big/\left(1-\left(1-\frac{102}{326}\right)^{\frac{364}{400.65}}\right)=0.44\rightarrow 0.44\times 0.76=0.33$ Where 0.44 is the RLAI/quetiapine ratio from the ConstaTRE study[17] and 0.76 is the relapse rate for haloperidol[26]
OLAI	0.46	Non-inferior efficacy to oral olanzapine[18]
Oral olanzapine	0.46	52-week probability of relapse/placebo probability of relapse[2]
Oral risperidone	0.63	52-week probability of relapse/placebo probability of relapse[2]
Oral paliperidone ER	0.37	52-week probability of relapse/placebo probability of relapse[2]
Perphenazine	0.76	Assumed similar to oral typical[2]; meta analysis[19]
Zuclopenthixol	0.63	Similar to oral risperidone[2]; meta analysis[20]
Clozapine	0.76	1.00 RR clozapine vs. haloperidol studies meta-analysis[26]; relapse prevention of 'oral typical' versus placebo[2]
Placebo	1.00	Reference
Risk ratio of relapse by level of adherence		
Adherent (reference)	1.00	Probability of relapse in adherent patients, 13.5%[10]
Partially adherent	1.81	(Probability of relapse in, partially adherent + excess filler)/ adherent = [24.1% * 0.16 + 24.8% * 0.19)/0.35]/ 13.5%[10]
Non-adherent	2.59	Probability of relapse in non-adherent, 34.9%/adherent, 13.5%[10]
Duration of relapse		
Relapse req. Hosp: *Acute psychiatric ward*	66.4	Days, Swedish national inpatient care statistics[27]
Relapse not req. Hosp: *Community*	30	Days, assumption
Probabilities of patients with side-effects (1-year)		
EPS		
PLAI	9.3%	PLAI/RLAI EPS AEs (PSY-3002[28] 53-week data on file) *RLAI[29]
RLAI	12.6%	RLAI/oral olanzapine[30] *annualized oral olanzapine[29]
OLAI	7.6%	Equal to oral olanzapine (no significant differences)[31]
Oral olanzapine	7.6%	Annualized oral olanzapine[29] (14.7% est. 2.02 years)
Oral risperidone	18.2%	Annualized oral risperidone[29] (32.2% est. 1.94 years)
Oral paliperidone ER	11.4%	OR paliperidone / OR risperidone[2] *annualized oral risperidone[29]
Perphenazine	19.7%	Annualized oral typical[29] 31.4% est. 1.71 years)
Zuclopenthixol	19.7%	Annualized oral typical[29] 31.4% est. 1.71 years)
Clozapine	8.8%	Annualized clozapine[29] (17.2% est. 2.04 years)
TD		
PLAI	0.3%	PSY-3001[32]
RLAI	1.2%	Rate at 50 weeks, open-label clinically stable patients[33]
OLAI	3.0%	Equal to oral olanzapine (no significant differences)[31]
Oral olanzapine	3.0%	Annualized oral olanzapine[29] (5.9% est. 2.02 years)
Oral risperidone	4.1%	Annualized oral risperidone[29] (7.8% est. 1.94 years)
Oral paliperidone ER	4.1%	Assumed equal to oral risperidone[2]
Perphenazine	5.2%	Annualized oral typical[29] 8.7 %(est. 1.71 years)
Zuclopenthixol	5.2%	Annualized oral typical[29] 8.7% est. 1.71 years)
Clozapine	3.1%	Annualized clozapine[29] (6.2% est. 2.04 years)
Weight gain (≥7%)		
PLAI	8.5%	PLAI/RLAI (PSY-3002[28] 53-week data on file) *RLAI[24]
RLAI	9.1%	RLAI/oral olanzapine[30] *annualized oral olanzapine[29]
OLAI	16.3%	Equal to oral olanzapine (no significant differences)[18]
Oral olanzapine	16.3%	Annualized oral olanzapine[29] (30.1% est. 2.02 years)
Oral risperidone	12.0%	Annualized oral risperidone[29] (22.0% est. 1.94 years)
Oral paliperidone ER	11.7%	Annualized oral paliperidone ER/annualized oral olanzapine[34] *oral olanzapine[29]
Perphenazine	9.5%	Annualized oral typical[29]15.7% (est. 1.71 years)
Zuclopenthixol	9.5%	Annualized oral typical[29] 15.7% (est. 1.71 years); meta-analysis confirms not significantly different from other typicals
Clozapine	12.6%	Annualized clozapine[29] (24.1% est. 2.04 years)
Diabetes		
PLAI	1.6%	Average of (NICE diabetes[2]/weight gain) risk ratios *risk of weight gain (PLAI)[28]
RLAI	1.7%	Average of (NICE diabetes[2]/weight gain) risk ratios *risk of weight gain (RLAI)
OLAI	4.2%	Equal to oral olanzapine (no significant differences)[18]

(continued)

Table 1. Continued.

Parameters	Value	Data/comment
Oral olanzapine	4.2%	Probability of diabetes – 1st year of initiation[2]
Oral risperidone	2.1%	Probability of diabetes – 1st year of initiation[2]
Oral paliperidone ER	2.1%	Probability of diabetes – 1st year of initiation[2]
Perphenazine	2.0%	Oral typical; probability of diabetes – 1st year of initiation[2]
Zuclopenthixol	2.0%	Oral typical; probability of diabetes – 1st year of initiation[2]
Clozapine	2.4%	Average of (NICE diabetes[2]/weight) ratios *weight (clozapine)

PLAI, paliperidone palmitate; RLAI, risperidone long-acting injectable; ConstaTRE, Risperdal Consta Trial of Relapse Prevention and Effectiveness; OLAI, olanzapine pamoate; ER, extended release; RR, relative risk; EPS, extrapyramidal symptom; AE, adverse event; OR, odds ratio; TD, tardive dyskinesia; est, estimated mean treatment duration; NICE, National Institutes of Clinical Excellence; MTC, mixed treatment comparison; OLE, open-label extension; DOF, data on file.
*means multiplication

patients were also based on the Gilmer *et al.* study[10], increasing internal consistency. No data were found in the literature on levels of adherence in a Swedish population, however, these estimates were consistent with other studies[24] including studies in Canadian patients[25] and recent-onset Norwegian patients[12].

To calculate the treatment-specific levels of adherence (Table 2), the patient population adherence level was adjusted by differential adherence between atypicals, typicals and clozapine for second- and third-line treatments based on the Gilmer *et al.* study: 0.91 for typical versus atypicals, and 1.48 for clozapine versus atypicals. For RLAI, the differential adherence between RLAI and oral atypicals (1.29) was calculated based on retention rates over 24 months' observation in e-STAR, a prospective, observational study of patients designed to evaluate long-term treatment outcomes in routine clinical practice[13,35]. For PLAI, conservatively, a 0.05 improvement in level of adherence over bi-weekly LAI was assumed in the base case and tested in sensitivity analysis. In order to reflect treatment outcomes in patients with at least two prior relapses, all adherence data are based on claims data reflective of a general schizophrenia population[10,36] or observational studies in patients with an average of 10 or more years of disease history[13,29,35].

To calculate the treatment-specific levels of non-adherence (Table 2), the patient population non-adherence level was adjusted by differential non-adherence for second- and third-line treatments based on the reported discontinuation rates for lack of compliance (hazard ratios [HR]) in a large 3-year observational study in ten European countries ($n = 7728$) (Schizophrenia Outpatient Health Outcome [SOHO] study)[29]. Since RLAI was not included in the SOHO study, for RLAI, the ratio of non-adherence between RLAI and oral atypicals (0.17) was calculated based on discontinuation from oral antipsychotics versus RLAI by reason for discontinuation (compliance) over 24 months in Spanish e-STAR data: HR = 5.99[35]. Similarly, given the opportunity for non- and partial adherence decreases with a once-monthly versus a twice-weekly treatment administration, the once-monthly dosing of PLAI was assumed likely to improve real-world adherence. Conservatively, a 0.05 reduction in level of non-adherence was assumed in the base case and tested in sensitivity analysis. For OLAI, strict monitoring requirements post-injection were assumed to result in a 0.05 reduction in adherence. The probability of adherence (or non-adherence) of a specific treatment was calculated as the risk ratio of treatment adherence (or non-adherence) (Table 2) multiplied by the reference probability of adherence (41%) (or non-adherence [24%]).

For example, the annual probability of a relapse when partially compliant to oral risperidone is 43.6% * 0.63 * 1.81 = 0.497, where 43.6% is the annual probability for a relapse on placebo[2], 0.63 is the relative annual risk for a relapse on risperidone (when fully compliant) compared to placebo[2], and 1.81 is the risk ratio of relapse when partially compliant compared to full compliance on atypicals[10]. After the calculation of annual probabilities, these were adjusted to monthly probabilities, e.g. 1 – (1 – 43.6% * 0.63 * 1.81)^(1/12).

Hospitalizations

In the model, to distinguish between relapses requiring and not requiring hospitalization, the proportion of relapses requiring hospitalizations was specified. In the absence of data from a Swedish patient population, the base-case analysis used data from a UK study in 145 randomly selected chronic patients with schizophrenia[37]. Relapse in this study was identified retrospectively as the re-emergence or aggravation of psychotic symptoms for at least 7 days during the past 6 months. Of those patients who had relapsed, 63% had been admitted to hospital during the 6-month observation period.

Swedish national inpatient care statistics include length-of-stay data for all available inpatient ICD-10 diagnoses[38]. For patients with a schizophrenia diagnosis (F20) these data suggest that the average hospitalization duration is 66.4 days[27] (Table 1). In the absence of data, the duration of a relapse not requiring hospitalization was

Table 2. Level of adherence by treatment.

Parameters	Value	Data source/comment
Risk ratio of adherence		
PLAI	1.34	5% improvement factor in adherence (once-monthly versus twice-weekly LAI)[36]
RLAI	1.29	Ratio of retention rates (RLAI/oral atypicals)[13]
OLAI	1.24	Assumes 3-hour post-injection monitoring reduces adherence by 5%
Oral olanzapine	1.00	Equal to 'other atypical'[10]
Oral risperidone	1.00	Equal to 'other atypical'[10]
Oral paliperidone ER	1.00	Equal to 'other atypical'[10]
Perphenazine	0.91	Ratio of retention rates (oral typicals/'other atypical')[10]
Zuclopenthixol	0.91	Ratio of retention rates (oral typicals/'other atypical')[10]
Clozapine	1.48	Ratio of retention rates (clozapine/'other atypical')[10]
Reference ('other atypical')	1.00	41% adherent[10]
Risk ratio of partial adherence (1 – [probability of adherence + probability of non-adherence])		
PLAI	1.21	
RLAI	1.23	
Oral olanzapine	1.00	
Oral risperidone	0.79	
Oral paliperidone ER	0.79	
Clozapine	0.49	
Reference ('other atypical')	1.00	
Risk ratio of non-adherence		
PLAI	0.12	5% improvement factor in adherence (once-monthly versus twice-weekly LAI)
RLAI	0.17	1/HR orals versus RLAI: disc. for compliance issues[35]
OLAI	0.22	Assumes 3-hour post-injection monitoring reduces adherence by 5%
Oral olanzapine	1.00	Olanzapine oral HR for disc – lack of compliance[29]
Oral risperidone	1.31	Risperidone oral HR for disc – lack of compliance[29]
Oral paliperidone ER	1.31	Risperidone oral HR for disc – lack of compliance [29]
Perphenazine	1.58	Oral typical HR for disc – lack of compliance[29]
Zuclopenthixol	1.58	Oral typical HR for disc – lack of compliance[29]
Clozapine	0.92	Clozapine HR for disc versus lack of compliance[29]
Reference ('other atypical')	1.00	24% non-adherent[10]

PLAI, paliperidone palmitate; RLAI, risperidone long-acting injectable; OLAI, olanzapine pamoate; ER, extended release; LAI, long-acting injectable; EFESO, Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapina; disc, discontinuation; HR, hazard ratio.

estimated to be 1 month (30 days), the duration of one cycle in the model.

Side-effects

Four treatment side-effects (EPS, TD, weight gain and diabetes) were included in the model as they generate additional healthcare resource utilization and impact patients' health-related quality of life (HRQoL)[37,39].

To be reflective of real-world clinical outcomes and a broad schizophrenia population, the large ten European country 3-year observational study ($n = 7728$) conducted by Haro *et al.* was selected as the primary source for side-effect input data for available treatments (Table 1) rather than short-term clinical trial data[29].

To improve comparability with the treatment data from Haro *et al.*, the proportion of patients with EPS over 1 year for RLAI was calculated based on the EPS ratio of RLAI to oral olanzapine in Keks *et al.* multiplied by the annualized oral olanzapine value from Haro and colleagues' observational study[29,30]. The same approach was used to estimate the proportion of patient with weight gain >7%. For PLAI, the EPS and weight gain (≥7%) side-effect rates relative to RLAI from a 53-week randomized comparative study[28] were used, multiplied by the calculated value for RLAI (Table 1). While this study did not initiate treatment with PLAI in accordance with the approved FDA and EU label, this approach is more conservative (yields less of a difference between PLAI and RLAI): instead of 6% from the 52-week open-label extension (OLE) for EPS[32] for PLAI, conservatively, the adjusted baseline value for PLAI EPS was 9.3%.

No incidence of TD occurred in either the PLAI or RLAI arm of the 52-week comparative study[28], however, instead of using 0% for the baseline side-effect rate, conservatively, data from a 52-week OLE study (0.26%)[40] for PLAI and data from a 50-week open-label study designed to assess TD for RLAI (1.20%) was used[33] (Table 1). This value for RLAI (1.20%)[33] was consistent with the rate of TD in Keks and colleagues' study for patients receiving RLAI (1.25%)[30].

For the proportion of patients with diabetes, in absence of data in Haro *et al.*, the NICE MTC values for probability of diabetes (first year of initiation) of a particular

Table 3. Proportion of patients switching medication by reason for discontinuation (1 year).

	Proportion of patients switching medication due to:				
	Lack of efficacy	Intolerability/ side-effects	Lack of compliance	Patient request	Source
PLAI	7.3%	1.4%	0.7%	3.3%	RLAI values adjusted by PLAI/RLAI ratios†
RLAI	7.3%	2.0%	0.9%	3.3%	Ratio of annualized RLAI/oral atypical discontinuation rates (per reason)[35] *oral atypical discontinuation rates (per reason)[29]
OLAI	6.6%	2.2%	0.7%	4.0%	Equal to oral olanzapine except for discontinuation due to lack of compliance (*risk of non-compliance)
Oral olanzapine	6.6%	2.2%	3.1%	4.0%	Annualized oral olanzapine[29]
Oral risperidone	8.2%	3.5%	4.3%	4.3%	Annualized oral risperidone[29]
Oral paliperidone ER	8.2%	3.5%	4.3%	4.3%	Annualized oral risperidone[29]
Perphenazine	13.9%	3.6%	4.5%	6.3%	Lack of compliance: annualized perphenazine[29]; other reasons: annualized perphenazine/oral olanzapine discontinuation hazard ratio from CATIE data[42] *oral olanzapine discontinuation rate
Zuclopenthixol	12.8%	4.6%	4.5%	6.0%	Annualized oral typical[29]
Clozapine	6.3%	2.5%	3.1%	2.1%	Annualized clozapine[29]

†Risk of relapse ratio for discontinuation due to lack of efficacy, average of PLAI to RLAI side-effects for discontinuation due to intolerability/side-effects, risk of non-compliance for discontinuation due to lack of compliance. Assumed equivalent discontinuation due to patient request.
PLAI, paliperidone palmitate; RLAI, risperidone long-acting injectable; OLAI, olanzapine pamoate; ER, extended release; CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness.
*means multiplication

antipsychotic were used for second- and third-line treatments where available. For all other treatments, the probability of diabetes was calculated based on the average of the ratios of NICE diabetes rates to weight gain rates of the available treatments, multiplied by the weight gain value for the specific medication (Table 1).

For OLAI, based on the European Medicines Agency (EMA) summary of product characteristics safety assessment stating similarity of adverse reactions with oral olanzapine, the same rates as for oral olanzapine were used for all AEs included in the model[31].

The duration of EPS and TD in the model were based on an analysis of the 3-year prospective observational study[29] of more than 10,000 patients in Europe with schizophrenia, which found the cumulative persistence rate of EPS was 82% and 80% for TD over a period of 2 years[41]. Therefore, the duration of EPS and TD was assumed to last for 2 years. Weight gain and diabetes were assumed to be permanent (i.e., the patient continued to have the side-effect until the end of the model time-horizon).

Treatment switch rates

To more closely reflect real-world clinical outcomes and to increase internal consistency, the same source of the side-effect values, the large European 3-year observational (SOHO) study[29], was used as the primary source for treatment switch data (Table 3). This study provides comparative probabilities of discontinuing treatments over a relatively long observation period (2–3 years) as well as specific reasons for discontinuation including lack of efficacy, intolerability, lack of compliance and patient request. To convert probabilities over 3 years into annual probabilities, the probability of discontinuation was assumed constant over time:

$$PX, T, Annual = 1 - (1 - PX, T, 3 - Year)^{1/3}$$

For RLAI, the source of switch data was based on the reasons for discontinuation during the 24-month e-STAR study – the Spanish arm of this study compared RLAI versus oral antipsychotics[35]. To ensure consistency with other treatment data derived from the large European observational study[29], the ratio of annualized RLAI (e-STAR) to annualized oral atypical (e-STAR) discontinuation rates (for insufficient response, tolerability and AEs, compliance issues and patient choice) were multiplied by oral atypical[29] values (Table 3).

Studies have indicated that discontinuation rates for clinical trials are often higher than naturalistic studies (e.g., Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE][42] versus SOHO[29]), which could likely be due to differences in patient populations and other protocol-driven factors. Therefore, with the exception of perphenazine (values were partly based on CATIE data) discontinuation data from randomized, double-blind clinical trials were not used in the model to calculate real-world treatment switch data. For paliperidone extended release (ER), in the absence of long-term naturalistic data regarding discontinuation, rates for oral risperidone were used. For PLAI, the proportion of patients discontinuing due to lack of efficacy was calculated as the proportion discontinuing due to lack of efficacy for RLAI adjusted by the ratio of PLAI to RLAI risk of relapse (7.3% * [0.33/0.33]). Similarly, the proportion of patients discontinuing due to tolerability or side-effects was

Table 4. Utility scores.

Health states	Mean utility	Source
Stable (no side-effects)	0.919	Elicited from patient sample[44]
Relapse (not req. hospitalization)	0.762	Mid-point between utilities for stable and relapse (requiring hospitalization)
Relapse (req. hospitalization)	0.604	Elicited from patient sample[44]
Dead	0.000	
Utility decrements for SEs		
Acute EPS	0.197	Elicited from patient sample (0.919–0.722)[44]
TD	0.197	Assumed = EPS
Weight gain	0.094	Elicited from patient sample (0.919–0.825)[44]
Diabetes	0.150	Elicited from patient sample (0.919–0.769)[44]

SE, side-effects; EPS, extrapyramidal symptom; TD, tardive dyskinesia.

calculated as the RLAI rate adjusted by the average of PLAI to RLAI side-effects ratios (2.0% * [average of (9.3%/12.6%), (0.26%/1.2%), (8.5%/9.1%), (1.6%/1.7%)]) and for the discontinuation due to lack of compliance: the RLAI rate (0.922%) adjusted by the PLAI to RLAI non-adherent risk ratio (0.12/0.17). Discontinuation due to patient request was assumed equivalent between RLAI and PLAI in the absence of relevant proxy information. These derived values for PLAI were very similar to discontinuation rates from the 52-week OLE data (5.7% discontinuation due to lack of efficacy, 1.5% due to AEs, 5.2% other)[32].

To calculate the probability of switch for each treatment based on health states, the following assumptions were made:

- Patients in any health state may switch treatment due to patient request
- Partially adherent or non-adherent patients may, in addition, switch due to lack of compliance
- Patients with side-effects may, in addition, switch due to intolerability
- Patients in the relapse state may, in addition, switch due to lack of efficacy

Mortality

Standardized mortality ratios (SMR) were derived from a 12-year Swedish mortality study for patients with schizophrenia which found a SMR of 2.8 in males and 2.4 in females[43]. The SMR observed in individuals with schizophrenia was multiplied by the age- and gender-specific mortality rates for adults in the Swedish general population to predict the number of deaths in patients with schizophrenia.

Utility estimates

Utility data for health states were obtained from a study eliciting values using a time trade-off (TTO) instrument administered by interview to 49 stable patients with schizophrenia in the UK and 75 lay persons (Table 4)[44]. No similar utility data elicited from Swedish patients were found in the literature. Utility values from the stable schizophrenia patients were used in the model in accordance with the general guidance for economic evaluations from the Pharmaceutical Benefits Board[45] where appraisals of persons in the health condition are preferred. Utility scores represent the HRQoL associated with specific health states on a scale from zero (death) to one (perfect health). The utility scores were multiplied by the cumulative time spent in each health state to provide an estimate of quality-adjusted life-years (QALYs). The presence of common side-effects relating to antipsychotic medication (EPS, TD, weight gain and diabetes) were taken into account in both the stable and relapse states by calculating utility decrements (absolute difference between the utility associated with stable schizophrenia and side-effect) and applying to the average duration of each side-effect. In the absence of published data, the utility for the relapse state not requiring hospitalization was calculated as the midpoint between stable and relapse with hospitalization. Conservatively, this is likely an underestimation of the utility decrement for this health state since the stable state was considered to have the highest utility by the respondents. The utility decrement for TD was assumed equal to EPS.

Resource use

Resource use is accumulated based on the time spent in different health states. Data on outpatient care resource use were obtained from Almond and colleagues' study[37], a 6-month comparison of UK patients who experienced a relapse in schizophrenia with a control group who did not relapse. To calculate the mean resource use over 1 month, the 6-month mean usage in Almond *et al.* was assumed constant over time (Table 5). The ambulatory care and additional resource used to manage side-effects relevant for the treatment of schizophrenia in the Swedish setting was included to account for side-effects management in clinical practice (Table 6). Information on

Table 5. Mean resource use – ambulatory care for schizophrenia by health state.

Resource use	Stable over 6 months (per month)	Relapse, not requiring hospitalization over 6 months (per month)
Psychiatric visit – outpatient	1.4 (0.233)	2.1 (0.350)
Psychiatrist – home visit	2.5 (0.417)	2.3 (0.383)
Primary care physician visit	1.8 (0.300)	1.6 (0.267)
Psychiatric nurse visit	12.6 (2.100)	5.2 (0.867)
Occupational therapist	0.0	0.8 (0.133)
Social worker visit	0.1 (0.017)	0.4 (0.067)
Group therapy	0.4 (0.067)	0.1 (0.017)
Community mental health center visit	2.4 (0.400)	1.4 (0.233)
Day hospital visit	2.3 (0.383)	2.1 (0.350)

Source: Adapted from Almond *et al.*, 2004[37] (mean usage/6 months, monthly rates in brackets).

Table 6. Mean resource use for the management of side-effects.

Management of side-effects	Side-effect	Resource use
Psychiatrist – consultant	Any	1.0 (0.167 per month)
Primary care physician	Any	2.0 (0.333 per month)
Nutritionist/dietician	Weight gain	0.6 (0.1 per month)
Laboratory test for cholesterol	Weight gain	0.5 (0.083 per month)
Laboratory test for glycemia associated with diabetes	Diabetes	0.5 (0.083 per month)
Pharmacological management for EPS (days of treatment)	EPS	30
Pharmacological management for diabetes (month of treatment)	Diabetes	1

Source: Assumptions from NICE guidelines, 2010[2].
EPS, extrapyramidal symptoms.

Table 7. Mean daily doses and drug cost per unit.

	Mean dose per day (mg)*	Cost per unit (SEK/mg)	Source/comment
PLAI	2.5	44.33	Assumed to have the same price/mg as RLAI†
RLAI	2.7	44.33	Derived from price for 37.5 mg RLAI†
OLAI	10.0	7.82	Average of unit prices for OLAI 210 mg, 300 mg and 405 mg
Oral olanzapine	10.0	4.47	Derived from price for 10 mg, 56 tablets package†
Oral risperidone	5.0	2.78	Average unit prices derived from prices of 60 tablet packages of 2 mg and 3 mg risperidone†
Oral paliperidone ER	6.0	5.90	Derived from price for 6 mg, 56 tablets package†
Perphenazine	30.0	0.36	Average of unit prices derived from prices of 100 tablet packages with 2 mg and 8 mg†
Zuclopenthixol	30.0	0.23	Average of unit prices derived from prices of 100 tablet packages with 2 mg, 10 mg and 25 mg†
Clozapine	300	0.06	Average of unit prices derived from prices of 100 tablet packages with 25 mg and 100 mg†

*World Health Organization defined daily dose, available at http://www.whocc.no/atc_ddd_index/[47].
†All prices per unit are derived from official published prices on the TLV website, except PLAI which was assumed to have the same price/unit as RLAI.
PLAI, paliperidone palmitate; RLAI, risperidone long acting injectable; OLAI, olanzapine pamoate; ER, extended release.

inpatient resource use (duration of inpatient care) was derived from Swedish national data (see earlier section: Hospitalization).

Drug costs

In the absence of utilization data of a new treatment, the average monthly maintenance dose of PLAI was 75 mg eq. in accordance with the FDA recommended label maintenance dose and the EMA SmPC[21,46]. The mean maintenance dose of RLAI (37.5 mg/2 weeks) was based on the defined daily dose as defined by the World Health Organization (2.7 mg/day)[47] and this was in line with the recommended doses in order to achieve a similar drug exposure. Drug costs were calculated assuming cost parity to RLAI at a per-mg level (Table 7). Drug costs per unit were derived from the Swedish Pharmaceutical Benefits Agency, TLV[48].

Table 8. Resource use unit costs (direct medical perspective).

Services	Unit cost (in SEK 2009)	Inflation rate (%)
Inpatient care		
Acute psychiatric ward (per day)[a]	6112	
Ambulatory care		
Psychiatrist – outpatient[b]	2114	4.46
Psychiatrist – home visit[c]	4230	0.00
Primary care physician[b]	878	4.46
Psychiatric nurse[b]	1391	4.46
Occupational therapist[b]	1155	0.00
Social worker[c]	358	4.46
Group therapy[c]	1666	0.00
Sheltered workshop[d]	572	0.00
Community mental health center visit[d]	572	0.00
Day care center visits[d]	572	0.00
Home help/care worker[b]	358	4.46
General medical ward (days)[b]	4438	4.46
Day hospital visit[e]	1923	0.00
Management of side-effects		
Nutritionist/dietician	1961[c]	—
Laboratory tests for cholesterol associated with weight gain[e]	47	0.00
Laboratory test for glycemia associated with diabetes[e]	18	0.00
Pharmacological management for acute EPS (day of treatment)[e]	2.67	0.00
Pharmacological management for diabetes without complications (month of treatment)[f]	225.50	0.00

Data sourced from: [a]Södra sjukvårdsregionen, Price list for University Hospital in Malmö 2006 (+3.4% inflation); [b]Regional prices and reimbursement for the Southern Health Care region 2008. Division 7, Psychiatry Lund (+4.46%); [c]Regional prislista för Uppsala-Örebroregionen 2009; [d]Landstinget Dalarna, Prislista 2009; [e]Regionala priser och ersättningar för Södra sjukvårdsregionen 2009; [f]Ringborg *et al.*, 2007[50].
EPS, extrapyramidal symptoms.

Resource use unit costs

Resource unit costs are expressed in SEK 2009 values (Table 8). The inflation rates were calculated from Statistika centralbyrån[49], using the rate for health goods for November 2009.

Discounting and sensitivity analysis

In accordance with the general guidance for economic evaluations from the Pharmaceutical Benefits Board[45], in the base case analysis, both costs and health effects were discounted by 3%. In order to evaluate the effect of the use of different discount rates for cost and effects on outcomes, a sensitivity analysis calculation was carried out using 0% for cost and 5% for health effects, as well as a calculation where the costs were discounted by 3% and health effects by 0%[51].

The incremental cost-effectiveness ratio (ICER) is calculated on the basis of total incremental drug costs and effects, and reflects the ratio of the difference in costs of a therapeutic intervention (here PLAI) compared with the alternative (RLAI or OLAI) divided by the difference in effects, i.e. the additional cost per additional unit of effect (if an intervention is dominant (less costly and more effective), an ICER is not calculated). The sensitivity of the base case results to input parameters was explored by deterministic sensitivity analysis (DSA) by varying key clinical and economic parameter estimates within ranges reflecting possible parameter values. The following one-way sensitivity was tested in the analysis:

- Proportion of relapses requiring hospitalization (±25%)
- Frequency of relapse (±25%)
- Average duration of relapse (requiring and not requiring hospitalization) (±25%)
- Level of adherence by treatment arm (PLAI = RLAI or = OLAI)
- Side-effects (PLAI = RLAI)
- Switch rates (PLAI = RLAI or = OLAI)
- Drug cost (±10%, +20%)
- Inpatient cost (±25%)
- 0%, 5% and 3%, 0% discounting (costs, effect)

In order to limit the number of analyses in the DSA, utilities were not included there but were included in the probabilistic sensitivity analyses (PSA). PSA on the ICER were run using 1000 simulations. Parameters included in the PSA were the following: probabilities of adherence, relapse and side-effects by treatment; effect of adherence on the probability of relapse; probability of hospitalization in case of relapse; average duration of relapse and time spent in hospital; health state utilities and utility decrement associated with side-effects; switch rates by reason,

Table 9. QALYs and costs (SEK, %) per patient over 5 years.

Values per patient over 5 years	PLAI	RLAI	OLAI
Antipsychotic acquisition costs; SEK (%)	160,011 (17.5)	168,389 (18.0)	114,481 (11.8)
Schizophrenia-related costs; SEK (%)			
Stable	380,281 (41.7)	379,602 (40.7)	374,671 (38.7)
Relapse	4633 (0.5)	4793 (0.5)	5952 (0.6)
Side-effects costs; SEK (%)	1989 (0.2)	2349 (0.3)	3088 (0.3)
Hospitalization costs; SEK (%)	365,805 (40.1)	378,449 (40.5)	470,370 (48.6)
Total; SEK	912,719	933,581	968,591
Total costs, SEK discounted (3%)	858,830	878,461	911,556
QALYs, discounted 3% (base case)	3.92	3.84	3.76
QALYs, per patient, undiscounted (sensitivity analysis)	4.15	4.06	3.98
QALYs, discounted 5% (sensitivity analysis)	3.78	3.70	3.68
Relapses, discounted 3% (base case)	1.37	1.41	1.76
Relapses, per patient, undiscounted (sensitivity analysis)	1.46	1.51	1.87
Relapses, discounted 5% (sensitivity analysis)	1.31	1.36	1.69

PLAI, paliperidone palmitate; RLAI, risperidone long-acting injectable; OLAI, olanzapine pamoate.
QALY, quality-adjusted life-year.

for PLAI; unit costs associated with hospitalizations; and number of workdays lost per month, by health state and treatment. The uncertainty in each probability and utility is assumed to possess a probability distribution and uncertainty in all values is considered simultaneously. Cost-effectiveness planes were used to present the results of the PSA.

Results

Based on the model and input variables, patients receiving PLAI had lower total costs per patient and were associated with better outcomes (more QALYs, fewer relapses) over the 5-year time-horizon (Table 9).

The overall total cost per treatment arm was largely attributed to the cost of hospitalizations (accounting for 40.1% of the total cost of PLAI, 40.5% of the total cost of RLAI) and 48.6% of the total cost for OLAI (Table 9).

Incremental cost effectiveness of the comparators

The base-case analysis showed that PLAI is economically dominant relative to RLAI and OLAI because it is a more effective treatment (more QALYs; versus RLAI 0.083; vs. OLAI: 0.161 with fewer relapses: vs. RLAI: 0.047; vs. OLAI: 0.392). PLAI is also a less costly treatment option over a 5-year time-horizon (versus RLAI: SEK −19,631; vs. OLAI: SEK −52,726). An incremental cost-effectiveness ratio is therefore not needed and has not been calculated for comparison of the products in this analysis (online supplement, OS Table 1).

Sensitivity analyses

Results of the sensitivity analyses generally confirmed the robustness of the model to variation in the input parameters (online supplement, OS Table 1).

The one-way sensitivity analyses support the base-case analyses demonstrating that PLAI is dominant (provides greater effectiveness and is also cost saving). The number of QALYs was most sensitive to side-effect assumptions; however PLAI remained the dominant treatment option when equivalence was assumed with RLAI. Changing the level of adherence and proportion of patients switching medication had the greatest impact on relapses avoided. However, when assuming no difference between PLAI and RLAI, or no difference between PLAI and OLAI, PLAI as a starting treatment remained the dominant treatment option in terms of QALYs gained and/or relapses avoided. When assuming a 20% higher PLAI price, PLAI remained dominant versus OLAI and cost effective, but no longer dominant, versus RLAI, with incremental cost-effectiveness ratios of SEK 110,337/QALY gained and SEK 194,851/relapse avoided.

Figure 3 presents the results of the PSA comparing the cost effectiveness of PLAI versus RLAI for QALYs gained and relapses avoided. In the majority of simulations (67% of 1000 simulations), PLAI was more cost effective than RLAI. Conversely, RLAI was the dominant option in 3.6% of cases. Moreover, applying a cost-effectiveness threshold of SEK 300,000 per QALY (approximately £26,500 or €31,000), the probability of cost effectiveness was 86% for PLAI. Similar results were observed for relapses avoided, with PLAI dominating RLAI in 69% of simulations and showing a 79% probability of cost effectiveness at a threshold of SEK 300,000 per QALY.

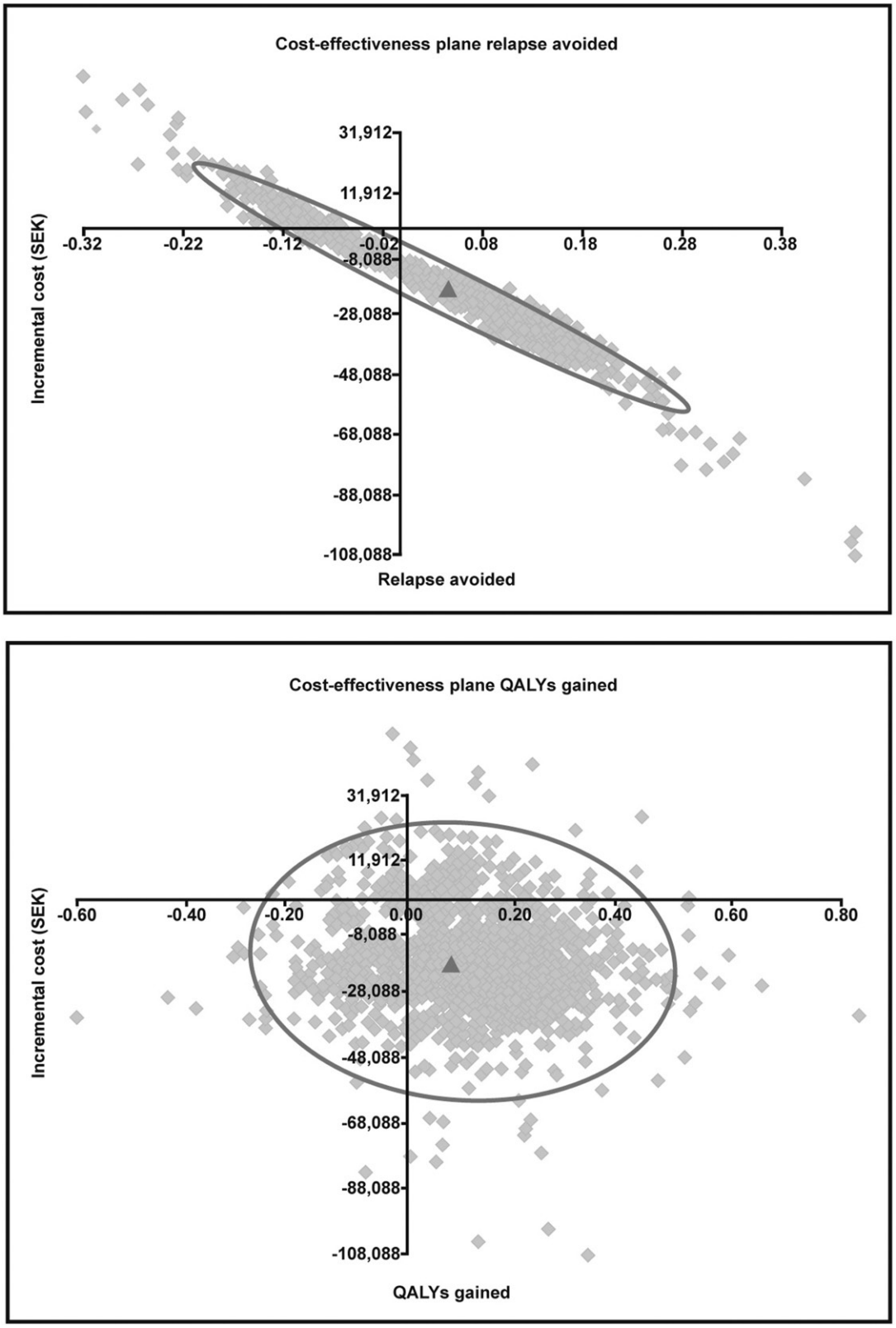

Figure 3. Cost-effectiveness plane (QALYs gained and relapses avoided), PLAI versus RLAI. Solid lines depict the 95% confidence interval; solid triangles depict the base-case values. QALY, quality-adjusted-life-year; PLAI, paliperidone palmitate; RLAI, risperidone long-acting injectable.

Figure 4 represents the results of the PSA comparing the cost effectiveness of PLAI versus OLAI for QALYs gained and relapses avoided. In 91% of 1000 simulations, PLAI was more cost effective than OLAI, and OLAI was never the dominant option. At a cost-effectiveness threshold of SEK 300,000 per QALY, the probability of cost effectiveness was 93% for PLAI. For relapses avoided, PLAI dominated OLA in 99.8% of simulations, suggesting that PLAI will be cost effective at a threshold of SEK 300,000 per QALY.

The online supplement, OS Table 2, presents details on the parameters included in the PSA.

Discussion

In this evaluation, maintenance treatment with PLAI over a 5-year time-horizon was estimated to result in lower total treatment costs and greater effectiveness (more QALYs gained and relapses avoided) when compared to RLAI and OLAI.

The modeled results of the RLAI treatment arm were consistent with the observational study data, thus supporting the validity of the model outcomes. Olivares and colleagues[13] reported that the percentage of patients remaining on RLAI for 24 months after initiating therapy was 81.8% in Spanish patients in e-STAR, a prospective, naturalistic observational study. In patients from the combined data of six European countries including Belgium, the Czech Republic, The Netherlands, Sweden, Slovakia and Spain, 85% remained on RLAI for 24 months after initiating therapy[14]. The model predicted that a similar percentage of patients remained on initial treatment over 24 months for RLAI (81.0%).

In the same prospective, observational study (e-STAR) which included data from six European countries, including Sweden, data showed that the hospitalization rate per completer and discontinuer with RLAI after the first 12 months was 0.1 and 0.6, respectively. The modeled data predicted a completion rate of 91% with RLAI. Using the e-STAR hospitalization rates for completers and discontinuers of RLAI $(0.1 * 91\% + 0.6 * 9\%) = 0.145$; this results in very similar results to the model, which predicts a hospitalization rate of 0.127 per patient. These data therefore support that the model is in line with the study results.

The model results were also consistent with other published economic evaluations of RLAI. In a discrete event simulation comparing RLAI, oral olanzapine and haloperidol depot injection over a 5-year time-horizon from the German perspective, total undiscounted costs per patient are very similar (SEK 909,053 vs. €95,318 or SEK 932,972; at €1 = SEK 9.788)[52]. Although treatment patterns may be expected to be different, the similar magnitude of costs suggests a similar burden of schizophrenia care between the countries. Using different utility input values in the models, however, yielded different results in terms of total QALYs. This model generated QALYs that were approximately twice as high in absolute terms as compared to the German model. The utility values in this model were derived from a more recent study where values used in the model were elicited from patients, the preferred perspective of the Swedish health authority, using the TTO approach[44] and gave rise to higher utility values by health state (0.919 stable, 0.604 relapse) than the German model input values. In the German model, utilities were derived from the linear analogue (LA) and standard gamble (SG) methods with states identified using cluster analysis on Positive and Negative Syndrome Scale (PANSS) data and preferences by psychiatric nurses giving rise to mean utility values of 0.61 (mild), 0.36 (moderate), and 0.29 (severe) schizophrenia[53]. These differences are consistent with the observations that quality of life elicited from patients gives rise to higher utilities than other groups such as lay persons[44]. Nevertheless, given the same utility values were used for PLAI and RLAI within the model, the incremental value between treatment arms is consistent regardless of absolute differences between different models.

Uncertainty and key drivers of the model results were explored by two different approaches: (1) one-way deterministic sensitivity analyses (varying key clinical and economic parameter estimates within ranges reflecting possible parameter values), and (2) probabilistic sensitivity analyses (uncertainty in all parameters tested is considered simultaneously). The results were robust when tested in sensitivity analyses in both one-way deterministic sensitivity analyses and PSA. Switch rates and level of adherence had a greater impact on relapses avoided and costs; and side-effects were found to have the greatest impact on the number of QALYs gained. The improved outcomes observed from switch rates can be attributed to patients switching earlier to later-line treatments that had mostly lower relapse prevention rates versus the starting treatment and underscores the value of starting patients on treatments with the greatest relapse prevention and retention on these treatments. Side-effect parameters had the strongest impact on QALY, with EPS being the most powerful. This suggests that even when relapse rates are improved by LAI antipsychotics, side-effect differences have an important relationship to overall outcomes. This is of particular relevance given that fewer extrapyramidal side-effects have been associated with atypical antipsychotics as compared with conventional antipsychotics[26].

The model used a baseline annual relapse rate from the NICE MTC calculating the probability of relapse in patients with schizophrenia on placebo treatment over 52 weeks (43.6%) from clinical trial data. Therefore, on average, an untreated patient would have 0.436 relapses

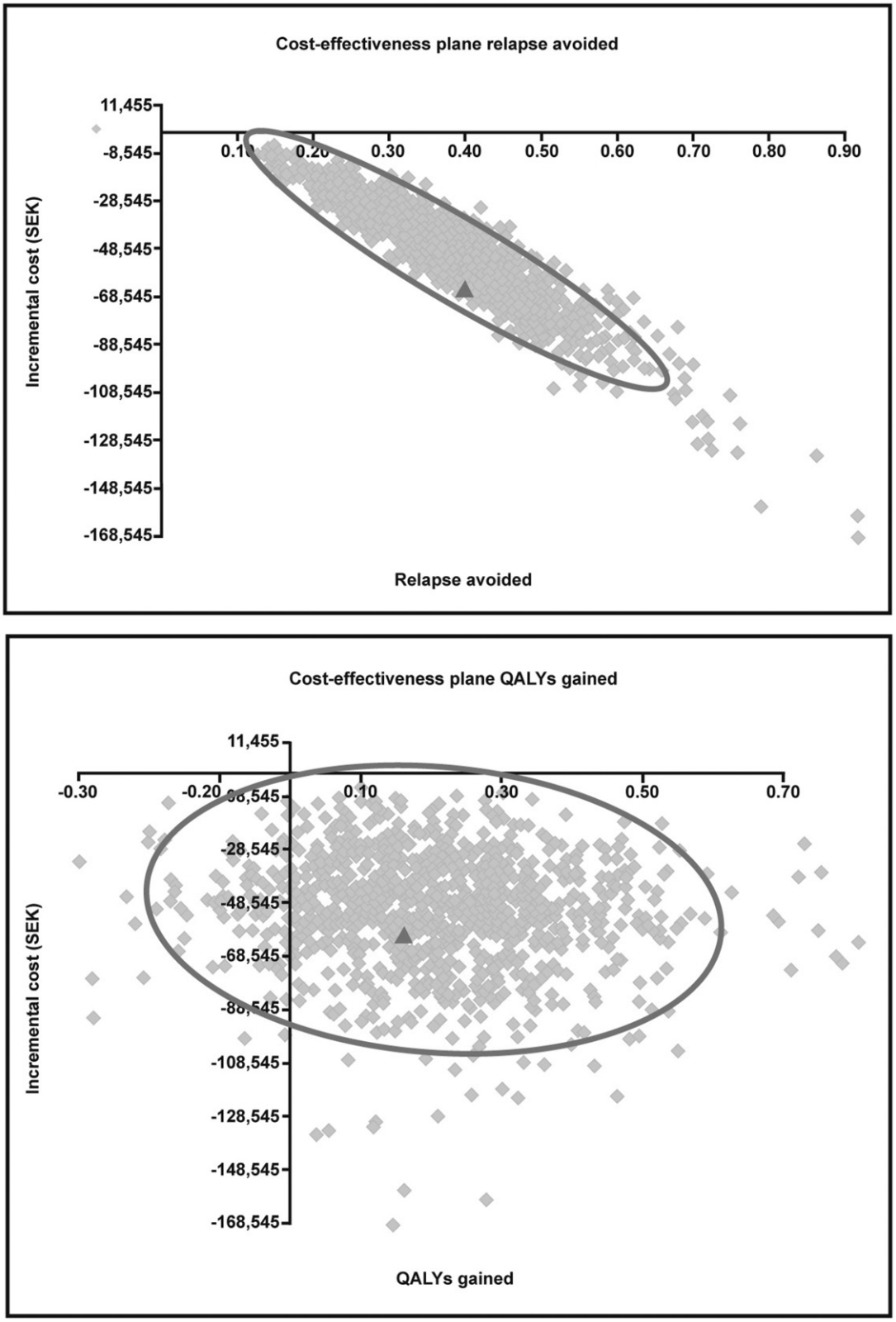

Figure 4. Cost-effectiveness plane (QALYs gained and relapses avoided), PLAI versus OLAI. Solid lines depict the 95% confidence interval; solid triangles depict the base-case values. QALY, quality-adjusted-life-year; PLAI, paliperidone palmitate; OLAI, olanzapine long-acting injectable.

per year or approximately 2.2 relapses over 5 years. The number of relapses per patient for RLAI over 5 years in the model was lower than earlier economic models that included RLAI treatment arms in high-risk, non-compliant patients in Canada[54], consistent with a lower expected baseline frequency of relapse in the different patient populations. As the baseline frequency of relapse increased in the model as tested in sensitivity analysis, the incremental benefits (cost savings and relapses avoided) of PLAI over RLAI were even greater. This suggests PLAI may have additional benefits in more frequently relapsing or patients with a higher risk of relapse.

A Markov model was developed to provide simple and transparent framework of the clinical course of a complex chronic disorder, such as schizophrenia, from which to calculate accumulated outcomes. More flexible than a decision tree model and more transparent than a DES, this modeling approach nevertheless has a number of limitations. Not all variables that could impact on real-world were included in the model, for example distance/access to facilities to receive injections, polypharmacy and related side-effects/relative risk of drug–drug interactions, ease of storage/lack or need for refrigeration or reconstitution, oral supplementation (or lack of) and onset of acute efficacy.

Partial or non- adherence to medication has been consistently associated with negative outcomes including more hospitalizations and higher costs. This model included the impact of poor adherence on risk of relapse to closer simulate real-world effectiveness. Clinical trials, evaluating treatment efficacy by protocol-driven design, eliminate confounding factors such as poor adherence and would therefore not reflect adherence-driven treatment benefits. In addition to rigorous, compliance-enhancing study schedules, the fact of a study itself may deter patients more likely to be poorly compliant from entering a study. While small differences in adherence was assumed in the base-case between LAIs and was tested in sensitivity analysis, the impact of once-monthly treatment on adherence levels is not yet known.

The base-case population was a cohort of multi-episode patients (two or more relapses) with schizophrenia. However, evidence suggests both PLAI and RLAI are effective in delaying time to relapse in recently diagnosed patients with schizophrenia ($\leq$5 years)[55] ($\leq$2 years)[56]. Given that there is a high rate of relapse within the first 5 years of a first episode of schizophrenia (cumulative rate of relapse 87%)[57] and a considerably higher overall economic burden in the year following their first schizophrenia event compared with chronic patients[58], differences in relapse prevention between the treatments would be even more relevant for this patient population. Further analyses should explore the use of longer interval LAIs in patients at the highest risk of relapse and high direct costs of care, such as recently diagnosed patients, especially since PLAI (in comparison with RLAI) has been shown to be more cost effective in patients considered to have a high risk of relapse.

This analysis focused on direct medical costs only. The indirect costs of schizophrenia such as reductions in work productivity and caregiver burden are substantial. Therefore, this model underestimates the full impact of schizophrenia and should be considered as conservative.

The presence of data in the literature on the availability of hospitalization rates, levels of adherence and rates of relapses that do not result in inpatient care in the Swedish naturalistic setting is currently lacking. Additional longer-term and in particular naturalistic data is needed to further validate these results and explore the effectiveness of PLAI in clinical practice.

Conclusions

Maintenance treatment with PLAI over a 5-year time-horizon was estimated to have lower total treatment costs and greater effectiveness (more QALYs gained and relapses avoided) in the treatment of multi-episode patients (two or more relapses) with schizophrenia, when compared to RLAI and OLAI from the direct medical perspective in Sweden. Results were modeled using prospective, observational data where feasible, however, not all variables that may affect real-world effectiveness were included, such as access to facilities to receive injections, polypharmacy and related side-effects/relative risk of drug–drug interactions, ease of storage/lack or need for refrigeration or reconstitution, oral supplementation (or lack of) and onset of acute efficacy on inpatient length of stay. Additional data, in particular naturalistic outcomes, are needed to further validate these results and explore the effectiveness of PLAI in clinical practice.

Transparency

Declaration of funding

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Declaration of financial/other relationships

A.M. has disclosed that she is employed by Janssen Pharmaceutica NV; D.N. has disclosed that she is an employee of Janssen Global Services, LLC; H.P. has disclosed that she is employed by Janssen Cilag Oy, Helsinki, Finland; M.M. has disclosed that she is a full-time employee of OptumInsight (formerly i3 Innovus, a company that was contracted by the sponsor to conduct this study). A.McG. has disclosed that he is an employee of LSE and a paid consultant and advisor for OptumInsight. He has no other conflicts of interest to declare.

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References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (Revised 4th ed). Washington: APA, 2000
2. National Institute of Clinical Excellence. CG82 Schizophrenia: full guideline (2010). http://www.nice.org.uk/nicemedia/live/11786/43607/43607.pdf. Accessed March 8 2012
3. McGrath J, Saha S, Chant D, et al. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 2008;30:67-76
4. Knapp M, Mangalore R, Simon J. The global costs of schizophrenia. Schizophr Bull 2004;30:279-93
5. Lindstrom E, Eberhard J, Neovius M, et al. Costs of schizophrenia during 5 years. Acta Psychiatr Scand 2007;116:33-40
6. Chang SM, Cho SJ, Jeon HJ, et al. Economic burden of schizophrenia in South Korea. J Korean Med Sci 2008;23:167-75
7. Ascher-Svanum H, Baojin Zhu B, Faries DE, et al. The cost of relapse and the predictors of relapse in the treatment of schizophrenia. BMC Psychiatry 2010;10:2
8. Fitzgerald P, de Castella A, Arya DS, et al. The cost of relapse in schizophrenia and schizoaffective disorder. Australas Psychiatry 2009;17:265-72
9. Lacro JP, Dunn LB, Dolder CR, et al. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. J Clin Psychiatry 2002;63:892-909
10. Gilmer TP, Dolder CR, Lacro JP, et al. Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. Am J Psychiatry 2004;161:692-9
11. Sun SX, Liu GG, Christensen DB, et al. Review and analysis of hospitalization costs associated with antipsychotic nonadherence in the treatment of schizophrenia in the United States. Curr Med Res Opin 2007;23:2305-12
12. Morken G, Widen JH, Grawe RW. Non-adherence to antipsychotic medication, relapse and rehospitalisation in recent-onset schizophrenia. BMC Psychiatry 2008;8:32
13. Olivares JM, Rodriguez-Morales A, Diels J, et al. Long-term outcomes in patients with schizophrenia treated with risperidone long-acting injection or oral antipsychotics in Spain: Results from the electronic Schizophrenia Treatment Adherence Registry (e-STAR). Eur Psychiatry 2009;24:287-96
14. Peuskens J, Olivares JM, Pecenak J, et al. Treatment retention with risperidone long-acting injection: 24-month results from the Electronic Schizophrenia Treatment Adherence Registry (e-STAR) in six countries. Curr Med Res Opin 2010;26:501-9
15. Glazer WM, Ereshefsky L. A pharmacoeconomic model of outpatient antipsychotic therapy in 'revolving door' schizophrenic patients. J Clin Psychiatry 1996;57:337-45
16. Haycox A. Pharmacoeconomics of long-acting risperidone: results and validity of cost-effectiveness models. Pharmacoeconomics 2005;23:3-16
17. Gaebel W, Schreiner A, Bergmans P, et al. Relapse prevention in schizophrenia and schizoaffective disorder with risperidone long-acting injectable vs quetiapine: results of a long-term, open-label, randomized clinical trial. Neuropsychopharmacology 2010;35:2367-77
18. Kane JM, Detke HC, Naber D, et al. Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. Am J Psychiatry 2010;167:181-9
19. Hartung B, Wada M, Laux G, Leucht S. Perphenazine for schizophrenia. The Cochrane Collaboration, John Wiley & Sons, Ltd, Issue 5, 2010
20. Kumar A, Strech D. Zuclopenthixol dihydrochloride for schizophrenia. The Cochrane Collaboration, John Wiley & Sons, Ltd, Issue 5, 2010
21. Review and evaluation of clinical data. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022264s006lbl.pdf. Accessed March 8 2012
22. Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health 2011;14:417-28
23. Pandina G, Lane R, Gopal S, et al. A double-blind study of paliperidone palmitate and risperidone long-acting injectable in adults with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2011;35:218-26
24. Valenstein M, Copeland LA, Blow FC, et al. Pharmacy data identify poorly adherent patients with schizophrenia at increased risk for admission. Med Care 2002;40:630-9
25. Ward A, Ishak K, Proskorovsky I, et al. Prescriptions for atypical antipsychotic agents and its association with the risks for hospitalisation, suicide, and death in patients with schizophrenia in Quebec and Saskatchewan: a retrospective database study. Clin Ther 2006;28:11
26. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009;373:31-41
27. Swedish national inpatient care statistics (hospitalization; average length of stay; schizophrenia diagnosis [F20]) 2008. Available at: http://192.137.163.40/epcfs/ParRes.asp. Accessed March 8 2012
28. Fleischhacker WW, Gopal S, Lane R, et al. A randomized trial of paliperidone palmitate and risperidone long-acting injectable in schizophrenia. Int J Neuropsychopharmacol 2011;15:107-118
29. Haro JM, Suarez D, Novick D, et al. Three-year antipsychotic effectiveness in the outpatient care of schizophrenia: observational versus randomized studies results. Eur Neuropsychopharmacol 2007;17:235-44
30. Keks NA, Ingham M, Khan A, et al. Long-acting injectable risperidone v. olanzapine tablets for schizophrenia or schizoaffective disorder randomised, controlled, open-label study. Br J Psychiatry 2007;191:131-9
31. Olanzapine pamoate Summary of Product Characteristics (Lilly) 2010
32. Gopal S, Vijapurkar U, Lim P, et al. A 52-week open-label study of the safety and tolerability of paliperidone palmitate in patients with schizophrenia. J Psychopharmacology 2011;25:685-97
33. Gharabawi GM, Bossie CA, Zhu Y, et al. An assessment of emergent tardive dyskinesia and existing dyskinesia in patients receiving long-acting, injectable risperidone: results from a long-term study. Schizophr Res 2005;77:129-39
34. Schreiner A, Niehaus D, Shuriquie NA, et al. Metabolic effects with paliperidone ER versus oral olanzapine in patients with schizophrenia: a prospective, randomized, controlled trial. J Clin Psychopharmacology 2011, in press
35. Olivares JM, Rodriguez-Morales A, Diels J, et al. 24-month treatment discontinuation rates in patients with schizophrenia treated with Risperidone Long-Acting Injection (RLAI) versus oral antipsychotics: results from the electronic Schizophrenia Treatment Adherence Registry (e-STAR) in Spain. ISPOR European Annual European Congress, 20–23 October 2007; Dublin, Ireland
36. Mehnert A, Diels J. Impact of administration interval on treatment retention with long-acting antipsychotics in schizophrenia. Tenth Workshop on Costs and Assessment in Psychiatry - Mental Health Policy and Economics, 25–27 March 2011; Venice, Italy
37. Almond S, Knapp M, Francois C, et al. Relapse in schizophrenia: costs, clinical outcomes and quality of life. Br J Psychiatry 2004;184:346-51
38. Statistikdatabaser. (2008). Diagnoser i slutenvård, Socialstyrelsen, Epidemiologiskt centrum. Available at www.socialstyrelsen.se. Accessed March 8 2012
39. Maehlum E, Hensen K. Pharmacoeconomic positioning of sertindole among antipsychotics in the management of schizophrenia in Norway. Value Health 2008;11:A585
40. Johnson & Johnson Pharmaceuticals. Clinical study report (CSR), data on file. PSY-3001N, 2009
41. Tenback De, van Harten PN, Slooff CJ, et al. Incidence and persistence of tardive dyskinesia and extrapyramidal symptoms in schizophrenia. J Psychopharmacol 2009;24:1031-5

42. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with schizophrenia. N Engl J Med 2005;353:1209-23
43. Ösby U, Correia N, Brandt L, et al. Mortality and causes of death in schizophrenia in Stockholm County, Sweden. Schizophr Res 2000;5:21-8
44. Briggs A, Wild D, Lees M, et al. Impact of schizophrenia and schizophrenia treatment-related adverse events on quality of life: direct utility elicitation. Health Qual Life Outcomes 2008;6:105
45. LFNAR. General guidelines for economic evaluations from the Pharmaceutical Benefits Board, 2003
46. Paliperidone palmitate Summary of Product Characteristics (Janssen) 2011
47. World Health Organization Collaborating Centre for Drug Statistics Methodology. (2010). ATC/DDD. Available at http://www.whocc.no/atc_ddd_index/. Accessed March 8 2012
48. TLV available at: http://www.tlv.se. Accessed March 8 2012
49. BSC. (2009). Using the rate for Health goods for November 2009: http://www.scb.se/Pages/List____250611.aspx. Accessed March 8 2012
50. Ringborg A, Martinell M, Stalhammar J, et al. Resource use and costs of type 2 diabetes in Sweden-estimates from population-based register data. Int J Clin Pract 2008;62:708-16
51. Drummond MD, Sculpher MJ, Torrance GW, et al. Methods for the Economic Evaluation of Health Care Programmes. New York, USA: Oxford University Press, 2005
52. Laux G, Hee BMS, van Hout BA, et al. Costs and effects of long-acting risperidone compared with oral atypical and conventional depot formulations in Germany. Pharmacoeconomics 2005;23:49-61
53. Chouinard G, Albright PS. Economic and health state utility determinations for schizophrenic patients treated with risperidone or haloperidol. J Clin Psychopharmacol 1997;17:298-307
54. Chue PS, Heeg BMS, Buskens E, et al. Modelling the impact of compliance on the costs and effects of long-acting risperidone in Canada. Pharmacoeconomics 2005;23:62-74
55. Alphs L, Bossie C, Kern Sliwa J, et al. Paliperidone palmitate: clinical response in subjects with schizophrenia with recent diagnosis vs. longer-time since diagnosis. APA, 16-21 May 2009; San Francisco, USA. Poster NR6-027
56. Olivares JM, Peuskens J, Pecenak J, et al. Clinical and resource-use outcomes of risperidone long-acting injection in recent and long-term diagnosed schizophrenia patients: results from a multinational electronic registry. Curr Med Res Opin 2009;25:2197-206
57. Robinson D, Woerner MG, Alvir JMJ, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry 1999;56:241-7
58. Nicholl D, Akhras KS, Diels J, et al. Burden of schizophrenia in recently diagnosed patients: healthcare utilisation and cost perspective. Curr Med Res Opin 2010;26:943-55