Outcomes and Costs of Risperidone versus Olanzapine in Patients with Chronic Schizophrenia or Schizoaffective Disorders: A Markov Model

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ABSTRACT

Objective: To compare expected outcomes and costs of care in patients with chronic schizophrenia or schizoaffective disorders who are treated with risperidone versus olanzapine.

Methods: A Markov model was developed to examine outcomes and costs of care in patients with chronic schizophrenia or schizoaffective disorders receiving risperidone or olanzapine. The time frame of interest was 1 year. The model focused particular attention on the likelihood of therapy switching and discontinuation as a result of treatment-emergent side effects, as the efficacy of these two agents is similar. Measures of interest included the incidence of relapse and selected side effects including extrapyramidal symptoms (EPS), prolactin-related disorders and diabetes, expected change in body weight, and the percentage of patients remaining on initial therapy at the end of 1 year. Costs of antipsychotic therapy and psychiatric and nonpsychiatric services also were examined.

Results: At 1 year, the rate of EPS was estimated to be slightly higher for risperidone, as was the incidence of

symptomatic prolactin-related disorders. The expected incidence of diabetes mellitus, while low, was slightly higher for olanzapine. Approximately 25% and 4% of olanzapine and risperidone patients, respectively, were projected to experience an increase in body weight ≥7%. The estimated percentage of patients remaining on initial therapy at the end of 1 year was higher for risperidone than olanzapine (76.9% vs. 45.6%, respectively). Expected mean total costs of care per month of therapy were $2163 for risperidone and $2316 for olanzapine. Results from sensitivity analyses suggest that the probability of therapy discontinuation following weight gain >5 kg would have to be lower than 0.1 for the number of patients remaining on therapy at the end of 1 year to be the same for risperidone and olanzapine.

Conclusions: Compared with risperidone, treatment with olanzapine may result in greater increases in body weight, higher rates of therapy discontinuation, and higher costs of medical-care services.

Keywords: atypical antipsychotics, costs, modeling, outcomes, side effects.

Introduction

While conventional antipsychotics are known to be effective in controlling symptoms in patients with schizophrenia, side effects—especially extrapyramidal symptoms (EPS)—have limited their utility in clinical practice [1,2]. The atypical antipsychotics, such as risperidone and olanzapine, have substantially better side-effect profiles and tolerability than conventional agents [2–4]. Nonetheless, while EPS occurs less frequently with these newer medications, other side effects remain a concern. Patients who

receive risperidone, for example, sometimes experience increased serum prolactin levels [5–7], although the incidence of symptomatic disease appears to be low [8–12]. Weight gain, on the other hand, appears to be more of a problem with olanzapine [13–34].

A meta-analysis that examined over 80 studies that included data on weight change in patients receiving antipsychotics concluded that olanzapine was associated with increases in body weight between 3.9 and 4.5 kg at 10 weeks of treatment on standard doses [15]; corresponding estimates for risperidone were 1.7 and 2.5 kg. Long-term studies have reported average increases of 4 kg to 11 kg over 6 months for olanzapine [17,18,34]. The percentage of olanzapine-treated patients with

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increases in body weight ≥7%—which the US Food and Drug Administration has defined to be "significant" [26]—has been estimated to exceed 26% [6,16,29]. The Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes [35] recently recommended that any patient who experiences a >5% increase in body weight following initiation of an atypical antipsychotic agent be considered for therapy switching. Drug-induced weight gain is of potential concern, as overweight and obesity have been linked to various acute and chronic disease conditions, including hypertension, diabetes, coronary heart disease (CHD), and stroke [36], and approximately 6% of total US health-care spending is attributable to obesity-related diseases [37].

Hyperglycemia, de novo diabetes, and diabetic ketoacidosis also have been reported in patients receiving olanzapine between 5 weeks and 17 months following therapy initiation; cases among patients receiving risperidone have been less frequent [38–50]; the annual incidence of diabetes has been estimated to range from 0.1% to 6.7% for risperidone, and from 0.7% to 14.3% for olanzapine [51–58]. The US Food and Drug Administration recently asked all manufacturers of atypical antipsychotics to include a warning in their package labeling concerning the risks of hyperglycemia and diabetes mellitus [59,60].

Side effects are an important cause of noncompliance, therapy switching, and treatment discontinuation, all of which can increase costs of care and decrease the effectiveness of pharmacotherapy in clinical practice. While the efficacy of risperidone and olanzapine in controlling symptoms of schizophrenia is well established, the impact of their side effects on outcomes and costs of care has not yet been fully investigated. We examine this in our study in light of its growing importance.

Methods

Overview

We developed a Markov model [61] to compare outcomes and costs of care in patients with chronic schizophrenia or schizoaffective disorders that are treated with risperidone versus olanzapine ("study therapies"). The model focuses particular attention on the likelihood of therapy switching and discontinuation as a result of treatment-emergent side effects, as the efficacy of these two agents is similar [62–69]. Patients are followed in the model up to 1 year, until they discontinue antipsychotic therapy, or die, whichever comes first.

Outcomes of interest include the incidence of relapse of symptoms and side effects, including EPS, selected prolactin-related disorders (amenorrhea, breast disorders, and sexual dysfunction), and diabetes, expected change in body weight, and the percentage of patients remaining on initial therapy at the end of 1 year. Expected costs of antipsychotic therapy and psychiatric and nonpsychiatric services were also examined. The perspective of the analysis was that of a third-party payer.

Model parameters were estimated using published and unpublished sources, including data from clinical trials RIS-USA-112 and RIS-USA-79 [6,70,71], expert opinion, and by assumption. First-order simulation (i.e., Monte Carlo) [72,73] techniques were used to generate expected outcomes and costs of care for a hypothetical cohort of 10,000 patients.

Description of Markov Model

The model has six unique health states (four live states plus two capture states). Live states were defined according to selected chronic side effects (none, diabetes, prolactin-related disorders, both). Capture states were defined for patients who died or discontinued study therapy.

Patients were assumed to receive risperidone 4.8 mg daily or olanzapine 12.4 mg daily; these dosages were selected based on the mean modal dosages observed during RIS-USA-112, a large, randomized, multicenter, clinical trial of risperidone and olanzapine in patients with chronic schizophrenia [6,70]. During each monthly cycle of the model, patients were assumed to be at risk of side effects of antipsychotic therapy and relapse of psychiatric symptoms. Side effects that were incorporated into the model included EPS, selected prolactin-related disorders (i.e., amenorrhea, breast disorders, and sexual dysfunction), and diabetes. The model also simulates changes in body weight over time, which is another potential side effect of therapy.

All side effects were assumed to be reversible following therapy discontinuation [2,10,74–76]. Patients were assumed to be at risk of EPS and prolactin-related disorders only during the first 8 weeks of therapy. Patients experiencing EPS or diabetes and who discontinue antipsychotic therapy were assumed to require short-term outpatient care and treatment with oral medications. Patients experiencing prolactin-related disorders or diabetes who remain on therapy were assumed to require long-term follow-up and treatment. Diabetes was assumed to take place independent of weight gain, as this relationship for patients receiving antipsy-

chotic therapy has not been well established in the published literature [29,78]. All patients were assumed to be free of diabetes at the time of model entry. Complications of diabetes (e.g., diabetic ketoacidosis, cardiovascular disease) were not considered.

Patients were assumed to be at risk of weight gain while on therapy; weight gain was assumed to differ by therapy. Changes in body weight during the first 2 months of therapy were assumed to be conditional on body mass index (BMI) at baseline, consistent with published reports (including RIS-USA-112) [29,34,79–81]. Weight gain was assumed to be much less pronounced between 8 weeks and 1 year, consistent with published reports that this phenomenon occurs principally in the first 4 to 12 weeks of treatment [19,82–86] and that further increases in body weight are not likely to exceed 30% [16,34].

All patients were assumed to be at risk of hospitalization for relapse of symptoms. Only one controlled study has examined the incidence of hospitalization for symptom relapse over 1 year for risperidone and haloperidol [71]. Given the lack of data for olanzapine, rates of hospitalization for relapse were assumed to be the same for patients receiving risperidone and olanzapine.

Patients who experience side effects and/or relapse of psychiatric symptoms were assumed either to remain on therapy or discontinue and switch to another agent. For patients experiencing more than one such event (e.g., diabetes and EPS) during any given cycle, the probability of therapy discontinuation was assumed to be equal to that of the event associated with the greater probability of therapy discontinuation. As all patients who discontinue antipsychotic therapy were assumed to switch to another antipsychotic agent, they were assigned the cost of outpatient services reflecting tapering of initial antipsychotic therapy and the initiation of another agent. No other additional costs of care were considered for these patients.

EPS, Prolactin-Related Disorders, and Type 2 Diabetes Mellitus

The risks of EPS and prolactin-related disorders during the first 2 months of risperidone and olanzapine therapy were derived from analyses of treatment-emergent adverse events of moderate or greater severity and "probable" or "very likely" relationship to study drug from the RIS-USA-112 study (Table 1) [6,70]. EPS was defined to include dyskinesia, dystonia, hyperkinesia, hypertonia, tremor, and other unspecified extrapyramidal

Table 1 Model probabilities

Parameter	Value	Source
EPS* (monthly for first 2 months)		
Risperidone	0.046	RIS-USA-112
Olanzapine	0.038	RIS-USA-112
Prolactin-related disorders* (monthly for first 2 months)		
Risperidone	0.024	RIS-USA-112
Olanzapine	0.010	RIS-USA-112
Diabetes (monthly)		
Risperidone	0.0001	Pooled data[†]
Olanzapine	0.0002	Pooled data[†]
Hospitalization for relapse of symptoms (monthly)		
Risperidone	0.009	RIS-USA-79
Olanzapine	0.009	RIS-USA-79
Death from all causes (monthly)	0.0003	Brown et al. 1997
Therapy discontinuation following:		
EPS	0.060	RIS-USA-112
Prolactin-related disorders	0.140	RIS-USA-112
Diabetes		
Risperidone	0.450	Expert opinion[‡]
Olanzapine	0.450	Expert opinion[‡]
Hospitalization for relapse of symptoms	1.000	Assumption
Weight gain		
>5 kg (11 lbs) since initiation	1.000	Russell et al. 2001[§]
≤5 kg (11 lbs) since initiation	0.000	Russell et al. 2001[§]

*Treatment-emergent side effects (relation to drug probable or very likely).
[†]Pooled data [51–57].
[‡]Personal communication, Dr J Meyer and D Henderson.
[§]And references to Masand PS 1998, Sachs GS and Guille C 1988, CWGCTE 1999, and Pjil H and Meinders AE 1996.
Abbreviation. EPS, Extrapyramidal symptoms.

events. Prolactin-related disorders included amenorrhea and unspecified menstrual disorders, breast disorders (i.e., nonpuerperal lactation, breast pain), and sexual dysfunction (i.e., anorgasmia, impotence, sexual dysfunction, ejaculation failure, decreased libido); the percentage of patients with amenorrhea among those experiencing prolactin-related disorders was 14%. Attention was focused on symptomatic disease, and events categorized only as "hyperprolactinemia" without further qualification were not included, as they were assumed not to require treatment and/or lead to discontinuation of antipsychotic therapy. Rates of EPS over 8 weeks of therapy were 9.4% for risperidone and 7.8% for olanzapine; corresponding rates for prolactin-related disorders were 5% and 2%. Monthly probabilities were derived as $1-e^{(-rate \times time)}$ (Declining exponential approximation of life expectancy [DEALE]) (Tree Age Software Inc., Williamstown, Massachusetts, 2001).

Rates of incident (i.e., new-onset) diabetes for patients receiving risperidone and olanzapine were estimated based on a review of data on "new" cases of diabetes from published reports and research abstracts [51–58]. While these studies are considered to have important limitations, the recent Consensus Development Conference position [35] was

that available data consistently showed an increased risk of diabetes in patients treated with olanzapine when compared with patients not receiving antipsychotic therapy, and that the risk in patients taking risperidone was less clear at that time. Model estimates of the monthly risk of diabetes were calculated by pooling data across studies using a random-effects model in which individual estimates from each study were weighted by the inverse of a combination of within- and between-study variation, a technique commonly known as the DerSimonian–Laird method [87]; monthly estimates reflected an annual incidence of 1.5% and 2.3% for risperidone- and olanzapine-treated patients, respectively.

Body Weight and Weight Gain

The distributions of body weight and body mass index (BMI) at therapy initiation were estimated using data from RIS-USA-112 (Table 2). Estimates of the change in body weight by BMI group (<25, 25–29, and ≥30 kg/m^2) for the first 2 months of therapy also were based on data from RIS-USA-112 on the distribution of the change in body weight at endpoint (or 8 weeks) (Table 3).

The mean monthly change in body weight from months 2 through 12 for patients receiving risperidone was calculated based on the mean weight gain (1.5 kg) at endpoint among patients receiving risperidone in RIS-USA-112, and the mean weight gain (2.49 kg) at 52 weeks among patients receiving risperidone (4.9 mg daily) in the RIS-USA-79 study [77]. The mean monthly change in body weight for patients receiving olanzapine was calculated based on the mean weight gain (3.3 kg) at endpoint for patients receiving olanzapine in

Table 2 Baseline body weight and body mass index (BMI)*

Parameter	Value
Distribution of body weight (kg)‡	
Min	41.7
25%	68.9
50%	81.6
75%	94.8
Max	167.4
Distribution of body mass index (BMI) (kg/m^2)‡	
Min	10.0
25%	23.0
50%	27.0
75%	32.0
Max	57.0

*Source: RIS-USA-112; all randomized patients (n = 359).
†RIS-USA-112: Risperidone (84.2 ± 20.4) and olanzapine (82.9 ± 19.8) (mean ± SD).
‡RIS-USA-112: Risperidone (29.4 ± 13.6) and olanzapine (28.0 ± 6.2) (mean ± SD).

Table 3 Changes in body weight over 1 year following therapy initiation, by study therapy and baseline BMI

Therapy/BMI	Value
Distribution of changes in body weight (kg) (monthly for first 2 months of therapy)*	
Risperidone (4.8 mg daily)	
BMI < 25	
Min	−1.80
25%	0.00
50%	0.68
75%	2.05
Max	4.75
BMI 25–29	
Min	−1.80
25%	0.00
50%	0.58
75%	1.83
Max	7.70
BMI ≥ 30	
Min	−4.50
25%	−0.90
50%	0.45
75%	1.60
Max	7.70
Olanzapine (12.4 mg daily)	
BMI < 25	
Min	−2.95
25%	0.80
50%	1.60
75%	2.70
Max	9.30
BMI 25–29	
Min	−3.85
25%	−0.20
50%	1.025
75%	3.15
Max	9.75
BMI ≥ 30	
Min	−4.10
25%	0.00
50%	1.35
75%	2.30
Max	9.05
Mean change in body weight (kg) (monthly) (months 3–12)	
Risperidone† (4.9 mg daily)	0.09
Olanzapine‡ (12.4 mg daily)	0.19

*RIS-USA-112: Risperidone (1.5 ± 3.5) and olanzapine (3.3 ± 5.1) (mean ± SD) and by BMI as follows: Risperidone (1.8 ± 3.1) and olanzapine (4.1 ± 4.6) (mean ± SD); Risperidone (1.9 ± 3.4) and olanzapine (3.0 ± 5.3) (mean ± SD); Risperidone (1.0 ± 3.9) and olanzapine (2.6 ± 5.3) (mean ± SD).
†RIS-USA-79, based on 2.49 kg at 52 weeks.
‡Beasley et al. 1996 and 1997 and assumption, based on 5.2 kg at 52 weeks.
Abbreviation. BMI = Body mass index (kg/m^2).

the RIS-USA-112 study, and the mean weight gain (5.2 kg) at 1 year as reported in two randomized, double-blind, controlled trials [32,33]. A mean weight gain at 1 year of 5.2 kg among patients receiving olanzapine was estimated by interpolation of the values for changes in body weight (3.8 kg and 12.0 kg, respectively) at 1 year among patients receiving olanzapine (11.6 mg daily and 16.3 mg daily), as changes in body weight for patients receiving long-term therapy with olanzapine 12.4 mg daily were not available from these sources.

Hospitalization for Relapse

The annual risk of hospitalization for relapse of symptoms of schizophrenia among patients receiving risperidone (11.2%) was estimated based on the 1 year risk of hospitalization for relapse among patients receiving risperidone in a randomized, double-blind, placebo-controlled clinical trial [71,77]. Risk of hospitalization for relapse among olanzapine patients was assumed to be the same as that of patients receiving risperidone.

Discontinuation of Antipsychotic Therapy

Probabilities of therapy discontinuation for risperidone and olanzapine patients experiencing EPS and prolactin-related disorders, respectively, were estimated based on rates of study discontinuation in RIS-USA-112 for treatment-emergent EPS and prolactin-related disorders of moderate or greater severity and "probable" or "very likely" relationship to study drug. Six and 14% of patients who experienced EPS and prolactin-related disorders, respectively, discontinued antipsychotic therapy as a result of these symptoms during RIS-USA-112. The probability of discontinuation due to type 2 diabetes was estimated to be 0.45 for patients receiving either risperidone or olanzapine, based on expert opinion (Drs J. Meyer and D. Henderson, June 2002). This probability reflects those patients who are candidates for alternative antipsychotic therapies who cannot maintain glucose control after 1 month of treatment.

As rates of therapy discontinuation following body weight gain associated with antipsychotic therapy are not available from clinical studies, this probability was estimated based on published recommendations [26,27,29,88,89] that patients switch to a different antipsychotic agent if weight gain is >5 kg (11 lbs) following therapy initiation, or >2.3 kg (or 5 lbs) during any 4-week period of treatment. A weight gain of 5 kg represents an increase of more than 5% of initial body weight for most patients and is associated with clinically meaningful changes in morbidity and early mortality [16]. This is also consistent with the recent recommendation of the Consensus Development Conference [35] which suggested that a 5% or greater increase in body weight be used as the threshold for consideration of switching antipsychotic therapy. Since 5% of 84 kg—the mean body weight at randomization among patients in the Conley and Mahmoud study [6]—represents an absolute increase in body weight of 4.2 kg, the threshold of an excess of 5 kg is—if anything—a conservative model assumption. In our base-case analyses, only those patients with weight gain of >5 kg [11 lbs]) were considered. The probability of therapy discontinuation following weight gain for this scenario was assumed to be equal to one.

All patients experiencing hospitalization for relapse of symptoms of schizophrenia were assumed to discontinue therapy.

Mortality

The annual rate of all-cause mortality among patients with chronic schizophrenia (0.036%) receiving risperidone or olanzapine was estimated by multiplying the annual mortality rate among persons aged 40 to 44 years (the mean age of patients participating in RIS-USA-122 was 40 years) in the general population (236 per 100,000) [90], by the standardized mortality ratio (SMR) reported in a recent meta-analysis of studies of mortality in patients with schizophrenia (i.e., 1.51) [91].

Resource Utilization

Estimates of the utilization of psychiatric and nonpsychiatric services were developed using published sources and expert opinion (Table 4). Patients who experience EPS were assumed to require dose adjustment and additional treatment with anticholinergic drugs (benztropine mesylate 2 mg daily) [2,92] for the first 60 days; no additional outpatient visits were assumed to be incurred for the management of EPS. While baseline testing of serum prolactin levels is not recommended in the risperidone package insert, we conservatively assumed that patients receiving risperidone would receive baseline serum prolactin tests prior to treatment initiation, based on expert opinion (Dr K Miller, July 2002) and the published literature [93]. Those experiencing symptomatic prolactin-related disorders, risperidone or olanzapine, were assumed to require additional diagnostic services, including two endocrinologist visits, repeat serum prolactin levels, a plasma gonadotropin test (FSH/LH) (females only 58% [70]), a pregnancy test (also, females only), a thyroid stimulating hormone (TSH) test, and a urea/creatinine determination; one-fourth of these patients were assumed to undergo magnetic resonance imaging (MRI) [93,94] of the brain to rule out the presence of a pituitary adenoma. Patients experiencing amenorrhea who remain on therapy were assumed to receive a bone mineral density (BMD) test and oral contraceptive therapy. They also were assumed to require two additional follow-up visits with an endocrinologist, two serum prolactin tests, one BMD evaluation, and to remain on oral contraceptive therapy.

Table 4 Estimated utilization of medical-care services

Parameter	Value	Source
Psychiatric services (monthly)		
Residential treatment (no. admissions)	0.02	Carter et al. 1998
Emergency crisis/intervention (no. visits)	0.03	Carter et al. 1998
Day treatment (no. visits)	1.14	Carter et al. 1998
Outpatient treatment (no. visits)	2.11	Carter et al. 1998
Case management (no. visits)	1.83	Carter et al. 1998
Outpatient care for cross-tapering medications following discontinuation of initial antipsychotic therapy		
Specialist (no. visits)	2	Peuskens, 2000
Nonpsychiatric services		
Outpatient care for EPS		
Days of oral treatment with benztropine mesylate (2 mg/d)	60	Gerlach 1999, Gray 2000
Outpatient care for prolactin-related disorders		
At initiation of therapy (risperidone only)		
Serum prolactin levels (no. tests)	1	Davies et al. 1997/Expert opinion*
Diagnosis		
Specialist (endocrinologist) (no. visits)	2	Expert opinion*
MRI of the brain (no. tests)	0.25	Expert opinion*
Plasma gonadotropin levels (no. tests) (females only)	1	Expert opinion*
Pregnancy test (no. tests)	1	Davies et al. 1997
Serum prolactin levels (no. tests)	1	Expert opinion*
Thyroid stimulating hormone (TSH) (no. tests)	1	Expert opinion*
Urea/creatinine	1	Expert opinion*
Bone mineral density (if amenorrhea)[§]	1	Expert opinion*
Monthly thereafter		
Specialist (endocrinologist) (no. visits)	0.18[‡]	Expert opinion*
Serum prolactin levels (no. tests)	0.18[‡]	Expert opinion*
Bone mineral density (if amenorrhea)[§] (%)	0.09[‡]	Expert opinion*
Oral contraceptive therapy (if amenorrhea)[§] (%)	100	Expert opinion*
Outpatient care for diabetes		
Screening		
Fasting blood glucose (no. tests) (monthly)		
Risperidone	0.17[†]	Luna B, 2001
Olanzapine	0.17[†]	Expert opinion[†]
Diagnosis		Expert opinion[†]
Specialist (psychiatrist) (no. visits)	1	Expert opinion[†]
Specialist (endocrinologist) (no. visits)	1	Expert opinion[†]
Fasting blood glucose (no. tests)	2	Expert opinion[†]
Hemoglobin A_{1c} (no. tests)	1	Expert opinion[†]
Oral glucose tolerance test	0.55	Expert opinion[†]
Purchase of blood glucose monitoring system (per patient)	1	Expert opinion[†]
Monthly thereafter		
Specialist (endocrinologist) (no. visits)	1	Expert opinion[†]
Primary care practitionner	1	Expert opinion[†]
Fasting blood glucose (no. tests)	2[¶]	Expert opinion[†]
Hemoglobin A_{1c} (no. tests)	1	Expert opinion[†]
Insulin therapy (% patients)	45	Expert opinion[†]
Oral treatment (% patients)	55	Expert opinion[†]
Counseling for weight reduction and maintenance		
Percentage of patients (among those who discontinue therapy due to weight gain)	50	Assumption
Number of individual sessions**	7	Umbricht et al. 2001

*Dr K Miller, July 2002.
[†]Drs J Meyer and D Henderson.
[‡]Based on two visits, two prolactin levels and one BMD evaluation.
[§]Or two annually.
[¶]Or one every 2 weeks.
**Therapist and registered dietician during each session.
Abbreviations. EPS, Extrapyramidal symptoms; MRI, magnetic resonance imaging.

All treated patients were assumed to undergo fasting blood glucose (FBG) tests to screen for therapy-induced hyperglycemia [95]; patients receiving risperidone and olanzapine were assumed to undergo FBG testing biannually, based on expert opinion (Drs J Meyer and D Henderson, June 2002) and consistent with recommendations of the recent Consensus Development Conference [35]. Patients who develop type 2 diabetes mellitus were assumed to require additional diagnostic services, including one additional psychiatrist visit, referral to an endocrinologist, and two FBG tests. Fifty-five percent of patients also were assumed to undergo an oral glucose tolerance test (OGTT); all patients were assumed to undergo hemoglobin A_{1c} testing at the time of diagnosis. All patients diagnosed with type 2

diabetes were assumed to receive treatment for this condition for 1 month following diagnosis prior to consideration of discontinuation of therapy. Diabetes was assumed to require chronic therapy and follow-up care for patients remaining on antipsychotic therapy. Clinical management of diabetes was assumed to involve bimonthly FBG tests, monthly evaluation of hemoglobin A_{1c} levels, dietary restriction, and treatment with insulin (45% of patients) or oral hypoglycemic drugs (55%); all patients were assumed to purchase a personal blood glucose monitoring system. Patients requiring insulin were assumed to receive twice daily injections (i.e., 25 units of NPH plus 10 units of regular insulin before breakfast and 10 units of NPH plus 5 units of regular insulin before dinner); those receiving oral therapy were assumed to be treated with metformin 500 mg twice daily. All patients requiring insulin therapy were assumed to be referred to an endocrinologist for initiation of therapy and monthly follow-on care. No additional follow-up care other than routine psychiatric visits was assumed to be required for patients whose diabetes was treated by psychiatrists.

Fifty percent of patients experiencing an increase in body weight >5 kg (or 11 lbs) were assumed to participate in a weight-management program. A variety of behavioral interventions have been recommended in the published literature for patients who gain considerable amounts of weight during treatment with antipsychotics [23,24,26,96,97], and in particular, among those with maximal weight gains between 2.5 and 8.0 kg [28,96]. This program was assumed to include elements of cognitive behavior therapy and counseling, and to consist of seven individual sessions with a therapist and a registered dietician, respectively, as reported in a study of treatment of weight gain among patients receiving atypical antipsychotics [96].

Patients discontinuing antipsychotic therapy due to hospitalization for relapse of symptoms or side effects of therapy were assumed to require additional outpatient services for switching antipsychotic agents (i.e., cross-tapering). Cross-tapering was also recommended by the Consensus Development Conference for patients who switch antipsychotic therapy following increases of body weight of 5% or more or for any other reason [35]. Cross-tapering was assumed to involve two additional psychiatrist visits over a period of 4 weeks; these are required for tapering down the daily dose of the previous neuroleptic agent, allowing for a wash-out period, and up-titrating the new treatment until a therapeutic response is achieved [98].

All patients hospitalized for relapse of symptoms were assumed to receive inpatient treatment. One-year estimates of the proportions of treated patients undergoing residential treatment, day treatment, case management, outpatient visits, and emergency/intervention services for the treatment of psychiatric symptoms were based on a retrospective study of the use of mental health services among 63 schizophrenic patients treated with risperidone [99]. The utilization of psychiatric services was assumed to be the same for patients receiving risperidone or olanzapine.

Costs of Care

Estimated costs of psychiatric and nonpsychiatric services are reported in Table 5. All costs were adjusted to 2003 (August) average price levels using the Consumer Price Index for Medical Care Services [100]. Costs of medications were estimated using average wholesale prices [101]. Average daily doses of risperidone (4.8 mg) and olanzapine (12.4 mg) were estimated based on mean daily modal doses in RIS-USA-112; assumed average doses of all other medications were based on the recommended daily dose [101,102] and expert opinion. The cost of a blood glucose monitoring system was estimated based on a survey of three on-line and three local pharmacies in the Boston area. An estimated dispensing fee was added to the cost of each prescription [103]. The cost of inpatient care for relapse as well as the costs of all other psychiatric services was based on a published retrospective study of mental health use among schizophrenic patients [99]. The costs of all specialist visits and diagnostic tests and procedures were estimated based on payment rates established under Medicare's Resource-Based Relative Value Scale (RBRVS) [104]. The cost of a nutritional counseling session by a registered dietician was estimated based on the average hourly fee for an outpatient consultation reported in an analysis of commercial weight-loss programs in the Boston area [105].

Analyses

First-order simulation (i.e., Monte Carlo) [72,73] techniques were used to generate expected outcomes and costs for a hypothetical sample of 10,000 patients assumed to initiate treatment with risperidone or olanzapine. First-order simulation allows for random sampling from distributions representing individual and/or temporal variation in patient characteristics and/or outcomes.

During simulation, 10,000 individuals alternatively assumed to receive risperidone or olanzapine

Table 5 Estimated unit costs of care

Parameter	Value	Source
Medications ($)		
Acquisition costs		
Risperidone (4.8 mg, daily)	$12.1	Red Book, 2003
Olanzapine (12.4 mg, daily)	$15.8	Red Book, 2003
Oral therapy for EPS (2 mg benztropine mesylate daily)	$0.2	Red Book, 2003
Insulin (25/10 U AM and 10/5 U PM)*	$2.1	Red Book, 2003
Metformin (1000 mg daily)	$1.6	Red Book, 2003
Oral contraceptives (monthly)	$32.8	Red Book, 2003
Blood glucose monitoring system (patient)	$60.3	Pharmacy Survey[†]
Dispensing fee (per 90-day prescription) (monthly)	$2	PBM, 1997
Psychiatric services ($)		
Inpatient care (per admission)		
Relapse of symptoms	$12,695	Carter et al. 1998
Other psychiatric care		
Residential treatment (per admission)	$4549	Carter et al. 1998
Emergency crisis/intervention	$441	Carter et al. 1998
Day treatment[‡]	$256	Carter et al. 1998
Outpatient treatment[§]	$588	Carter et al. 1998
Case management	$14	Carter et al. 1998
Nonpsychiatric services ($)		
Outpatient care		
Specialist visit (psychiatrist or endocrinologist)	$141	RBRVS (99205), 2003
Primary care practitioner (PCP) visit	$59	RBRVS (99214), 2003
Bone mineral density test	$46	RBRVS (78350), 2003
Fasting blood glucose	$6	RBRVS (82947), 2003
Hemoglobin A_{1c}	$15	RBRVS (83036), 2003
MRI of brain	$682	RBRVS (70552), 2003
Oral glucose tolerance test (OGTT)	$20	RBRVS (82951), 2003
Plasma gonadotropin levels	$57	RBRVS (83001, 83002), 2003
Pregnancy test	$9	RBRVS (81025), 2003
Serum prolactin levels	$29	RBRVS (84146), 2003
Thyroid stimulating hormone (TSH)	$26	RBRVS (84443), 2003
Urea/creatinine	$14	RBRVS (84520, 82565), 2003
Counseling for weight reduction and maintenance		
Therapist session	$96	RBRVS (99403), 2003
Registered dietician individual session	$87	Spielman et al. 1992

*Includes cost of syringes for twice a day administration.
[†]Based on a survey of three on-line and three local pharmacies in the Boston area.
[‡]Assumed weighted average of <6 h and >6 h duration.
[§]Includes assessment, counseling, medication management, and collateral services.
Abbreviations. EPS, Extrapyramidal symptoms; MRI, Magnetic resonance imaging.

were randomly stepped through the Markov process—one person at a time—yielding individual expected values for all measures of interest. Clinical and economic outcomes were subsequently summarized for each treatment group using Data Interactive ActiveX DLL (Tree Age Software Inc., Williamstown, Massachusetts, 2001) and Microsoft Excel 2000 (Microsoft Corporation, 2000) as the host application. Because the expected duration of therapy could differ between the two treatment groups, expected monthly costs of care were calculated by dividing total costs of care up to 12 months by the estimated mean number of months on therapy for patients in each treatment group.

One- and two-way sensitivity analyses were conducted to examine the robustness of study findings with respect to changes in selected parameter estimates. A set of two-way sensitivity analyses was undertaken in which estimated changes in body weight gain were allowed to vary simultaneously across a range of probabilities (0–1) of therapy discontinuation for this reason.

Results

Estimated outcomes and costs of care per month of therapy are presented in Table 6. The expected percentage of patients experiencing EPS was 9.2% and 7.2% for risperidone and olanzapine, respectively. Corresponding figures for prolactin-related disorders were 5.4% and 2.2%, consistent with findings from the RIS-USA-112 study. Approximately 1.7% of olanzapine patients were estimated to experience new-onset type 2 diabetes mellitus, compared with 1% among those receiving risperidone. Mean weight gain was estimated to be 1.7 kg and 3.9 kg for risperidone and olanzapine, respectively, at the end of 1 year. Approximately

Table 6 Estimated outcomes at 1 year following therapy initiation and cost of care per month of therapy

	Treatment		
	Risperidone	Olanzapine	Difference
Clinical outcomes			
Patients on initial therapy (%)	76.9	45.6	31.3
Mean time on therapy (months)	10.6	8.0	2.6
Side effects			
EPS (%)	9.2	7.2	2.0
Prolactin-related disorders (%)	5.4	2.2	3.2
Type II diabetes (%)	1.0	1.7	−0.7
Body weight (kg) (mean)			
Baseline	83.4	83.7	−0.3
End of 1 year or therapy discontinuation	85.2	87.6	−2.4
Change from baseline	1.7	3.9	−2.2
Patients with body weight gain ≥7% than baseline (%)	3.7	25.4	−21.7
Discontinuation of antipsychotic therapy and switching (%)			
Weight gain	5.3	42.3	−37.0
Other	17.8	12.1	5.7
Total	23.1	54.4	−31.3
Cost of care (mean)			
Antipsychotic therapy	$369	$479	−$110
Screening	$4	$1	$3
Side effects			
EPS*	$0.11	$0.11	$0
Prolactin-related disorders	$5	$2	$2
Diabetes	$1	$2	−$1
Weight gain	$3	$33	−$31
Total	$8	$37	−$29
Discontinuation and switching therapies	$6	$19	−$13
Psychiatric services	$1776	$1779	−$3
Total	$2163	$2316	−$153

*Cost of EPS treatment were higher for risperidone ($1.5 vs. $0.9 at 1 year) but the same per month of therapy.

4% and 25% of risperidone- and olanzapine-treated patients were estimated to experience an increase in body weight ≥7%. The percentage of patients remaining on therapy at the end of 1 year was estimated to be 76.9% for risperidone and 45.6% for olanzapine; the difference reflects a higher incidence of side effects leading to therapy discontinuation among patients receiving olanzapine. Consistent with these findings, the mean expected number of months on study therapy was 10.6 for risperidone and 8.0 for olanzapine. Forty-two percent of olanzapine patients were projected to discontinue antipsychotic therapy due to increases in body weight exceeding 5 kg; the corresponding percentage for risperidone was 5%. Expected rates of hospitalization for relapse of psychiatric symptoms and mortality per month of therapy were the same in the two treatment groups (0.9% for relapse, and 0.03% for mortality), consistent with our assumptions.

Expected mean total costs of care per month of therapy were $2163 for risperidone and $2316 for olanzapine, or a difference of $153. Costs of antipsychotic therapy, diagnosis and treatment of side effects, and discontinuation and switching of antipsychotic therapy were higher among olanzapine patients.

Sensitivity Analyses

Results from one-way sensitivity analyses (Table 7) suggest that study findings were overall insensitive to changes in any single model parameter, with the exception of the change in body weight and the assumed probability of therapy discontinuation following weight change in excess of 5 kg (or 11 lbs). Our findings suggest that the value of this probability would have to be lower than 0.1 for the proportion of patients remaining on therapy at the end of 1 year to be the same for risperidone and olanzapine. Costs of care per month of therapy were consistently lower for risperidone. Results from two-way sensitivity analyses are reported in Table 8.

Discussion

The purpose of our study was to examine the potential impact of side effects on therapy discontinuation and switching and the cost of psychiatric and nonpsychiatric services in patients with chronic schizophrenia or schizoaffective disorders receiving risperidone or olanzapine. Our findings indicate that patients treated with risperidone would be more likely to remain on initial therapy at the end of 1 year (76.9% vs. 45.6%, respectively, for

Table 7 One-way sensitivity analyses of impact of selected model parameters on patient outcomes and cost of care per month of therapy up to 1 year

Parameter	Risperidone				Olanzapine				Difference			
	(%) On Tx	Months On Tx	Δ Weight*	Cost	(%) On Tx	Months On Tx	Δ Weight*	Cost	(%) On Tx	Months On Tx	Δ Weight†	Δ Cost†
Base case	76.9	10.6	1.7	$2163	45.6	8.0	3.9	$2316	31.3	2.6	−2.2	−$153
Probability of EPS												
2 × base case (RIS)	72.4	10.3	1.7	$2169	45.7	8.0	3.9	$2316	26.8	2.2	−2.2	−$147
OLZ = RIS	76.9	10.6	1.7	$2163	44.1	8.0	4.0	$2322	32.9	2.6	−2.3	−$159
Probability of PRD												
2 × base case (RIS)	73.6	10.3	1.7	$2168	45.7	8.0	3.9	$2316	27.9	2.3	−2.3	−$148
Probability of DM												
2 × base case (OLZ)	76.9	10.6	1.7	$2163	44.4	8.0	4.0	$2323	32.5	2.6	−2.3	−$159
RIS = OLZ	76.1	10.5	1.7	$2165	45.7	8.0	3.9	$2316	30.5	2.5	−2.2	−$152
Probability of discontinuation following EPS												
0.5 × base case	77.7	10.6	1.7	$2170	45.7	8.0	4.0	$2321	32.0	2.6	−2.2	−$151
2 × base case	75.1	10.4	1.7	$2166	43.9	7.8	3.9	$2316	31.1	2.5	−2.2	−$150
Probability of discontinuation following PRD												
0.5 × base case	77.7	10.6	1.7	$2166	45.7	8.1	3.9	$2312	32.1	2.6	−2.2	−$146
2 × base case	75.0	10.3	1.7	$2172	44.1	7.9	4.0	$2318	30.9	2.4	−2.2	−$147
Probability of discontinuation following diabetes												
0.5 × base case	77.2	10.6	1.7	$2162	45.5	8.0	3.9	$2322	31.7	2.6	−2.2	−$160
2 × base case	76.5	10.5	1.7	$2169	45.5	8.0	3.9	$2314	31.0	2.6	−2.2	−$145
Change in body weight (OLZ)												
0.5 × base case	76.9	10.6	1.7	$2163	74.6	10.4	2.3	$2286	2.3	0.2	−0.6	−$122
2 × base case	76.9	10.6	1.7	$2163	30.4	5.4	5.3	$2365	46.5	5.1	−3.6	−$202
Change in body weight (RIS)												
2 × base case	46.6	7.5	3.4	$2081	45.7	8.0	3.9	$2316	0.9	−0.4	−0.5	−$235
Probability of discontinuation following cumulative weight gain >5 kg (11 lbs)												
0	80.7	10.8	1.7	$2161	82.3	11.0	4.6	$2293	−1.7	−0.1	−2.9	−$131
0.1	78.2	10.7	1.7	$2168	62.3	9.9	4.4	$2305	15.9	0.9	−2.6	−$138
0.3	77.6	10.6	1.7	$2161	50.2	8.2	4.2	$2315	27.4	2.4	−2.5	−$154
0.5	76.5	10.5	1.7	$2166	47.1	8.4	4.1	$2310	29.4	2.1	−2.4	−$144
0.7	77.5	10.6	1.7	$2163	46.2	8.2	4.1	$2308	31.3	2.4	−2.4	−$145
Probability of discontinuation following weight gain >2.3 kg (5 lbs) in 4-week period												
0.5	70.7	9.8	1.6	$2167	41.0	7.1	3.8	$2322	29.6	2.7	−2.2	−$155
1	65.3	9.1	1.5	$2168	36.7	6.1	3.5	$2317	28.6	3.0	−2.0	−$149
Cost of diagnoses and treatment of PRD												
2 × base case	—	—	—	$2168	—	—	—	$2318	—	—	—	−$151
Cost of weight management programs												
0	—	—	—	$2161	—	—	—	$2283	—	—	—	−$122
0.5 × base case	—	—	—	$2162	—	—	—	$2299	—	—	—	−$137
Cost of discontinuation/switching												
0	—	—	—	$2157	—	—	—	$2297	—	—	—	−$140
0.5 × base case	—	—	—	$2160	—	—	—	$2306	—	—	—	−$146
2 × base case	—	—	—	$2170	—	—	—	$2335	—	—	—	−$166

*Versus baseline (kg).
†Risperidone minus olanzapine.
Other than (%) On Tx, all other parameters reported as means.
Abbreviations. EPS, extrapyramidal symptoms; OLZ, olanzapine; PRD, prolactin-related disorders; RIS, risperidone.

olanzapine); costs of care per month of therapy were estimated to be $153 (or 7%) lower among risperidone-treated patients. Our findings are driven primarily by higher weight gain resulting in therapy discontinuation and switching, and by higher costs of medication and side effects of treatment among patients receiving olanzapine. The estimated proportion of olanzapine-treated patients who would experience an increase in body weight ≥7% was approximately 25% (vs. 4% for risperidone). To the best of our knowledge, our study is the first to address these issues for patients receiving atypical agents.

As EPS is typically controlled with reductions in drug dosage and treatment with relatively inexpensive anticholinergic medications, its overall clinical and economic impact is minimal, as supported by our findings. However, the expected incidence of other side-effects—namely, prolactin-related disorders, weight gain, and diabetes—influence outcomes in this patient population. Symptomatic prolactin-related disorders, while infrequent, occur

Table 8 Two-way sensitivity analyses of impact of changes in body weight and assumed probability of therapy discontinuation following weight gain on patient outcomes and cost of care per month of therapy up to 1 year

Parameter	Risperidone				Olanzapine				Difference			
	(%) On Tx	Months On Tx	Δ Weight*	Cost	(%) On Tx	Months On Tx	Δ Weight*	Cost	(%) On Tx	Months On Tx	Δ Weight†	Δ Cost†
Base case	76.9	10.6	1.7	$2163	45.6	8.0	3.9	$2316	31.3	2.6	−2.2	−$153
Olanzapine weight gain (0.5 × base case)												
Probability of discontinuation following weight gain >5 kg (11 lbs)												
0	80.7	10.8	1.7	$2161	82.3	11.0	2.3	$2272	−1.7	−0.1	−0.6	−$111
0.1	78.2	10.7	1.7	$2168	79.1	10.8	2.3	$2272	−0.9	−0.1	−0.6	−$104
0.3	77.6	10.6	1.7	$2161	77.2	10.6	2.2	$2273	0.4	0.0	−0.5	−$112
0.5	77.0	10.5	1.7	$2166	76.0	10.5	2.3	$2279	1.0	0.0	−0.5	−$113
0.7	77.4	10.6	1.7	$2163	75.6	10.5	2.3	$2281	1.8	0.1	−0.6	−$118
1	76.9	10.6	1.7	$2163	74.6	10.4	2.3	$2286	2.3	0.2	−0.6	−$122

*Versus baseline (kg).
†Risperidone minus olanzapine.
Other than (%) On Tx, all other parameters reported as means.

more often among patients receiving risperidone. The decision to discontinue antipsychotic therapy among these patients, however, is heavily weighted in favor of the degree of control of psychiatric symptoms. Most patients who experience drug-induced prolactin-related disorders are likely to remain on therapy provided that they undergo periodic outpatient follow-up and treatment as appropriate. While the costs of medical services associated with screening, diagnosis, follow-up, and treatment of patients with hyperprolactinemia are not negligible, they represented only about 1.4% of expected monthly costs in our analysis, reflecting the relatively low incidence of symptomatic disease. Rates of EPS and prolactin-related disorders were considered for the first 8 weeks of treatment only, based on evidence that these side effects typically occur early in the course of therapy, and lessen and/ or stabilize subsequently [75,76]. We believe that the inclusion of long-term risks for these side effects would have had minimal impact in our findings, given the small magnitude of costs associated with their treatment and the low rates of discontinuation of antipsychotic therapy for these reasons.

While all atypical agents cause some degree of weight gain, this is more frequent and marked for olanzapine. Findings from controlled clinical trials of olanzapine suggest that mean weight gain among patients receiving dosages similar to that assumed in our analysis ranges from 3.5 to 8 kg over 1 year [18,32,33], although higher values have been reported [17]. In light of these findings, we believe that our estimate of an approximately 4 kg increase in body weight at 1 year among olanzapine-treated patients (12.4 mg/day) is conservative. Strengths of our analysis include the fact that we modeled early changes in body weight conditional on a patient's initial BMI, and the assumption of gradual plateau-ing of weight over time, both consistent with the current characterization of drug-related weight gain in the published literature. Our estimates for the early months of treatment, where increases in body weight have been demonstrated to be highest [16], are based on the actual distribution of individual changes in weight among 316 patients who participated in a randomized head-to-head comparison of the study therapies.

We are aware that our model generates estimates of the proportions of patients who would discontinue olanzapine and risperidone therapy over 1 year that may be inconsistent with current clinical practice. In two randomized controlled trials, the percentage of risperidone and olanzapine patients remaining on therapy has been reported to be 72% and 77.2%, respectively, at 8 weeks in one study (NS), and 47.3% and 56% at 28 weeks in the other (NS) [6,63]. In two other prospective clinical trials, rates of discontinuation for any reason were reported not to differ [106,107]. A meta-analysis of studies of second-generation antipsychotics in patients with treatment-resistant schizophrenia estimated that completion rates for risperidone and olanzapine were 84.8% and 65.7%, respectively, over a similar period of follow-up [108]. Unfortunately, published data were not available to use for the probability of therapy discontinuation conditional on changes in body weight. Thus, we based our estimates on published recommendations concerning therapy change following weight gain and the threshold for "significant" body weight gain (7%) employed by the US Food and Drug Administration. To examine the robustness of our findings, we conducted extensive sensitivity analyses in which we varied the probability of therapy discontinuation due to changes in body weight in excess of 5 kg from zero to one. The value of this probability

would have to be less than 0.1 for the proportion of patients remaining on therapy at the end of 1 year to be the same for risperidone and olanzapine. Increasing awareness of the link between adiposity and adverse clinical and economic outcomes has led to development of recommendations for close monitoring and more aggressive management of weight gain in this patient population. Strictly speaking, our model therefore provides estimates of outcomes that would result from implementation of these guidelines.

Finally, the increased number of cases of hyperglycemia and diabetes mellitus in patients receiving olanzapine is of concern. Although the true incidence of these conditions is unknown, observational studies suggest that the risk of diabetes mellitus among patients receiving olanzapine is higher than that reported in early trials of the drug [94,109,110]. The position of the Consensus Development Conference [35] is also supportive of this finding. While our estimates are not adjusted for body weight and BMI, weight gain has been reported to be a characteristic of patients who develop insulin-dependent diabetes [78]. In this 5-year naturalistic study of clozapine—the longest follow-up study addressing this issue conducted to date—neither weight, change in weight, BMI, nor change in BMI were shown to be associated with the development of confirmed or unconfirmed diabetes mellitus.

We note that our assumed dosages of study therapies (12.5 mg (olanzapine) and 4.8 mg (risperidone) per (day) are consistent with prescription data from the IMS National Disease and Therapeutic Index (NDTI) for years 2001 and 2002 [111], which reports a range from 12.8 to 13.7 mg daily for olanzapine, and from 3.99 mg to 4.08 mg for risperidone. We assumed that the effectiveness of risperidone and olanzapine in controlling psychiatric symptoms would not differ and that they would result in similar utilization of psychiatric services. Although perhaps debatable, both agents have been shown to be similarly efficacious in reducing positive and negative symptoms of psychosis. Two head-to-head randomized controlled trials of these agents have been conducted to date [6,63]. The study by Tran et al. reported superior efficacy of olanzapine in the control of negative symptoms, but its design has been criticized due to the rapid titration and high dosages of risperidone [112–115]; experience with risperidone suggests that higher drug dosages may be associated with lower efficacy and higher rates of side effects. The other randomized, double-blind head-to-head compari-

son of these agents was the RIS-USA-112 study, the findings of which were reported by Conley and Mahmoud [6]. Greater reductions in the severity of positive and affective symptoms were observed among patients receiving risperidone, and there was no efficacy measure on which olanzapine was found to be superior. A prospective, nonrandomized comparison [106] of these agents (mean modal dosages: olanzapine, 17.7 mg daily; risperidone, 7.9 mg daily) reported that olanzapine-treated patients were more likely to "maintain response" than risperidone-treated patients; the difference in the percentage of patients who improved based on Positive and Negative Syndrome Scale (PANSS) at study endpoint was not statistically significant, however. Moreover, there is no comparative data suggesting that rates of hospitalization for relapse of psychiatric symptoms—a key cost driver in this patient population—differ between patients receiving risperidone or olanzapine. The above-cited prospective, nonrandomized study of these agents—which included economic outcomes—did not report rates of hospitalization for relapse for psychiatric symptoms. Finally, a small, retrospective, naturalistic study [66] of olanzapine (mean daily dose: 15.2 mg) and risperidone (4.2 mg daily) reported significantly higher readmission rates at 1 year for patients receiving olanzapine. After careful consideration of the clinical relevance of the dosages employed in our model, and the controversy sparked by evidence from published sources, we believe that our assumption of similar efficacy is reasonable, and warrants an examination of the outcomes and cost of care associated with these agents in light of their side effects.

Despite these limitations, we believe our study has important clinical and economic implications. While patients receiving risperidone are more likely to experience increased risks of EPS and symptomatic prolactin-related disorders, those treated with olanzapine are more likely to experience greater gains in body weight, a slightly higher risk of diabetes mellitus, higher rates of therapy discontinuation, and higher costs of care per month of therapy over 1 year. Our findings accordingly may be of interest to clinicians and others interested in outcomes and costs of mental health services among patients with chronic schizophrenia or schizoaffective disorders.

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