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Original article

Cost-effectiveness of several atypical antipsychotics in orally disintegrating tablets compared with standard oral tablets in the treatment of schizophrenia in the United States

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Abstract

Objective:
Although the use of innovative drug delivery systems, like orally disintegrating antipsychotic tablets (ODT), may facilitate medication adherence and help reduce the risk of relapse and hospitalization, no information is available about the comparative cost-effectiveness of standard oral tablets (SOT) vs ODT formulations in the treatment of schizophrenia. This study compared the cost-effectiveness of olanzapine ODT and olanzapine SOT in the usual treatment of outpatients with schizophrenia from a US healthcare perspective. The study also compared olanzapine ODT with risperidone and aripiprazole, two other atypical antipsychotics available in both ODT and SOT formulations.

Methods:
Published medical literature and a clinical expert panel were used to populate a 1-year Monte Carlo Micro-simulation model. The model captures clinical and cost parameters including adherence levels, treatment discontinuation by reason, relapse with and without inpatient hospitalization, quality-adjusted life years (QALYs), treatment-emergent adverse events, healthcare resource utilization, and associated costs. Key outcomes were total annual direct cost per treatment, QALY, and incremental cost-effectiveness (ICER) per 1 QALY gained.

Results:
Based on model projections, olanzapine ODT therapy was more costly ($9808 vs $9533), but more effective in terms of a lower hospitalization rate (15% vs 16%) and better QALYs (0.747 vs 0.733) than olanzapine SOT therapy. Olanzapine ODT was more cost-effective than olanzapine SOT (ICER: $19,643), more cost-effective than risperidone SOT therapy (ICER: $39,966), and dominant (meaning less costly and more effective) than risperidone ODT and aripiprazole in ODT or SOT formulations.

Limitations:
Lack of head-to-head randomized studies comparing the three studied atypical antipsychotics required making input assumptions that need further study.

Conclusions:
This micro-simulation found that the utilization of olanzapine ODT for the treatment of schizophrenia is predicted to be more cost-effective than any other ODT or SOT formulations of the studied atypical antipsychotic medications.

Introduction

Among the greatest challenges in the treatment of schizophrenia is poor patient adherence with antipsychotic medications. Despite the need for long-term maintenance on the medication, more than half of patients are non-adherent with their antipsychotic regimens[1]. Non-adherence has long been recognized as a potent predictor of relapse and hospitalization[2–4], the costliest component in the treatment of schizophrenia in both economic and personal terms[5].

Non-adherence is a complex phenomenon, and successful pharmacotherapy depends on many factors. Although efficacy and tolerability are clearly important, innovative drug delivery systems may enhance adherence and help reduce suboptimal outcomes[6–8]. Among delivery systems that may facilitate medication adherence are antipsychotics in orally disintegrating tablet (ODT) formulations, currently available for clozapine, olanzapine, risperidone, and aripiprazole. The ODTs disintegrate within seconds of contact with saliva without requiring water[9], mask the taste of the medication[10], and are bioequivalent to comparable dosages of the standard oral tablet (SOT)[11].

Although ODTs may be more costly than SOTs, there are no published studies comparing their cost-effectiveness. Prior research has, however, shown that olanzapine ODT is associated with improved patient attitudes toward medication[11,12] and with improved medication adherence in inpatient and outpatient settings[11–13]. The most robust data supporting the adherence advantage of olanzapine ODT over its SOT formulation is based on findings of significantly better adherence on olanzapine ODT than olanzapine SOT in the only randomized, double-blind, double-dummy, controlled study to offer a head-to-head comparison of adherence levels on the two formulations in the treatment of schizophrenia[13]. Moreover, a recent randomized, cross-over, open-label multinational study comparing patient preference of olanzapine ODT vs olanzapine SOT among outpatients with schizophrenia[14] found that patients were 2-times more likely to prefer olanzapine in ODT formulation over SOT formulation. Current findings suggest that olanzapine ODT may provide an adherence advantage over its SOT formulation[15], which may translate to a reduced risk of relapse and hospitalization, and thus translate to improved cost-effectiveness.

In a previously published 1-year micro-simulation model[16], we compared the cost-effectiveness of five atypical antipsychotics in SOT formulations (olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole) in the treatment of patients with schizophrenia in usual care settings in the US. That model predicted utilization of olanzapine SOT would improve clinical outcomes and lower total direct healthcare costs better than utilization of comparators, suggesting that olanzapine SOT may be a cost-effective therapeutic option for patients with schizophrenia.

The current study aimed to update and expand our previous cost-effectiveness model[16] by comparing the cost-effectiveness of several ODT and SOT formulations of atypical antipsychotic drugs (olanzapine, risperidone, and aripiprazole). Our primary objective was to compare the cost-effectiveness of olanzapine ODT and olanzapine SOT during the usual treatment of schizophrenia patients from the perspective of third-party payers within the US healthcare system. As a secondary objective, we compared olanzapine ODT with the ODT and SOT formulations of risperidone and aripiprazole, two other frequently used atypical antipsychotics available in both SOT and ODT formulations.

Patients and methods

Model overview

A Monte Carlo Micro-simulation (MCM) model was developed to compare, from the perspective of a public or private third-party healthcare payer in the US, the cost-effectiveness of atypical antipsychotics in SOT and ODT formulations in the usual care of adult patients treated for schizophrenia. The model includes three frequently used atypical antipsychotics (olanzapine, risperidone, and aripiprazole) in their ODT and SOT formulations, thus comprising six treatment cohorts (including three ODT formulations and their respective three SOT formulations). The model simulates the dynamic nature of usual care over a 1-year period, using quarterly cycles and various input parameters which include adherence levels, relapse with and without hospitalization, health state utilities, treatment discontinuation, treatment-emergent adverse events, healthcare resource utilization, suicide risk, and direct healthcare costs, such as medication costs. Results are based on a simulation of 1,000,000 patients. Key clinical outcomes predicted include quality-adjusted life years (QALYs) and psychiatric inpatient hospitalization rates. Costs are expressed in US dollars based on 2010 values. In the US, the ODT formulations cost more than the SOT formulations of the same antipsychotic medication. The model assumes an intent-to-treat approach that attributes all estimated direct medical costs to the initial therapy. Since the current model is an expansion and update of the previous model, further details are available in the publication of the parent study[16], which only included antipsychotics in SOT formulations. The updates implemented in the current evaluation include use of the most current cost and utilization data whenever possible.

Considering this is a cost-effectiveness model rather than an analysis of patient-level data from a pre-existing study, there are no reported *p*-values. To assess the

robustness of the base case findings—which were based on 100,000 simulations per treatment group—numerous sensitivity analyses were conducted (one-way sensitivity analyses and probabilistic sensitivity analyses). These sensitivity analyses enabled us to run so many replications (e.g., probabilistic simulations of 1000 cohorts of 1000 patients for each of the key parameters) that they essentially reflect a much lower *p*-value than the traditional $p<0.05$ reported in patient-level trial data analyses. Generally, *p*-values are as much dependent on '*n*'—sample size—as they are the characteristics of the underlying distributions around result estimates. When running so many replications the '*n*' dominates *p*-value calculations (especially because the implied distributions are normal and relatively narrow).

Figure 1 presents a conceptual overview of the micro-simulation model over the first quarter for patients initiated on an antipsychotic medication. Depending on their adherence level, patients may remain stable (no relapse), suffer relapse(s) requiring hospitalization, or relapse(s) not severe enough to warrant psychiatric hospitalization. Patients may also experience treatment-emergent adverse events such as extra-pyramidal symptoms (EPS), clinically significant weight gain (≥7%), diabetes, or hyperlipidemia. Medication discontinuations involve either a switch (S) to another antipsychotic or discontinuing antipsychotic treatment, at least for a while (D). The model takes into account switching patterns and the primary reason for medication discontinuation (poor efficacy, intolerability, patient decision, or other reasons). The patient's health state at the end of each quarter constitutes the base for the next quarter until the end of four quarters (1 year). If certain adverse events (i.e., diabetes and hyperlipidemia) occur, they are assumed to remain and contribute to treatment costs for the remainder of the study period.

Sensitivity analyses

We first used sequential bifurcation, a process that iteratively samples inputs and assesses the impact of each input against a pre-determined cost threshold value[17], to determine what variables affecting total treatment costs warrant focus during sensitivity analyses. Our sequential bifurcation tested more than 120 input parameters before selecting the variables for sensitivity analyses. Sensitivity analyses were not conducted on input variables that did not vary between antipsychotic medications, such as the cost of most healthcare resources. We also conducted multivariable probabilistic sensitivity analyses (PSAs) to examine the uncertainty in the model and the stability of the results when varying the input values for adherence rates, relapse rates, and treatment discontinuation rates.

Key clinical and economic input values

Key clinical and economic input values were based on evidence reported in peer-reviewed articles. We used input values derived from a clinical expert panel when information was not available in peer-reviewed articles. Consistent with published comparative data[11–13], we also assumed that each of the three ODT formulations is equal to its SOT counterpart on all clinical input values except for better adherence on ODT.

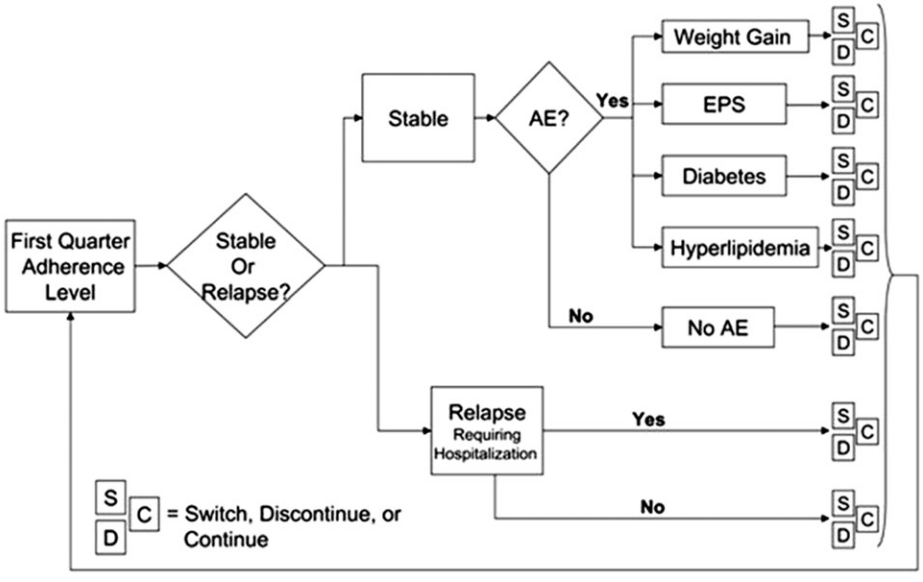

Figure 1. Conceptual view of the Monte Carlo Micro-simulation (MCM) model. AE, treatment-emergent adverse event; EPS, extrapyramidal symptoms; Patient's Treatment Status at the End of Quarter: C, Continue; D, Discontinue; S, Switch.

Adherence levels

Level of medication adherence was based on the annual medication possession ratio, which is the proportion of days with the prescribed antipsychotic medication during the 1-year study period, using patient medical or pharmacy claims records[18–22]. Patients were categorized into one of three adherence levels: fully adherent, partially adherent, or non-adherent[23]. Table 1[16, 23–25] reports the base case adherence level by medication, along with the data source. Consistent with prior research[20,23,25], adherence levels were categorized as: adherent (MPR $\geq$ 80%), partially adherent (MPR $\geq$ 60%, <80%), and non-adherent (MPR < 60%).

The model also incorporates information about adherence level in subsequent cycles following a relapse in the previous quarterly cycle, because US data indicates that adherence levels change from pre-relapse to post-relapse in the usual treatment of schizophrenia[23]. Table 2 reports these baseline assumptions.

Relapse rates

The model requires a series of assumptions concerning patient relapse rate by adherence levels. To that end, we used data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[26,27], a large US study sponsored by the National Institute of Mental Health (NIMH). The CATIE schizophrenia study is a randomized, double-blind, 18-month study of antipsychotic therapy in the treatment of schizophrenia, and the only US study to provide comparative data on relapse rates for the studied SOT antipsychotics (olanzapine and risperidone), except for aripiprazole. Table 3[26–28] presents the base case assumptions for the risk of an initial relapse resulting in an inpatient hospitalization by adherence category for each medication. These were estimated using a 3-step process: first, a baseline relapse rate by adherence level was adopted from a study[20] of Medicaid patients with schizophrenia. Second, relapse rates for each medication group were derived from CATIE, Phase 1, the primary phase of the CATIE schizophrenia trial[26,27]. Consistent with a prior model comparing the cost-effectiveness of antipsychotics in the treatment of schizophrenia[29], we assumed that the rates of relapse for aripiprazole were equivalent to ziprasidone[28] and also assumed a constant proportion of inpatient-to-outpatient rates of relapse by adherence level: 1.00 for fully adherent, 1.13 for partially adherent, and 1.11 for non-adherent for all antipsychotic medications studied[28].

The model also requires conditional probabilities to allow for rates of inpatient relapse given a history of inpatient relapse (Table 4)[30,31] and for multiple relapses within a single quarter (Table 5)[32]. We assumed the same conditional probabilities for all studied antipsychotics. These baseline conditional probabilities resulted in a weighted average number of relapses that was nearly identical to the crude rate of relapse for individuals with a history of one relapse reported in the literature[30,31]. Additionally, the model incorporates the risk of attempted and completed suicide (Table 6)[16,25,33]. A suicide attempt is considered a relapse event requiring hospitalization.

Table 1. Adherence rates by medication.

Medications	Full adherence	Partial adherence	Non-adherence	Data source
Olanzapine	23%	43%	34%	Ahn *et al.*[25], Ascher-Svanum *et al.*[23]
Risperidone	21%	39%	40%	
Aripiprazole	19%	35%	46%	Assumption: equal to quetiapine; Furiak *et al.*[16]
ODT Olanzapine	37%	29%	34%	Karagianis *et al.*[24]
ODT Risperidone	35%	25%	40%	
ODT Aripiprazole	33%	21%	46%	

ODT, orally disintegrating tablet [formulation]; Using the Medication Possession Ratio (MPR), adherence levels are defined as: full adherence (MPR $\geq$ 80%), partial adherence (MPR $\geq$ 60%, <80%), and non-adherence (MPR < 60%).

Table 2. Adherence rates by adherence level in cycle following relapse.

Adherence level prior to relapse	Full adherence after relapse	Partial adherence after relapse	Non-adherence after relapse	Data source
Full adherence	92.03%	1.45%	6.52%	Ascher-Svanum *et al.*[23]
Partial adherence	75.00%	12.50%	12.50%	
Non-adherence	38.70%	9.70%	51.60%	

Using the Medication Possession Ratio (MPR), adherence levels are defined as: full adherence (MPR $\geq$ 80%), partial adherence (MPR $\geq$ 60%, <80%), and non-adherence (MPR < 60%).

Table 3. Relapse rates requiring and not requiring hospitalization.

Parameter	Value (%)			Data source
	Full adherence	Partial adherence	Non-adherence	
Requiring hospitalization—For initial relapse				
Olanzapine	2.0%	3.6%	5.2%	Lieberman *et al.*[26]; Lieberman *et al.* [erratum][27];
Risperidone	3.5%	6.4%	9.2%	Gilmer *et al.*[20]
Aripiprazole	4.7%	8.5%	12.2%	Assumed same as ziprasidone. Zimbroff *et al.*[28]
ODT Olanzapine	2.0%	3.6%	5.2%	Lieberman *et al.*[26]; Lieberman *et al.* [erratum][27];
ODT Risperidone	3.5%	6.4%	9.2%	Gilmer *et al.*[20]
ODT Aripiprazole	4.7%	8.5%	12.2%	Assumed same as ziprasidone. Zimbroff *et al.*[28]
Not requiring hospitalization				
Olanzapine	2.0%	3.2%	4.8%	Lieberman *et al.*[26]; Lieberman *et al.* [erratum][27];
Risperidone	3.5%	5.7%	8.5%	Gilmer *et al.*[20]; Edwards *et al.*[32]
Aripiprazole	4.7%	7.5%	11.3%	Assumed same as ziprasidone. Zimbroff *et al.*[28]
ODT Olanzapine	2.0 %	3.2%	4.8%	Lieberman *et al.*[26]; Lieberman *et al.* [erratum][27];
ODT Risperidone	3.5%	5.7%	8.5%	Gilmer *et al.*[20]; Edwards *et al.*[32]
ODT Aripiprazole	4.7%	7.5%	11.3%	Assumed same as ziprasidone. Zimbroff *et al.*[28]

ODT, orally disintegrating tablet [formulation].

Table 4. Adjusted relapse rates given a history of relapse.

History of relapse	Full adherence	Partial adherence	Non-adherence	Data source
Probability given history of one relapse	19%	40%	58%	Olfson *et al.*[30];
Probability given history of two relapses	36%	75%	100%	Tiihonen *et al.*[31]
Probability given history of three relapses	42%	88%	100%	

Table 5. Probability of multiple relapses within a single quarter.

Multiple relapse type	Value	Data source
Additional inpatient relapse given one prior relapse	20%	Edwards *et al.*[32]
Additional outpatient relapse given one prior relapse	75%	

Treatment-emergent adverse events

The model requires assumptions about the likelihood of patients experiencing four types of treatment-emergent adverse events that are relevant to the studied antipsychotics: EPS, clinically significant weight gain (≥7% weight gain from baseline weight), diabetes, and hyperlipidemia. Table 7[26,30,34–36] reports baseline assumptions concerning these treatment-emergent adverse events by medication and data source.

Treatment discontinuation rates

Consistent with results of the primary phase of the CATIE schizophrenia trial, Phase 1[26], patients were assumed to have discontinued medications due to lack of efficacy, medication intolerability, patient decision, or other reasons. Annual discontinuation rates were also based on Phase 1 of the CATIE trial[26] (except for aripiprazole, which was not included in CATIE) and are reported in Table 8[26,35]. Following medication discontinuation, patients could switch to another antipsychotic medication. Table 9 presents baseline assumptions concerning the medication switch patterns by reason for switching. The new medication to which a patient was switched depended on the reason for the switch and the medication from which the patient was being switched. Patients who were treated with a given ODT or SOT formulation and required a switch to another antipsychotic were assumed to have switched to another medication in the same formulation.

Utility and quality-adjusted life years

Disease-specific utility values for eight schizophrenia disease states were reported by Lenert *et al.*[37] using the Positive and Negative Syndrome Scale, a standard measure of symptom severity in schizophrenia research. Table 10 presents the baseline utility values assigned to each of the nine possible combinations of three adherence levels by three relapse statuses in the model. A panel of 12 schizophrenia experts was surveyed to determine which of the eight health states[37] that best match the utility of a schizophrenia patient in each of

Table 6. Probability of suicide event given adherence level.

Probability of suicide event	Fully adherent	Partially adherent	Non-adherent	Data source
Probability of suicide attempt	0.25%	0.76%	1.00%	Ahn *et al.*[25]
Probability suicide attempt is fatal	10.00%			Siris[33]
Cost of non-fatal suicide attempt		$140 (in addition to relapse costs)		Assumption: Furiak *et al.*[16]
Healthcare cost of fatal suicide attempt		$0		Assumption: Furiak *et al.*[16], Edwards *et al.*[32]

Table 7. Treatment emergent adverse event values.

Parameter	Value (%)	Data source
Adverse event rates for EPS		
Olanzapine	15.5%	Carlson *et al.*[36]
Risperidone	24.7%	
Aripiprazole	21.0%	Fleischhacker *et al.*[35]
ODT Olanzapine	15.5%	Assume ODT is equal to its
ODT Risperidone	24.7%	respective SOT formulation
ODT Aripiprazole	21.0%	
Adverse event rates for clinically significant weight gain (≥7%)		
Olanzapine	30.0%	Lieberman *et al.*[26]
Risperidone	14.0%	
Aripiprazole	7.3%	Fleischhacker *et al.*[35]
ODT Olanzapine	30.0%	Assumption: ODT is equal to its
ODT Risperidone	14.0%	respective SOT formulation
ODT Aripiprazole	7.3%	
Adverse event rates for diabetes		
Olanzapine	3.3%	Lambert *et al.*[34]
Risperidone	3.2%	
Aripiprazole	2.0%	
ODT Olanzapine	3.3%	Assume ODT is equal to its
ODT Risperidone	3.2%	respective SOT formulation
ODT Aripiprazole	2.0%	
Adverse event rates for hyperlipidemia		
Olanzapine	16.8%	Lieberman *et al.*[26];
Risperidone	14.0%	Lambert *et al.*[34];
Aripiprazole	3.6%	Olfson *et al.*[30]
ODT Olanzapine	16.8%	Assumption: ODT is equal to its
ODT Risperidone	14.0%	respective SOT formulation
ODT Aripiprazole	3.6%	

EPS, extrapyramidal symptoms; ODT, orally disintegrating tablet [formulation]; SOT, standard oral tablet [formulation].

the model's nine possible adherence/relapse outcomes. Each average survey response was assigned the published utility value[37].

Table 10 also reports baseline assumptions concerning disutility among patients experiencing treatment-emergent adverse events. The disutility multipliers for EPS and clinically significant weight gain were derived from Lenert *et al.*[37]. Since there are no known peer-reviewed articles reporting utility information for patients with schizophrenia experiencing diabetes or hyperlipidemia, we assumed that utilities among patients experiencing diabetes or hyperlipidemia were equal to utilities of patients experiencing EPS. This assumption was based on the highest, thus most conservative, estimate of adverse event disutility in the Lenert utility study among model's disutility values.

Medication costs

Medication cost is often related to daily dose levels. To use comparable medication doses for the treatment of schizophrenia patients, we used daily dose levels reported in published, randomized, controlled, schizophrenia studies[26,38,39]. Table 11[26,38–41] reports baseline model assumptions concerning dosing and cost for each medication, reflected by 2010 net wholesale price (NWP)[40], showing that, in the US, antipsychotics in ODT formulations cost more than their SOT counterparts.

Health services resource utilization

Resource utilization assumptions for nine types of healthcare services across five patient outcomes and their data sources are reported in Table 12[29,32]. The length of stay during psychiatric inpatient hospitalization for schizophrenia is derived from the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample[29]. All other baseline utilization assumptions made were consistent with prior US cost-effectiveness research[16,32].

Health service resource costs

The baseline costs of each health service resource are reported in Table 13. All unit costs were inflated to reflect the value of 2010 US dollars using the medical services component of the consumer price index[42].

Cost of adverse events

The model captures the direct healthcare cost associated with treating four types of treatment-emergent adverse events. Input values and their data sources are presented in Table 14[42–45]. The model assumes that all patients have undergone metabolic monitoring according to published expert consensus guidelines[44], which include lab costs for fasting glucose level or hemoglobin A1c at the time of initiation, 4 months after starting, and at 12 months. However, we assumed patients with clinically significant weight gain would incur the cost of undergoing metabolic monitoring every 4 months.

Table 8. Treatment discontinuation rates.

Parameter	Value (%)				Data Source
Annual all-cause discontinuation rates					
Olanzapine	54%				Lieberman *et al.*[26]
Risperidone	63%				Lieberman *et al.*[26]
Aripiprazole	61%				Fleischhacker *et al.*[35]
ODT Olanzapine	54%				Assumption: ODT is equal to its respective SOT formulation
ODT Risperidone	63%				
ODT Aripiprazole	61%				
Annual discontinuation rates by reason					
	Lack of efficacy	Intolerability	Patient decision	Other	
Olanzapine	13%	16%	20%	5%	Lieberman *et al.*[26]
Risperidone	22%	10%	22%	9%	Lieberman *et al.*[26]
Aripiprazole	15%	18%	23%	5%	Fleischhacker *et al.*[35]
ODT Olanzapine	13%	16%	20%	5%	Assumption: ODT is equal to its respective SOT formulation
ODT Risperidone	22%	10%	22%	9%	
ODT Aripiprazole	15%	18%	23%	5%	

ODT, orally disintegrating tablet [formulation]; SOT, standard oral tablet [formulation].

Table 9. Treatment switch patterns by reason for switching.

Medication switch to→	OLZ/ODT-OLZ	RIS/ODT-RIS	ARI/ODT-ARI	Ziprasidone-SOT	Clozapine-SOT
Medication switched from ↓ by reason					
Lack of efficacy					
OLZ/ODT-OLZ	0%	0%	0%	0%	100%
RIS/ODT-RIS	100%	0%	0%	0%	0%
ARI/ODT-ARI	50%	50%	0%	0%	0%
Weight gain/diabetes/hyperlipidemia					
OLZ/ODT-OLZ	0%	0%	100%	0%	0%
RIS/ODT-RIS	0%	0%	100%	0%	0%
ARI/ODT-ARI	0%	0%	0%	100%	0%
EPS					
OLZ/ODT-OLZ	0%	0%	100%	0%	0%
RIS/ODT-RIS	50%	0%	50%	0%	0%
ARI/ODT-ARI	100%	0%	0%	0%	0%
Patient preference					
OLZ/ODT-OLZ	0%	70%	30%	0%	0%
RIS/ODT-RIS	70%	0%	30%	0%	0%
ARI/ODT-ARI	70%	30%	0%	0%	0%

ARI, aripiprazole; EPS, extrapyramidal symptoms; OLZ, olanzapine; RIS, risperidone; ODT, orally disintegrating tablet [formulation]; SOT, standard oral tablet [formulation].

Table 10. Utility values for health states and disutility multipliers for treatment-emergent adverse events.

Parameter	Value			Data source
	Full adherence	Partial adherence	Non-adherence	
Health states				
While stable	0.88	0.75	0.75	Lenert *et al.*[37]; Expert opinion
Outpatient relapse	0.74	0.63	0.63	
Inpatient psychiatric relapse	0.53	0.53	0.42	
TEAE				
EPS	0.888			Lenert *et al.*[37]
Clinically significant weight gain	0.959			
Diabetes	0.888			Assumption: diabetes, hyperlipidemia and metabolic syndrome, utilities equal EPS utility in Lenert *et al.*[37]
Hyperlipidemia	0.888			

EPS, extrapyramidal symptoms; ODT, orally disintegrating tablet [formulation]; TEAE, treatment-emergent adverse event.

Table 11. Economic input parameters; medication costs.

	Cost (US Dollars)	Mean modal daily dose (mg)	Data source
Olanzapine	$21.06	15	NWP Prices: Analysource Data[40]
Risperidone	$0.83	4	Doses: Conley and Mahmoud[38]; Tunis *et al.*[41]; Lieberman *et al.*[26]; Kern *et al.*[39]
Aripiprazole	$14.27	15	
ODT Olanzapine	$22.04	15	
ODT Risperidone	$15.46	4	
ODT Aripiprazole	$16.99	15	Assumption: Generic risperidone NWP price = $0.83 per 4 mg/day

Table 13. Economic input parameters: unit costs of health service resources.

Health services	Unit cost (US Dollars) [42]	Data source
Inpatient hospital, per day	$828	AHRQ HUCP[29]
Day hospital treatment, per day	$501	
Emergency room visit, per visit	$480	
Outpatient Care		Edwards, 2005[32]
Physician visit, per visit	$74	
Mental health clinic visit	$75	
Home healthcare, per hour	$82	
Group therapy, per hour	$71	
Nutritionist visit, per hour	$111	

EPS = extrapyramidal symptoms; no. = number; NWP = 2010 net wholesale price; ODT = orally disintegrating tablet [formulation]

Table 12. Economic input parameters: health service resource utilization.

Health service	Per stable quarter*	Per outpatient relapse event*	Per inpatient relapse event*	EPS*	Clinically significant weight gain*	Diabetes	Hyper-lipidemia	Data source
Hospitalization, days	0.0	0.0	11.7**	0.0	0.0	0	0	*Edwards 2005[32]
Day hospital treatment, days	0.0	1.25	1.25	0.0	0.0	0	0	*Furiak 2009[16]
Emergency room visits, no.	0.0	1.0	1.0	0.0	0.0	0	0	**AHRQ HCUP[29]
Physician visits, no.	3.0	1.0	1.0	1.0	0.5	0	0	
Mental health clinic visits, no.	4.5	2.0	2.0	1.0	2.5	0	0	
Home care, hours	0.0	2.75	2.75	0.0	0.0	0	0	
Group intervention, hours	1.5	1.5	1.5	0.0	5.0	0	0	
Nutritionist visits, hours	0.0	0.0	0.0	0.0	2.5	0	0	

EPS = extrapyramidal symptoms; no. = number; NWP = 2010 net wholesale price; ODT = orally disintegrating tablet [formulation]

Model outcome measures

Clinical outcomes

The model estimates three key clinical outcomes: the proportion of patients experiencing outpatient relapse, those experiencing inpatient relapse, and those without an inpatient or outpatient relapse (i.e., stable).

Economic outcomes

The model also reports mean total direct healthcare costs for the following outcomes: cost of stable patients, cost of outpatient relapse, cost of inpatient relapse, and cost of adverse events. Finally, the model reports the total annual antipsychotic medication cost by medication group.

Cost-effectiveness information

The major cost-effectiveness outcome is cost per 1 QALY gained for each medication. The model also calculates incremental cost-effectiveness ratios (ICERs) as the difference in costs divided by the difference in the appropriate measure of effectiveness.

Results

Clinical outcomes

Figure 2 presents base case results for the key clinical outcomes. Overall, olanzapine ODT was the most effective option reflecting the lowest outpatient relapse rate (14%), lowest inpatient relapse rate (15%), and highest percentage of stable patients (not relapsed) during the study period (72%). Olanzapine SOT was the second most effective medication across these clinical outcomes. Olanzapine ODT yielded the fewest mean inpatient relapses per patient (Figure 3) and the highest QALY (Figure 4). Results also indicate that each of the three antipsychotics in ODT formulations (olanzapine, risperidone, and aripiprazole) outperformed their respective SOT formulations.

Economic outcomes

Figure 5 presents the base case overall direct healthcare cost for each treatment group. The model predicted that the mean total annual costs associated with risperidone SOT—the only atypical antipsychotic available generically in the US—were the lowest ($8881), with olanzapine SOT having the second lowest estimated total

Table 14. Economic input parameters: costs of adverse events.

Adverse event	Cost (US Dollars)	Unit	Data source
Diabetes	$600	Per quarter costs, costs of total care	Vera-Llonch, 2004[43]; BLS CPI[42]
Hyperlipidemia	$225	Per quarter statin therapy	Online drugstore costs[45]
EPS	$12	Per quarter anticholinergic therapy	Online drugstore costs[45]
Metabolic monitoring (laboratory costs)	$40	At therapy initiation, at 4 and 12 months; every 4 months if clinically significant weight gain	Marder, 2004[44]

EPS = extrapyramidal symptoms; no. = number; NWP = 2010 net wholesale price; ODT = orally disintegrating tablet [formulation]

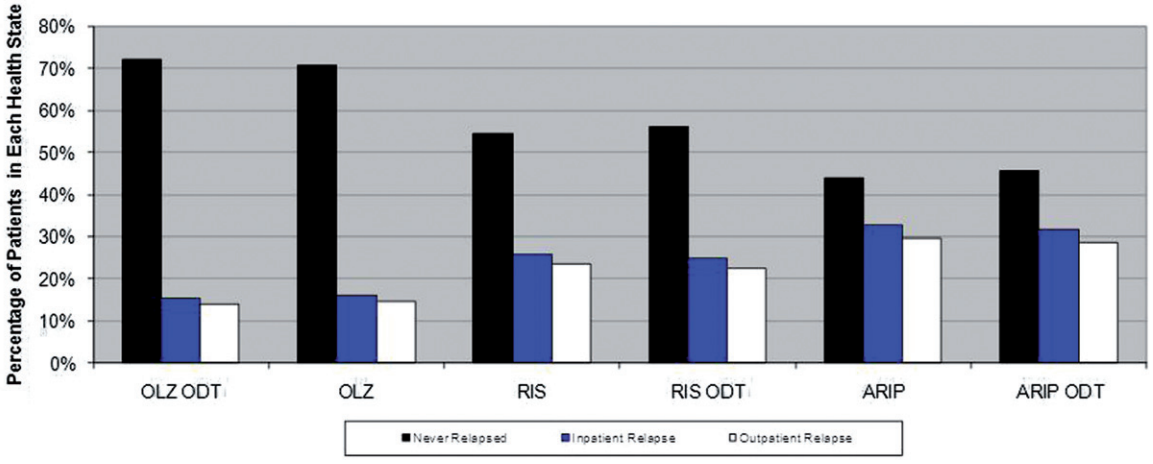

Figure 2. Base case clinical outcomes: Relapse rates. ARIP, aripiprazole; ODT, orally disintegrating tablet [formulation]; OLZ, olanzapine; RIS, risperidone.

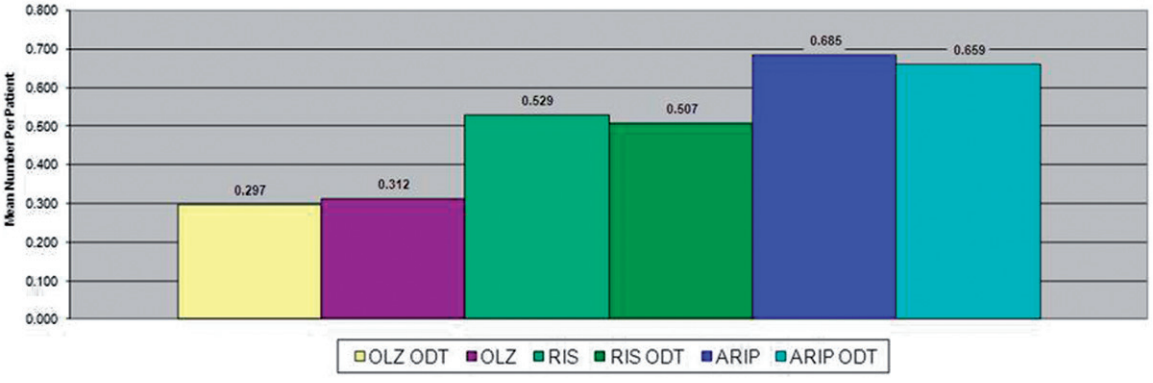

Figure 3. Base case clinical outcomes—Inpatient relapses. Mean number of inpatient relapses per patient. ARIP, aripiprazole; ODT, orally disintegrating tablet [formulation]; OLZ, olanzapine; RIS, risperidone.

direct medical cost ($9533) followed by olanzapine ODT ($9808). Figure 5 also presents the mean annual direct costs for selected estimated cost components (i.e., outpatient, inpatient, adverse events, and medication). These results indicate that the mean annual cost varied by selected cost component. For example, olanzapine ODT and olanzapine SOT had the highest annual medication acquisition cost ($4007 and $3566, respectively), while risperidone SOT (generic cost) had the lowest ($463). In addition, olanzapine ODT and SOT had the highest mean annual total cost of treating relapse-free (stable) patients, $1621 and $1607, respectively. On the other hand, the model estimated that olanzapine ODT had the lowest annual mean cost of treating relapses in either inpatient ($3376) or outpatient ($432) settings, and olanzapine SOT had the second lowest cost for both types of relapses ($3541 and $449, respectively).

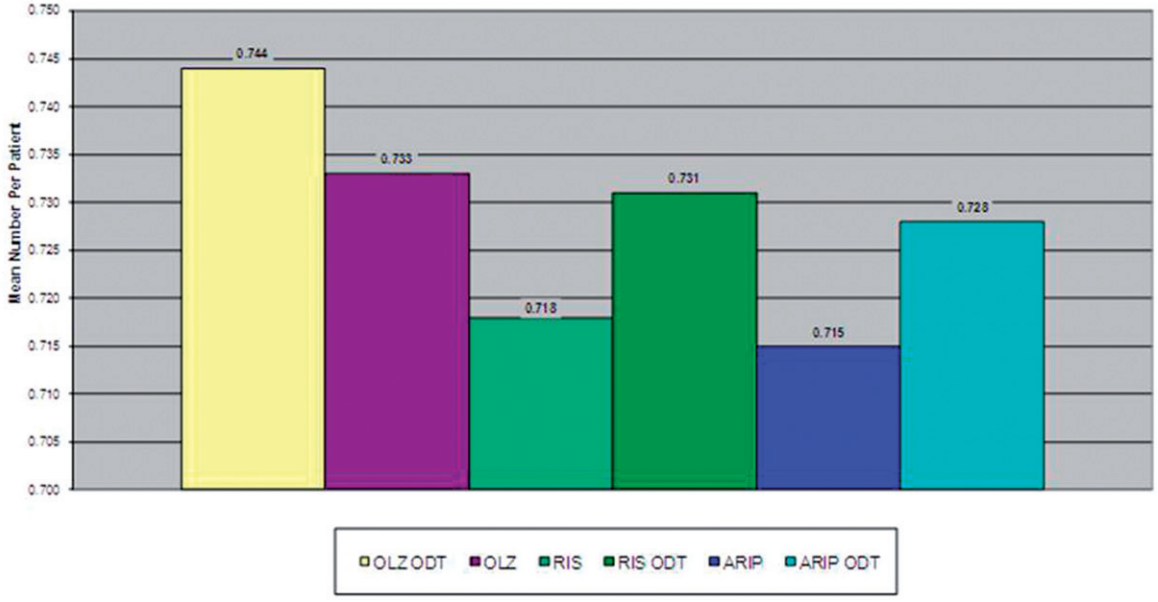

Figure 4. Base case clinical outcomes—Mean QALYs gained. ARIP, aripiprazole; ODT, orally disintegrating tablet [formulation]; OLZ, olanzapine; QALYs, quality-adjusted life years; RIS. risperidone.

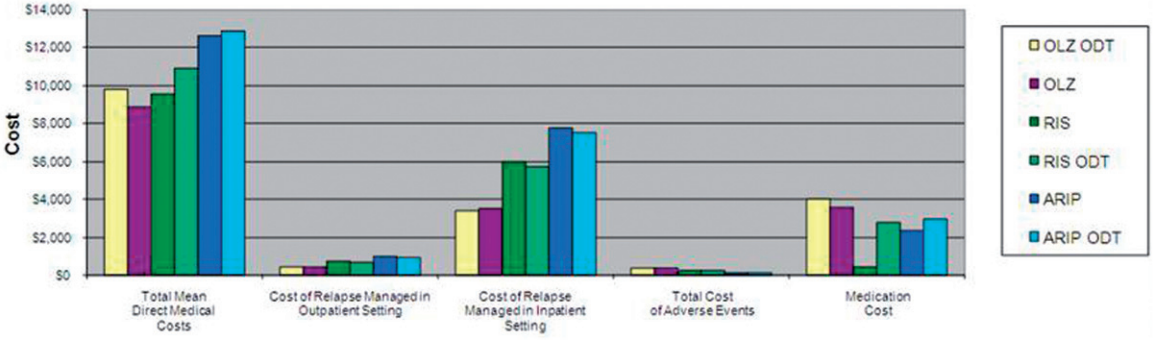

Figure 5. Base case economic outcomes. ARIP, aripiprazole; ODT, orally disintegrating tablet [formulation]; OLZ, olanzapine; RIS, risperidone.

Cost-effectiveness

Cost-effectiveness results for the base case (Table 15) show that, compared with olanzapine SOT therapy, olanzapine ODT therapy was more costly ($9808 vs $9533) but more effective in terms of better QALYs (0.747 vs 0.733) and a lower hospitalization rate (15% vs 16%) (Table 16). Direct pairwise comparisons (Table 15) of olanzapine ODT and other therapies show that olanzapine ODT was cost-effective compared with olanzapine SOT (ICER: $19,643) and risperidone SOT therapy (ICER: $39,966), and dominant (less costly and more effective) compared with risperidone ODT and aripiprazole in ODT or SOT formulations.

Table 16 shows the base case relapse rates and mean number of inpatient relapses per person per treatment group, indicating that the cost-effectiveness of olanzapine ODT is driven by its lower rates of relapse and its higher proportion of patients who are relapse-free (stable).

Table 15. Base case cost-effectiveness results.

	Total cost (US Dollars)	Mean QALYs	ICER (Cost/QALY)
Olanzapine	$9,533	0.733	$19,643
Risperidone	$8,881	0.718	$39,966
Aripiprazole	$12,589	0.715	Dominated
ODT Olanzapine	$9,808	0.747	–
ODT Risperidone	$10,922	0.731	Dominated
ODT Aripiprazole	$12,863	0.728	Dominated

ODT, orally disintegrating tablet [formulation]; QALY, quality-adjusted life years.

Table 16. Base case relapse rates.

	Relapse rate resulting in an inpatient admission	Relapse rate resulting in an outpatient visit	Proportion of stable patients (never relapsed)	Mean number of inpatient relapses per person
Olanzapine	16%	15%	71%	0.312
Risperidone	26%	23%	55%	0.529
Aripiprazole	33%	30%	44%	0.685
ODT Olanzapine	15%	14%	72%	0.297
ODT Risperidone	25%	23%	56%	0.507
ODT Aripiprazole	32%	29%	46%	0.659

ODT, orally disintegrating tablet [formulation].

Table 17. One-way sensitivity analysis and QALY ICERs for ODT olanzapine vs olanzapine (standard oral tablet formulation).

	Parameter values		ICER
	ODT Olanzapine	Olanzapine	ODT Olanzapine vs Olanzapine
Absolute proportion of patients fully adherent	23%	23%	Dominated
	33%	23%	$27,100
	37%*	23%	$19,643
	53%	23%	$8,700
Absolute rates of annual discontinuation	60%	54%	$15,923
	54%*	54%	$19,643
	48%	54%	$20,750
	42%	54%	$22,942
Relative risk of relapse	1.00*	1.00	$19,643
	0.85	1.00	Dominant
	0.80	1.00	Dominant
	0.75	1.00	Dominant
Cost of therapy, US dollars	$21.06	$21.06	$8,071
	$22.04*	$21.06	$19,643
	$22.04*	$22.04	$8,571

*Indicates model base case value.
ICER, incremental cost-effectiveness ratios; ODT, orally disintegrating tablet [formulation].

Sensitivity analyses results

Three parameters were evaluated in one-way sensitivity analysis: adherence, persistence, and differential rates of relapse between olanzapine ODT and olanzapine SOT (Table 17). In real life, patients who are considered poorly adherent can be non-adherent or partially adherent to their medication regimen. It was of interest to assess whether results of the model will change in a meaningful manner if the non-adherent become fully adherent or whether the partially adherent become fully adherent in usual care. The sensitivity analysis varied the proportion of patients who become fully adherent after being previously non-adherent or partially adherent. The analyses on the proportion of fully adherent patients show that olanzapine ODT is cost-effective when this proportion is increased. Additional analysis (data not shown) predicted that olanzapine ODT is cost-effective regardless of the patients' prior adherence level (partial adherence or non-adherence): olanzapine ODT yielded nearly as many QALYs gained when the proportion of fully adherent patients was 23%, regardless of the category from which patients were taken (partial adherence or non-adherence).

The analyses on the absolute rates of annual discontinuation (persistence) show that olanzapine ODT is cost-effective for a 60% annual discontinuation rate as well as a 54% rate of discontinuation and remains cost-effective when the discontinuation is less than the discontinuation rate for olanzapine SOT. The costs in the last two scenarios are a consequence of higher costs due to greater persistence of a slightly more costly therapy. One-way results on the relative risk of relapse showed that, when the relapse rates of olanzapine ODT and olanzapine SOT were the same, olanzapine ODT was more costly, more effective, and cost-effective relative to the $50,000/QALY threshold. Olanzapine ODT afforded greater cost savings as the relative risk of relapse decreased. Furthermore, when medication acquisition costs of olanzapine ODT and oral are equal, there is an ICER of $8071 per QALY, which is half the base case ICER ($19,643). The total healthcare costs are not equal due primarily to the more expensive switch pattern for olanzapine ODT than olanzapine SOT (as the model assumes that switching from any ODT formulation is preferred over another ODT formulation).

The PSA was performed on adherence (proportion of fully adherent patients, Figure 6), persistence (annual discontinuation rate, Figure 7), and relative risk of relapse (Figure 8) as well. The PSA results are presented as 'willingness to pay' curves, which are based upon 1000 simulations of 1000 person cohorts, and they show the proportion of cohorts whose mean cost per QALY was at or below selected threshold levels. Distributions were created for all model parameters except for the aforementioned. Beta distributions were used for probabilities and log-normal distributions for cost parameters. Cost parameters were correlated, as were parameters affecting relapse, adherence, and persistence. The simulation was then executed, changing each of the parameters listed across four values, one of which was the base case.

Figures 6–8 illustrate the results of each of these simulation groups. When sampling model parameters from distributions, adherence had a large impact on the range of results (Figure 6). The black line in Figure 6 indicates that when the difference in initial adherence between olanzapine ODT and olanzapine SOT is 30% the proportion of cohorts below any threshold is relatively constant (58–65%). In contrast, the remaining three series in Figure 6 indicate that the proportion of cohorts below a selected

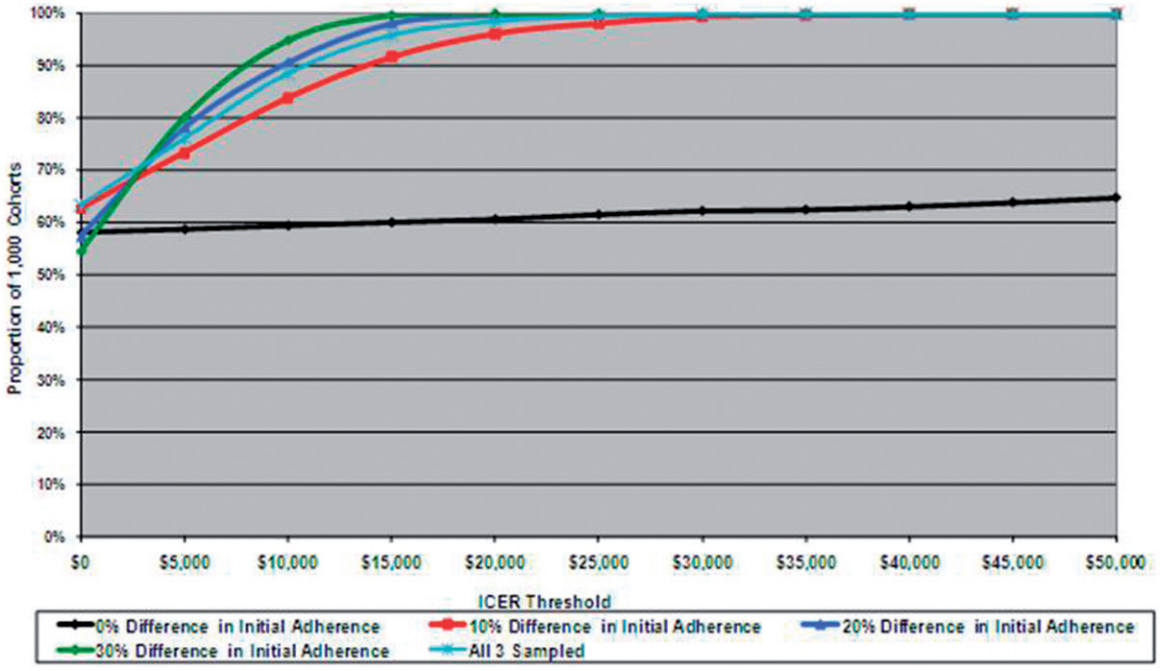

Figure 6. Proportion of cohorts at or below selected ICER thresholds varying proportion of patients fully adherent. *The increase in full adherence for olanzapine ODT is assumed to come from the partially adherent patients. ICER, incremental cost-effectiveness ratios; ODT, orally disintegrating tablet [formulation]; OLZ, olanzapine.

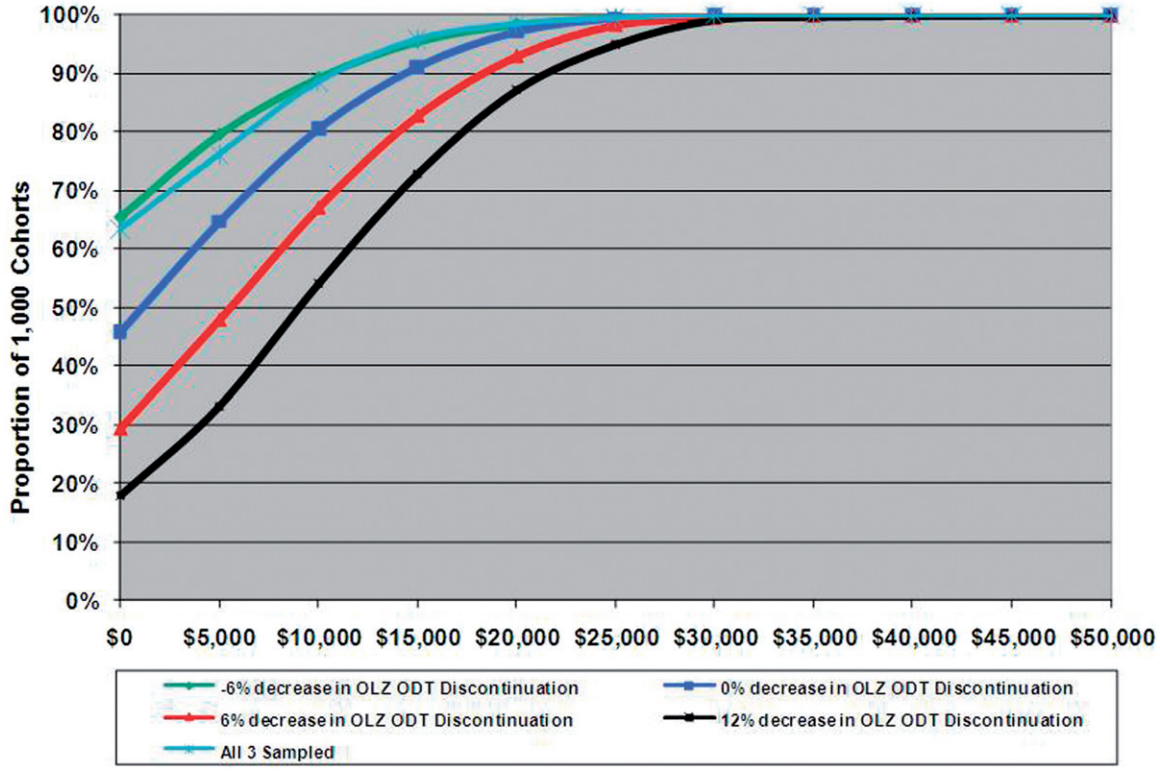

Figure 7. Proportion of cohorts at or below selected ICER thresholds varying the absolute difference in annual discontinuation rate. ICER, incremental cost-effectiveness ratios; ODT, orally disintegrating tablet [formulation]; OLZ, olanzapine.

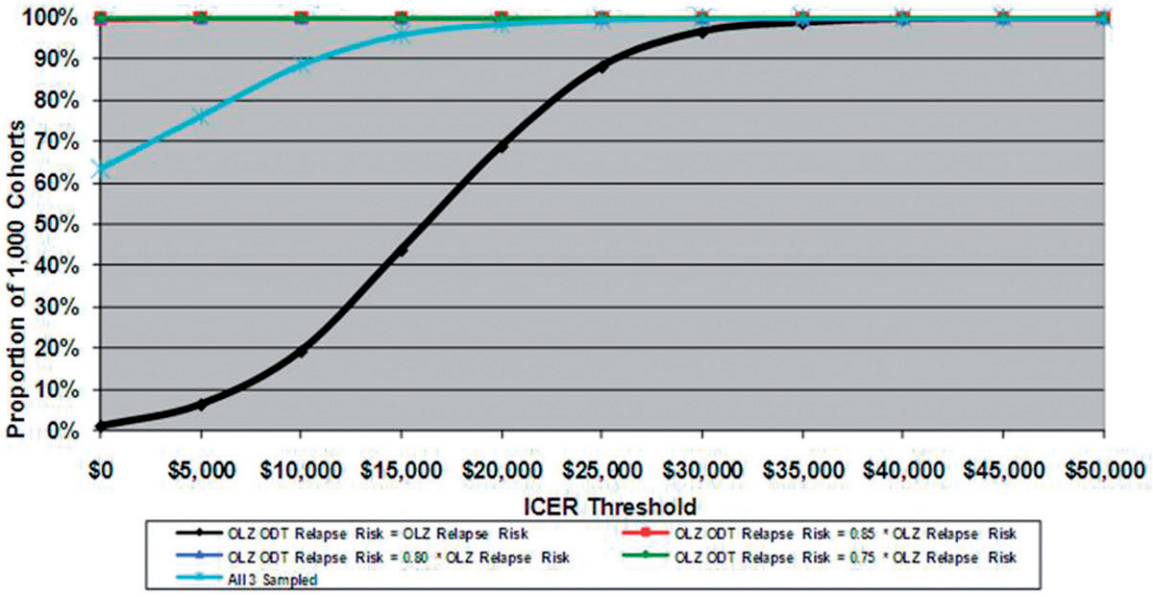

Figure 8. Proportion of cohorts at or below selected ICER thresholds varying the relative risk of relapse. Relative risk (RR) is used to calculate ODT OLZ relapse rates relative to OLZ (ODT OLZ = RR * OLZ). ICER, incremental cost-effectiveness ratios; ODT, orally disintegrating tablet [formulation]; OLZ, olanzapine.

ICER threshold increase as the value of the threshold increases.

Figure 7 demonstrates that persistence (annual discontinuation rate) increases the proportion of cost-effective cohorts by ~10% for each 6% absolute change in annual persistence rate. However, all cohorts for all persistence values were generally cost-effective if the willingness to pay to gain one QALY was $25,000.

Perhaps the greatest range of values can be gained by manipulating the relative risk of relapse. In Figure 8, the data represented by the black line are based upon equal rates of relapse between olanzapine ODT and olanzapine SOT, where 100% of the simulations were cost-effective at the $40,000 level. However, a relative risk of 0.85 (ODT vs SOT) moves the results significantly, where 100% of the cohorts simulated are cost-effective at the $5000 level. Finally, all olanzapine ODT cohorts were cost-effective if the relative risk of relapse for olanzapine ODT was 75% of the risk of relapse for olanzapine SOT (risk reduction = 25%). A 'willingness to pay' curve represents the probability that an intervention is cost-effective as a third-party payer changes the CE threshold at which they accept that a treatment is cost-effective. For example, in the 'willingness to pay' curve depicted in Figure 8, the dependent axis represents the probability that OLZ ODT is cost-effective when compared to OLZ SOT. The black line in Figure 8 shows that if a third-party payer accepts that $50,000/QALY gained is a suitable CE threshold then all of the cases simulated on OLZ ODT are predicted to be cost-effective compared to OLZ SOT. However, if a third-party payer has a lower acceptable threshold of $10,000/QALY gained, then the probability of OLZ ODT being cost-effective is ~0.20 (20% of cases).

Discussion

This is the first study to compare the cost-effectiveness of an ODT with its respective SOT formulation to help estimate the cost-effectiveness of this innovative drug delivery system in the treatment of schizophrenia. This study compared the cost-effectiveness of olanzapine ODT and olanzapine SOT in the usual treatment of schizophrenia patients from a US healthcare perspective, and further compared olanzapine ODT with two other atypical antipsychotics available in both ODT and SOT formulations—risperidone and aripiprazole. By expanding and updating our previously published micro-simulation economic decision-making model[16], which compared the cost-effectiveness of olanzapine SOT with other atypical antipsychotics in SOT formulations in the treatment of schizophrenia in the US, this study projected that antipsychotics in ODT formulations are more cost-effective than their respective SOT formulations. This micro-simulation model further projects that olanzapine ODT is cost-effective compared with risperidone and aripiprazole in both SOT and ODT formulations.

Base case results of this study, reinforced by results of multiple one-way and PSA (e.g., PSA results based on 1000 simulations of 1000 person cohorts), show that utilization of olanzapine ODT for the treatment of schizophrenia was slightly more costly (by $275 per patient per

year), but more effective in terms of a lower relapse and hospitalization rate and better disease-specific QALYs than olanzapine SOT therapy, translating to an ICER of $19,643. Olanzapine ODT was also projected to be more cost-effective compared with risperidone SOT using its generic cost (ICER: $31,966) and less costly and more effective—thus considered a dominant choice—compared with risperidone ODT and aripiprazole in ODT and SOT formulations.

In developing this micro-simulation model, we tried to accurately simulate the dynamic treatment of schizophrenia in usual care settings in the US, where patients may start then switch, continue, or discontinue their medication for a number of reasons, including lack of medication efficacy or treatment-emergent adverse events. Taking into account the heterogeneity of schizophrenia (e.g., differences in patient health states profiles, variations in their adherence levels) and the complexity of its treatment in clinical practice, this micro-simulation model used scientifically sound published data to populate clinical and economic parameters, such as event probabilities, types of resource used and their direct costs, and minimize the need to rely on expert opinion.

Importantly, one of the core assumptions of the model was that better adherence on ODT would lead to more favourable clinical outcomes, including a lower risk of relapse and hospitalization, and thereby alter the cost-effectiveness ratio. The robust link between medication adherence and outcomes has been repeatedly demonstrated in numerous schizophrenia studies, using various methods that range from double-blind randomized trials[26] to prospective observational studies[20,23] and retrospective claims database analyses[3,4,31]. In addition, the assumption that patients are more adherent on ODT formulations than on SOT formulations of the same antipsychotic medication was based on data from a published 16-week randomized double-blind, double-dummy study that compared olanzapine ODT and olanzapine SOT in the treatment of patients with schizophrenia[13]. Although that study had a robust experimental design, it is unknown whether its findings will extrapolate to long-term adherence in real life. Further naturalistic observational research will be needed to address this important question. While this model's core assumption was based on data from a single study, the only randomized study to offer a head-to-head comparison of adherence levels of the two formulations, this study is augmented by other studies in which olanzapine ODT was associated with improved patient attitudes toward medication[11,12] and with improved medication adherence at inpatient and outpatient settings[11–13]. These findings are also consistent with a published randomized, open-label, cross-over study that compared patient preference for olanzapine ODT vs olanzapine SOT[14], which found the majority of patients (61%) preferred olanzapine ODT, whereas only 27% preferred olanzapine SOT, and 12% expressed no preference. Taken in conjunction with the high probability of cost-effectiveness predicted by the model, the scientific literature shows consistent support for this model's core assumptions, although additional supportive data will be needed from usual care settings.

To maximize the model's validity and transparency, we examined the uncertainty in the model and the stability of the results using one-way sensitivity analysis and PSA for the model's core assumptions on differential adherence, persistence, and rates of relapse, showing the robustness of the base case findings. Although adherence had a relatively large impact on the range of results, the main driver of the model's findings was relapse requiring inpatient hospitalization, which is the costliest component in the treatment of schizophrenia. However, adherence and relapse are related, as better adherence is linked to a lower risk of psychiatric hospitalization in the treatment of schizophrenia. Generally, prior schizophrenia research[3,4,20,23] has shown that, compared to adherent patients, the non-adherent are about twice as likely to have psychiatric hospitalizations over a 1-year period. Considering that hospitalization (i.e., relapse requiring inpatient hospitalization) was the core driver in this model, it is important to underscore that psychiatric hospitalization rates in this model were based on the National Institute of Mental Health-sponsored CATIE trial[26], in which olanzapine-treated patients had the lowest annual rate of hospitalization for exacerbation of schizophrenia. While the CATIE trial showed that atypical antipsychotics significantly differ from each other on effectiveness as well as on safety and tolerability profiles, it is important to note that differential efficacy among atypical antipsychotics has also been shown in a recent meta-analysis. In their comprehensive meta-analysis, Leucht *et al.*[46] included 293 publications of 78 studies, with 13,558 participants manifesting a relatively chronic course of schizophrenia, and found the SOT formulation of olanzapine to be superior to aripiprazole and risperidone (also superior in comparisons with quetiapine and ziprasidone). Their sensitivity analyses showed that results were robust with regard to the effects of pharmaceutical industry sponsorship of some studies, antipsychotic dosages, study quality, and trial duration. Findings of our cost-effectiveness study—as they specifically pertain to olanzapine and aripiprazole in SOT formulations—are consistent with a recent cost-effectiveness study comparing these two antipsychotics[47]. That study used patient-level data from a randomized, double-blind study comparing olanzapine and aripiprazole in the treatment of patients with schizophrenia. Olanzapine was found to be a dominant cost-effective choice, because it was associated with greater effectiveness at lower total healthcare costs[47].

Our model has, however, a number of limitations. First, lack of published medical literature for some model input

parameters (e.g., QALYs by health states and adherence levels) required using expert panel opinions. In addition, lack of head-to-head randomized studies comparing all three studied atypical antipsychotics (i.e., olanzapine, risperidone, and aripiprazole) required making input assumptions that need further study (e.g., that aripiprazole and ziprasidone are similar on clinical and safety features). Second, the model does not include all antipsychotics currently available in the US in ODT formulation, thus excludes clozapine ODT. This exclusion was made *a priori*, as clozapine is used infrequently in the US and is often reserved for treatment-resistant patients with schizophrenia.

Third, the model used a 1-year time horizon, although schizophrenia is a life-long illness. While this follow-up duration is used in most other schizophrenia cost-effectiveness models, it may not be sufficiently long to observe changes in costs and outcomes over the course of a chronic illness or the potential long-term medical and economic impact of metabolic changes such as weight gain, diabetes, and hyperlipidemia. Moreover, it may also not allow for accurate assessment of specific treatment-emergent adverse events such as tardive dyskinesia which could take longer to develop. However, the use of a 1-year time horizon is often deemed to be sufficient for demonstrating the cost implications of treatment strategies for US payers who typically work with annual budgets and to be also clinically meaningful, as schizophrenia patients tend to frequently change their medication regimens[26].

A fourth limitation of the model is its focus on direct cost and exclusion of indirect cost, which can be substantial in the treatment of schizophrenia. However, this study considered the perspective of the healthcare payers in the US, thus excluded indirect, non-medical costs, such as cost of lost productivity or cost of patient involvement with the criminal justice system. Had indirect costs been considered in the model, it was hypothesized that treatment with olanzapine ODT would have resulted in more favourable results, because the indirect costs of relapse (the major cost driver in the model) would have been much greater. Another limitation is that this model used the 2010 prices and changes in the price of antipsychotics have occurred since that time. To address this issue, we re-ran the model using the generic Net Wholesale Price (accessed December 19, 2011) of risperidone ODT, and found that the results (not shown) were essentially unchanged, except that olanzapine ODT no longer dominated (was less costly and more effective) risperidone ODT, but was more cost-effective than risperidone ODT at ICER of $34,062/QALY. This was not unexpected, as this model's results appear to be driven primarily by the cost of relapse. We also re-run the model using generic NWP (accessed December 19, 2011) of both olanzapine (ODT; SOT) and risperidone (ODT; SOT), as the US patent for branded olanzapine (Zyprexa®) has expired recently in the US (October 23, 2011). Again, results (not shown) remained essentially unchanged; only this time olanzapine ODT was found to dominate—to be less costly and more effective—all of the studied comparators.

Finally, the model did not take into account that some patients may have pre-existing adverse events and medical conditions, including diabetes and hyperlipidemia, which may impact future costs and outcomes. Additional research is needed to help identify which patients with what profiles respond best to which antipsychotic after failure on specific medications for what reasons.

Conclusions

Results from this micro-simulation model, which are evaluated from the perspective of payers in the US healthcare system, suggest that utilization of an antipsychotic in its ODT formulation is more cost-effective than using its SOT formulation in the treatment of schizophrenia. More specifically, olanzapine ODT was found to be more cost-effective than olanzapine SOT and more cost-effective than risperidone and aripiprazole in either ODT or SOT formulations. This model simulates real-world treatment processes and provides projections that should be used only to inform decision-making processes from the US healthcare system perspective. As with any other economic model, current findings will require future revision and validation of baseline assumptions when new and additional relevant scientific data are available.

Transparency

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This study was funded by Eli Lilly and Company.

Author contributions
HAS initiated the model, helped with model development, interpretation of the results, and preparation of the manuscript. NMF developed the model, conducted the sensitivity analyses, interpreted the results, and helped draft the manuscript. AHL, RRC, and SDC helped interpret the results and assisted with manuscript preparation and revision. RWK and LJS helped develop the model and its sensitivity analyses. All authors read and approved the final manuscript.

Declaration of financial and other relationships
Haya Ascher-Svanum, Anthony Lawson, and Robert Conley are all full-time employees and minor shareholders of Eli Lilly and Company. Nicolas Furiak, Robert Klein, Lee Smolen, and Steven Culler have had consulting agreements with Eli Lilly and Company.

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