Hospitalization Rates and Therapy Costs of German Schizophrenia Patients Who are Initiated on Long-Acting Injectable Medication: A Mirror-Image Study

Jörg Mahlich[1,2] · Kerstin Olbrich[1] · Adrian Wilk[3] · Antonie Wimmer[4] · Claus Wolff-Menzler[5]

Abstract

Background Long-acting injectable (LAI) antipsychotics can reduce relapse, hospitalization, and costs in patients with schizophrenia. However, real-world evidence assessing the impact of treatment with LAIs in Germany is limited.

Objective To provide updated evidence on the impact of LAI initiation on hospitalization rates and therapy costs.

Methods Using a mirror-image design, claims data of 850 German patients with schizophrenia who initiated treatment with LAIs during 2013–2015 was retrospectively analyzed. For the included patients, costs and resource utilization were compared for the 12 months before the index date (first initiation of LAI) and the 12 months after the index date. Annual treatment costs, hospitalization rates, ambulatory visits, sick leaves and medical aids were assessed. Two models were used to evaluate hospitalization and its costs. In model 1, hospitalization during the index date (first LAI prescription in 2013–2015) was allocated to the "pre-" time interval, while in model 2 it was neither attributed to the pre- nor to the post-index date. Regression analysis was performed to identify patients who benefited the most in terms of cost reduction from LAI initiation.

Results Medication costs were significantly higher post-switching to LAI compared with pre-switching period (€3832 vs €799; $p < 0.001$). In model 1, number of hospitalizations, days hospitalized, and associated costs were significantly lower post-switching compared with pre-switching (2.3 vs 2.6; 59.2 vs 73.4; and €5355 vs €11,908, respectively; all $p < 0.001$). Similar results were obtained for costs in model 2 (€5355 vs €10,276; $p < 0.001$). Mean total costs reduced significantly from pre-switching to post-switching period in model 1 (€13,776 vs €10,418; $p < 0.001$). Patients with characteristics such as higher number of non-psychiatric and psychiatric inpatient stays during the pre-index period (all $p < 0.05$) benefited the most from cost reduction after LAI initiation.

Conclusion In this cohort of German patients with schizophrenia, treatment initiation with LAI resulted in reduced hospitalization rates and total costs.

1 Introduction

Schizophrenia is a severe mental disorder, characterized by profound disruptions in thinking, language, perception, and the sense of self [1]. According to the Global Burden of Disease 2016 study, the prevalence of schizophrenia in Germany is 0.29% [2]. Schizophrenia adversely affects cognitive performance [3], thus impairing daily activities, work productivity, and social functioning [4], and increasing the economic burden. In 2008, the annual economic burden of schizophrenia for German society was estimated to be €9.6–€13.5 billion [5].

✉ Jörg Mahlich
joerg.mahlich@gmail.com

1 Health Economics and Outcomes Research, Janssen, Pharmaceutical Companies of Johnson & Johnson, Neuss, Germany

2 Düsseldorf Institute of Competition Economics (DICE), University of Düsseldorf, Düsseldorf, Germany

3 Team Gesundheit, Gesellschaft für Gesundheitsmanagement mbH, Essen, Germany

4 Medical Affairs, Janssen, Pharmaceutical Companies of Johnson & Johnson, Neuss, Germany

5 Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Georg-August-University, Göttingen, Germany

Key Points

Usage of long-acting injectable (LAI) antipsychotics increased the medication costs but reduced the number of hospitalizations, duration of hospitalization, and its costs. This resulted in a net reduction in total costs.

LAIs should be used more frequently in the treatment of schizophrenia in Germany to reduce the economic burden of schizophrenia.

Hospitalization is a driver of healthcare costs, contributing to 43% of the total direct medical costs of treating German patients with schizophrenia [5]. Moreover, relapses in schizophrenia have been shown to increase healthcare resource utilization (HRU) and associated costs as well as reduce the quality of life [6, 7]. Antipsychotic usage can reduce the adverse influence of schizophrenia on a patient's life. However, poor adherence due to young age, low education level, alcohol and substance abuse, poor cognition, lack of awareness or insight about schizophrenia, and a complex medication regime [8], result in relapse and rehospitalization as well as increased costs [9–11]. Therefore, treatment strategies that improve compliance as well as reduce relapse and rehospitalization are critical to successfully manage schizophrenia.

Long-acting injectable (LAI) antipsychotics have been shown to increase medication adherence [12, 13], reduce relapse and rehospitalization [13–15], and be more cost effective [16–18] compared with oral antipsychotics (OAP). However, in Germany, second-generation antipsychotic LAIs are prescribed less due to their high costs [19]. Although savings in HRU can offset the pharmacy costs of LAI usage, the cost effectiveness could vary based on the drug prices and procedural costs in individual countries. Hospitalization rates and costs among LAI users in Germany have been mostly assessed in clinical trials [20–23]. A few studies have utilized model-based approaches [16, 17, 24] to estimate the aforementioned outcomes; however, they used pre-2012 data for the model or compared a single LAI to other antipsychotics [25]. The current study utilized a large German claims database in order to provide updated evidence regarding the impact of LAI initiation.

2 Methods

2.1 Data Source

De-identified records were obtained from a claims database provided by Team Gesundheit, Essen, Germany. The database encompasses healthcare resource utilization of approximately 4.2 million insured individuals in Germany and contains detailed electronic records of health insurance claim information on inpatient, outpatient, and prescription drug data at the individual member level. These data originated from different company health insurance funds (Betriebskrankenkassen), which are part of the German statutory health insurance scheme. Membership in the statutory health insurance scheme is compulsory for 87% of the German population. The remaining 13% of the population is privately insured. The database is extensively utilized for health services research [26, 27].

2.2 Study Population

Patients who were diagnosed with schizophrenia according to ICD-10-GM (International Classification of Diseases German Modification, 10th Revision) code F20.x (Supplementary Table 1) from 2012 to 2015 were included in this retrospective cohort study. The diagnosis could have been made in the in-patient setting (primary and secondary diagnosis) or in the out-patient setting (verified diagnosis). Next, all patients who had prescriptions of the pre-defined LAIs in the timeframe from 2013 to 2015 but did not have a preceding LAI prescription documented in the prior 365 days, were identified. The index date was defined as the first prescription of a LAI. The following LAIs were identified: fluphenazine, haloperidol, flupentixol, zuclopenthixol, fluspirilene, olanzapine, risperidone, aripiprazole, and paliperidone. Patients were required to have an ICD-10 F20.x diagnosis in the quarter of index date or in the preceding quarter, be aged ≥ 18 years at the index date and have at least 365 days of continuous enrollment prior to and after the index date. Patients who were first prescribed a LAI in 2012 and those who were identified with certain comorbidities such as attention deficit/hyperactivity disorder (ICD-10 F90.x-F98.x); epilepsy (ICD-10 G09.x, G40.x, G41.x, I69.4, and O99.3); or dementia (ICD-10 F0.x, G30.x, G31.x, G10.x, G20.X, B22.0, and E75.6) in the quarter of the index date or in the preceding quarter were excluded (Fig. 1) as patients with these comorbidities often receive off-label antipsychotic medications [28].

2.3 Covariates

Baseline covariates of interest included age, gender, common comorbidities, and the Charlson Comorbidity Index (CCI) [29]. The CCI included 19 comorbidities as given in Supplementary Table 2 (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, diabetes without chronic complication, diabetes with chronic complication, hemiplegia or paraplegia, renal disease, tumors without metastasis, lymphoma, leukemia, moderate or severe
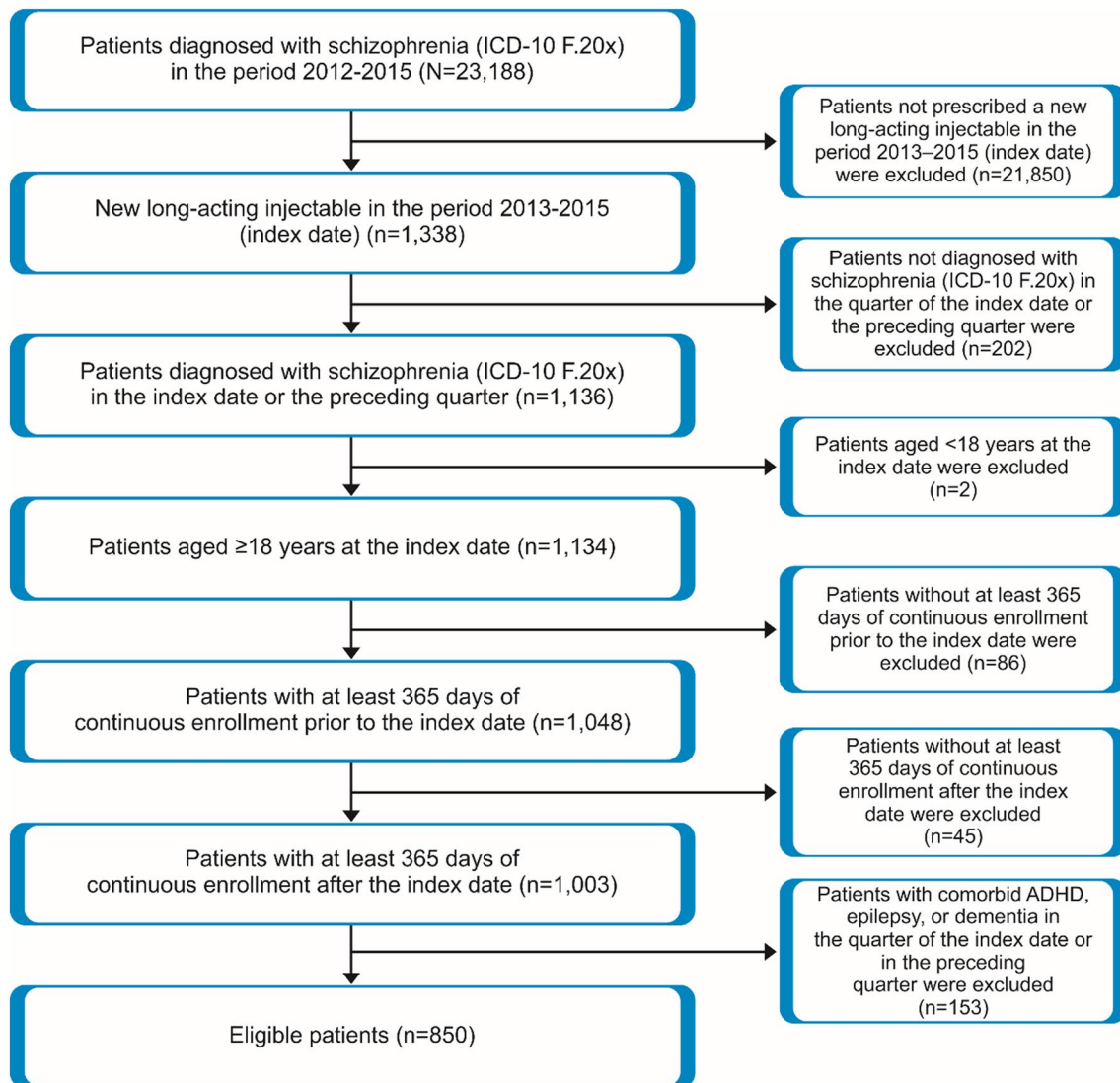
Fig. 1 Data set for analysis. *ADHD* attention-deficit/hyperactivity disorder, *ICD* International Classification of Diseases

liver disease, metastatic solid tumors, and AIDS/HIV) and assigned a weight between 1 and 6 to each comorbidity. Higher CCI indicates a greater morbidity of the patient.

2.4 Outcomes

HRU and costs for the 12 months before and after the index date were compared using a mirror-image design (Fig. 2). The evaluated outcomes included number of hospitalizations, length of stay and associated costs; number of outpatient office visits and associated costs; drug acquisition costs; cost of medical aids; duration of unemployment in months and work status change; and number and duration of sick leave periods and associated costs that were covered by health insurance. In Germany, during an employee's illness, the agreed salary wage continues to be paid for a period of

42 days by the employer. After that, health insurance covers sick pay for up to 546 days. Patients get up to 90% of their net salary, with a cap of €103.25 per day.

In order to assess the robustness of our results, we followed the method from Spill et al. [30] and tested two models to decipher whether hospitalization of patients during their index LAI prescription should be allocated to the pre- or post-index period. In model 1, a hospitalization during the index date was allocated to the "pre-" time interval, while in model 2 it was neither attributed to the pre- nor to the post-index date.

2.5 Statistical Analysis

This mirror-image study compares outcomes before and after the index date. Means and standard deviations (SD)

Fig. 2 Mirror-image study design. *HCP* health-care professional, *LAI* long-acting injectable antipsychotic

for continuous variables and counts and percentages for categorical variables were calculated. Differences were tested for statistical significance using Wilcoxon rank tests for non-normally distributed variables. A *p* value of ≤ 0.05 was considered statistically significant.

Regression analysis with the ordinary least squares method was performed to identify patients who have benefited most in terms of cost reduction from LAI initiation. The model comprised variables such as age; gender; insurance status; HRU during pre-index period (number of different agents, number of psychiatric and non-psychiatric inpatient and outpatient stays, and number of office visits); and whether or not a consulting psychiatric interview was conducted. The analysis was undertaken using SAS software (ver. 9.4; SAS Institute Inc. Cary, NC, USA).

3 Results

3.1 Population Characteristics

Among 23,188 patients diagnosed with schizophrenia, 850 were eligible for the study (Fig. 1). Among the 850 included patients, at index date, 27.1% received paliperidone palmitate), 20.7% received risperidone decanoate, and 15.2% received flupentixol decanoate. The overall mean (SD) age was 45 (15) years with substantial variation across different LAIs. In general, patients on first-generation antipsychotics were older and had more comorbidities than those treated with second-generation antipsychotics. Specifically, patients prescribed olanzapine and haloperidol were the youngest and oldest in the sample, respectively. Overall, 45.4% of the patients were female, with distribution varying from 17.4% for olanzapine to 69.7% for fluspirilene. More than one-third of the overall sample were retired (38.9%), with the distribution of retired patients varying from 24.8% for

the paliperidone cohort to 55.0% for the flupentixol cohort. Chronic pulmonary disease (16.9%) and diabetes without chronic complications (12.4%) were among the more common comorbidities. Common addiction-related comorbidities were mental and behavioral disorders due to use of tobacco (24.2%), alcohol (18.5%), and cannabinoids (16.1%) (Table 1). We observed a huge degree of heterogeneity between the different LAIs regarding patient characteristics, making comparisons across different LAIs difficult. Although outcomes are reported on a compound base as well, we want to remind the reader that the design of the study is to assess the effect of treatment initiation with a LAI and not to compare different LAIs with each other.

3.2 Outcomes

3.2.1 Medications and Associated Costs

Overall, the mean number of agents used, antipsychotic costs, and medication costs were significantly higher in the post-index period compared with pre-index (2.3 vs 1.4; €3458 vs €508; and €3832 vs €799, respectively; $p < 0.001$ for all). The lowest increase in both antipsychotic and medication costs in the post-index period was observed for fluspirilene (up to 1.1-fold) and the highest increase was for olanzapine (up to 17.8-fold, Table 2). Overall, risperidone was the most prescribed agent in both the pre-index (24.1%) and post-index (33.1%) periods, while paliperidone palmitate was the most prescribed LAI in the post-index period (30.8%, Supplementary Table 3).

3.2.2 Hospitalization and Associated Costs

Two models were tested to evaluate hospitalizations and associated costs. In model 1 the overall mean number of all hospitalizations, number of days hospitalized, and costs

Table 1 Baseline characteristics of study population

Parameter	Overall (n=850)	First-generation antipsychotics					Second-generation antipsychotics			
		Fluphenazine (n=35)	Haloperidol (n=96)	Flupentixol (n=129)	Zuclopenthixol (n=19)	Fluspirilene (n=76)	Olanzapine (n=23)	Risperidone (n=176)	Aripiprazole (n=66)	Paliperidone (n=230)
Age, years, mean (SD)	45 (15.0)	51.9 (17.0)	55.3 (15.1)	49.7 (14.3)	47.4 (13.4)	55.1 (13.2)	37.4 (10.5)	40.2 (13.6)	39.7 (11.4)	39.4 (12.5)
Age groups, n (%)										
18–24	47 (5.5)	2 (5.7)	1 (1.0)	3 (2.3)	1 (5.3)	1 (1.3)	1 (4.3)	11 (6.3)	5 (7.6)	22 (9.6)
25–34	221 (26.0)	6 (17.1)	12 (12.5)	20 (15.5)	1 (5.3)	4 (5.3)	10 (43.5)	68 (38.6)	20 (30.3)	80 (34.8)
35–44	168 (19.8)	4 (11.4)	9 (9.4)	24 (18.6)	6 (31.6)	8 (10.5)	7 (30.4)	36 (20.5)	16 (24.2)	58 (25.2)
45–54	185 (21.8)	7 (20.0)	25 (26.0)	32 (24.8)	6 (31.6)	27 (35.5)	2 (8.7)	36 (20.5)	19 (28.8)	31 (13.5)
55–64	128 (15.1)	9 (25.7)	20 (20.8)	23 (17.8)	3 (15.8)	20 (26.3)	3 (13.0)	15 (8.5)	5 (7.6)	30 (13.0)
≥65	101 (11.9)	7 (20.0)	29 (30.2)	27 (20.9)	2 (10.5)	16 (21.1)	0 (0.0)	10 (5.7)	1 (1.5)	9 (3.9)
Female gender, n (%)	386 (45.4)	15 (42.9)	46 (47.9)	74 (57.4)	8 (42.1)	53 (69.7)	4 (17.4)	73 (41.5)	29 (43.9)	84 (36.5)
Index year, n (%)										
2013	265 (31.2)	15 (42.9)	30 (31.3)	37 (28.7)	5 (26.3)	28 (36.8)	8 (34.8)	64 (36.4)	0 (0.0)	78 (33.9)
2014	297 (34.9)	8 (22.9)	32 (33.3)	50 (38.8)	8 (42.1)	26 (34.2)	5 (21.7)	69 (39.2)	17 (25.8)	82 (35.7)
2015	288 (33.9)	12 (34.3)	34 (35.4)	42 (32.6)	6 (31.6)	22 (28.9)	10 (43.5)	43 (24.4)	49 (74.2)	70 (30.4)
Insurance status, n (%)										
No compulsory insurance	3 (0.4)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
Compulsory insurance	176 (20.7)	5 (14.3)	16 (16.7)	18 (14.0)	2 (10.5)	16 (21.1)	7 (30.4)	36 (20.5)	14 (21.2)	62 (27.0)
Voluntary insurance	83 (9.8)	3 (8.6)	8 (8.3)	14 (10.9)	3 (15.8)	5 (6.6)	2 (8.7)	20 (11.4)	7 (10.6)	21 (9.1)
Unemployed person	107 (12.6)	0 (0.0)	7 (7.3)	9 (7.0)	1 (5.3)	4 (5.3)	3 (13.0)	29 (16.5)	11 (16.7)	43 (18.7)
Pension claimant	6 (0.7)	0 (0.0)	1 (1.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.9)
Retired	331 (38.9)	19 (54.3)	49 (51.0)	71 (55.0)	9 (47.4)	39 (51.3)	7 (30.4)	61 (34.7)	19 (28.8)	57 (24.8)
Special group of persons	9 (1.1)	2 (5.7)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	4 (1.7)
Family member	70 (8.2)	3 (8.6)	7 (7.3)	11 (8.5)	3 (15.8)	9 (11.8)	1 (4.3)	11 (6.3)	8 (12.1)	17 (7.4)
Unknown	65 (7.6)	2 (5.7)	8 (8.3)	4 (3.1)	1 (5.3)	2 (2.6)	3 (13.0)	15 (8.5)	6 (9.1)	24 (10.4)
CCI, mean (SD)	0.7 (1.3)	0.7 (1.0)	1.3 (1.9)	0.8 (1.3)	1.1 (1.4)	1.5 (2.2)	0.4 (0.7)	0.5 (1.1)	0.4 (0.8)	0.5 (1.0)

Table 1 (continued)

Parameter	Overall (n = 850)	First-generation antipsychotics					Second-generation antipsychotics			
		Fluphenazine (n = 35)	Haloperidol (n = 96)	Flupentixol (n = 129)	Zuclopenthixol (n = 19)	Fluspirilene (n = 76)	Olanzapine (n = 23)	Risperidone (n = 176)	Aripiprazole (n = 66)	Paliperidone (n = 230)
Comorbidities										
MI	10 (1.2)	1 (2.9)	5 (5.2)	1 (0.8)	1 (5.3)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
CHF	34 (4.0)	1 (2.9)	7 (7.3)	6 (4.7)	0 (0.0)	5 (6.6)	0 (0.0)	6 (3.4)	1 (1.5)	8 (3.5)
Peripheral vascular disease	19 (2.2)	1 (2.9)	7 (7.3)	1 (0.8)	2 (10.5)	3 (3.9)	0 (0.0)	0 (0.0)	1 (1.5)	4 (1.7)
Cerebrovascular disease	38 (4.5)	1 (2.9)	7 (7.3)	6 (4.7)	2 (10.5)	10 (13.2)	0 (0.0)	4 (2.3)	3 (4.5)	5 (2.2)
Dementia	5 (0.6)	0 (0.0)	3 (3.1)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Chronic pulmonary disease	144 (16.9)	2 (5.7)	19 (19.8)	22 (17.1)	4 (21.1)	18 (23.7)	3 (13.0)	34 (19.3)	7 (10.6)	35 (15.2)
Rheumatic disease	10 (1.2)	0 (0.0)	1 (1.0)	1 (0.8)	1 (5.3)	5 (6.6)	0 (0.0)	1 (0.6)	1 (1.5)	0 (0.0)
Peptic ulcer disease	9 (1.1)	0 (0.0)	0 (0.0)	3 (2.3)	0 (0.0)	3 (3.9)	0 (0.0)	3 (1.7)	0 (0.0)	0 (0.0)
Mild liver disease	72 (8.5)	4 (11.4)	12 (12.5)	12 (9.3)	3 (15.8)	6 (7.9)	2 (8.7)	12 (6.8)	7 (10.6)	14 (6.1)
Diabetes without chronic complication	105 (12.4)	6 (17.1)	21 (21.9)	19 (14.7)	5 (26.3)	22 (28.9)	2 (8.7)	12 (6.8)	4 (6.1)	14 (6.1)
Hemiplegia or paraplegia	7 (0.8)	0 (0.0%)	1 (1.0)	2 (1.6)	0 (0.0)	0 (0.0)	1 (4.3)	1 (0.6)	0 (0.0)	2 (0.9)
Renal disease	26 (3.1)	0 (0.0%)	9 (9.4)	4 (3.1)	0 (0.0)	3 (3.9)	0 (0.0)	4 (2.3)	0 (0.0)	6 (2.6)
Diabetes with chronic complication	33 (3.9)	3 (8.6%)	7 (7.3)	7 (5.4)	1 (5.3)	8 (10.5)	1 (4.3)	3 (1.7)	0 (0.0)	3 (1.3)
Tumor	26 (3.1)	2 (5.7%)	8 (8.3)	3 (2.3)	1 (5.3)	4 (5.3)	0 (0.0)	4 (2.3)	0 (0.0)	4 (1.7)
Leukemia	0 (0.0)	0 (0.0%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphoma	1 (0.1)	0 (0.0%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
Moderate or severe liver disease	2 (0.2)	0 (0.0%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Metastatic solid tumor	2 (0.2)	0 (0.0%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AIDS/HIV	2 (0.2)	0 (0.0%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

Table 1 (continued)

Parameter	Overall (n=850)	First-generation antipsychotics					Second-generation antipsychotics			
		Fluphenazine (n=35)	Haloperidol (n=96)	Flupentixol (n=129)	Zuclopenthixol (n=19)	Fluspirilene (n=76)	Olanzapine (n=23)	Risperidone (n=176)	Aripiprazole (n=66)	Paliperidone (n=230)
Addiction (Mental and behavioral disorders due to-)										
Use of alcohol	157 (18.5)	4 (11.4)	14 (14.6)	30 (23.3)	1 (5.3)	6 (7.9)	7 (30.4)	36 (20.5)	12 (18.2)	47 (20.4)
Use of opioids	21 (2.5)	1 (2.9)	2 (2.1)	1 (0.8)	0 (0.0)	1 (1.3)	1 (4.3)	4 (2.3)	0 (0.0)	11 (4.8)
Use of cannabinoids	137 (16.1)	3 (8.6)	7 (7.3)	12 (9.3)	0 (0.0)	1 (1.3)	4 (17.4)	39 (22.2)	13 (19.7)	58 (25.2)
Use of sedatives or hypnotics	40 (4.7)	0 (0.0)	2 (2.1)	12 (9.3)	0 (0.0)	6 (7.9)	2 (8.7)	8 (4.5)	1 (1.5)	9 (3.9)
Use of cocaine	15 (1.8)	0 (0.0)	1 (1.0)	1 (0.8)	0 (0.0)	0 (0.0)	2 (8.7)	3 (1.7)	0 (0.0)	8 (3.5)
Use of other stimulants, including caffeine	52 (6.1)	2 (5.7)	2 (2.1)	6 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)	13 (7.4)	3 (4.5)	26 (11.3)
Use of hallucinogens	4 (0.5)	0 (0.0)	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.4)
Use of tobacco	206 (24.2)	10 (28.6)	23 (24.0)	39 (30.2)	6 (31.6)	14 (18.4)	4 (17.4)	47 (26.7)	9 (13.6)	54 (23.5)
Use of volatile solvents	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Multiple drug use and use of other psychoactive substances	128 (15.1)	5 (14.3)	6 (6.3)	16 (12.4)	1 (5.3)	4 (5.3)	4 (5.3)	38 (21.6)	6 (9.1)	46 (20.0)

ADHD attention deficit/hyperactivity disorder, *CCI* Charlson Comorbidity Index, *CHF* congestive heart failure, *MI* myocardial infarction, *SD* standard deviation

Table 2 Change in medications and costs from pre-index to post-index period

Parameter	First generation antipsychotics						Second-generation antipsychotics			
	Overall (n=850)	Fluphenazine (n=35)	Haloperidol (n=96)	Flupentixol (n=129)	Zuclopenthixol (n=19)	Fluspirilene (n=76)	Olanzapine (n=23)	Risperidone (n=176)	Aripiprazole (n=66)	Paliperidone (n=230)
Number of different agents used, mean (SD)										
Pre-index	1.4 (1.3)	0.8 (1.0)	1.0 (1.1)	1.4 (1.4)	1.4 (1.3)	0.8 (1.0)	1.0 (0.9)	1.5 (1.3)	1.5 (1.3)	1.6 (1.4)
Post-index	2.3 (1.3)	2.1 (1.3)	1.8 (0.9)	2.3 (1.3)	2.6 (1.7)	2.1 (1.3)	1.9 (0.9)	2.2 (1.3)	2.2 (1.3)	2.6 (1.5)
p value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Antipsychotic costs, € mean (SD)										
Pre-index	508 (963)	252 (593)	318 (652)	424 (837)	395 (635)	406 (1038)	367 (500)	463 (810)	831 (919)	671 (1255)
Post-index	3458 (3439)	827 (1074)	670 (1125)	832 (1177)	1546 (2235)	419 (1014)	6548 (3102)	4589 (2804)	4298 (2,071)	6240 (3466)
p value	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Medication costs, € mean (SD)										
Pre-index	799 (1269)	503 (857)	763 (1107)	718 (994)	845 (1057)	1098 (1360)	419 (557)	638 (934)	964 (1,024)	915 (1735)
Post-index	3832 (3549)	1244 (1300)	1096 (1293)	1312 (1872)	2009 (2226)	1209 (1459)	6762 (3199)	4873 (2977)	4413 (2,091)	6541 (3776)
p value	<0.001	<0.001	<0.001	<0.001	0.003	0.010	<0.001	<0.001	<0.001	<0.001

SD standard deviation

were significantly lower in the post-index period compared with pre-index (2.3 vs 2.6; 59.2 vs 73.4; and €5355 vs €11,908, respectively; $p < 0.001$ for all). Similar reductions were observed for psychiatric and non-psychiatric inpatients, although only the paliperidone palmitate group showed significant changes in the latter ($p < 0.05$). Significant increases were also observed across all the parameters for psychiatric outpatients ($p < 0.001$ for all, Table 3).

In model 2, overall there were no significant changes in the mean number of all hospitalizations and number of days hospitalized. Costs were significantly lower in the post-index period compared with pre-index (€5355 vs €10,276; $p < 0.001$). Overall, psychiatric inpatients showed a significant decrease while psychiatric outpatients showed a significant increase ($p < 0.001$ for all) across parameters. Similar to model 1, only the paliperidone group showed significant changes in non-psychiatric inpatients ($p < 0.05$, Table 4). Supplementary Table 4 shows the changes in the number of patients with at least one hospitalization.

The decrease in hospitalization was especially triggered by a reduced number of psychiatric inpatient stays. The number of patients with at least one psychiatric inpatient stay was reduced by half from 60.1 to 31.2% in model 1 (Supplementary Table 4). Therefore, the number of days spent hospitalized in a psychiatric institution decreased from a mean of 47 days during pre-index period to 18.5 days during post-index period (Table 3). These results are supported by model 2 where a reduction of 23.4% in patients with at least one psychiatric inpatient stay (Supplementary Table 4) and a reduction of the number of days spent hospitalized by 21.8 days (Table 4).

3.2.3 Ambulatory Healthcare Resource Utilization and Associated Costs

The mean overall number of visits and costs increased significantly from pre-index to post-index period (19.4 vs 26.0 and €581 vs €739; $p < 0.001$ for all). Differentiating by specialty, a significant increase in the mean number of visits was observed for general practitioners, neurologists and psychiatrists, laboratory medicine, psychological psychotherapists, and unknown ($p < 0.05$ for all; Table 5). Supplementary Table 5 shows the changes in the number of patients with these visits.

3.2.4 Sick Leave and Sickness Benefits

Overall, the number of patients with sick leave periods and sickness benefit periods decreased from pre-index to post-index (20.6% vs 17.6% and 13.6% vs 11.6%). The overall mean number and duration of sick leave periods also significantly decreased from pre-index to post-index (0.6 vs 0.5 and 20.6 vs 16.9; $p < 0.01$ for all). However, group-wise

Table 3 Change in hospitalizations and costs from pre-index to post-index period (hospitalization model 1)

Parameter	First-generation antipsychotics						Second-generation antipsychotics			
	Overall (n=850)	Fluphenazine (n=35)	Haloperidol (n=96)	Flupentixol (n=129)	Zuclopenthixol (n=19)	Fluspirilene (n=76)	Olanzapine (n=23)	Risperidone (n=176)	Aripiprazole (n=66)	Paliperidone (n=230)
All hospitalizations, mean (SD)										
Number of hospitalizations										
Pre-index	2.6 (2.6)	2.2 (2.6)	2.1 (2.3)	2.5 (2.7)	2.3 (2.6)	0.8 (1.3)	3.8 (3.0)	3.1 (2.8)	2.8 (2.4)	3.1 (2.4)
Post-index	2.3 (2.4)	2.5 (3.3)	1.3 (1.7)	2.4 (2.7)	1.9 (2.3)	0.9 (1.1)	4.0 (3.8)	2.8 (2.4)	2.7 (2.2)	2.6 (2.3)
p value	<0.001	0.712	<0.001	0.660	0.438	0.674	0.899	0.096	0.769	<0.001
Days hospitalized										
Pre-index	73.4 (88.6)	67.8 (110.5)	63.8 (102.3)	73.4 (98.1)	56.4 (96.2)	11.2 (38.7)	90.6 (67.5)	84.3 (88.6)	79.2 (73.2)	88.6 (81.7)
Post-index	59.2 (88.4)	73.1 (109.7)	35.7 (73.9)	52.1 (80.7)	57.2 (80.1)	9.6 (19.6)	119.2 (116.5)	73.9 (95.7)	83.6 (92.3)	63.4 (89.9)
p value	<0.001	0.712	<0.001	0.001	0.339	0.173	0.725	0.015	0.789	<0.001
Costs, €										
Pre-index	11,908 (14,391)	10,283 (15,794)	10,471 (17,558)	9937 (13,772)	9569 (18,454)	1722 (3948)	16,821 (13,388)	13,776 (14,225)	13,167 (13,438)	15,137 (13,694)
Post-index	5355 (9744)	5468 (10,894)	3096 (6300)	5214 (8,582)	9224 (15,186)	2173 (4701)	6082 (10,658)	6966 (11,156)	6453 (12,899)	5470 (9433)
p value	<0.001	0.085	<0.001	0.001	0.850	0.138	<0.001	<0.001	<0.001	<0.001
Non-psychiatric inpatient stay, mean (SD)										
Number of hospitalizations										
Pre-index	0.2 (0.6)	0.4 (0.9)	0.3 (0.6)	0.2 (0.5)	0.2 (0.6)	0.3 (0.6)	0.1 (0.3)	0.2 (0.7)	0.1 (0.4)	0.2 (0.6)
Post-index	0.2 (0.6)	0.5 (1.0)	0.3 (0.6)	0.3 (0.7)	0.2 (0.5)	0.4 (0.8)	0.2 (0.6)	0.2 (0.5)	0.1 (0.4)	0.1 (0.5)
p value	0.339	0.512	0.734	0.149	1	0.458	0.500	0.083	0.672	0.007
Days hospitalized										
Pre-index	1.7 (6.4)	2.1 (6.3)	2.7 (8.0)	1.0 (3.3)	1.5 (4.6)	2.0 (4.8)	0.3 (0.9)	1.8 (8.7)	1.3 (5.3)	1.5 (6.0)
Post-index	1.4 (5.2)	3.4 (8.6)	1.8 (4.7)	2.2 (6.7)	1.0 (3.5)	2.7 (6.4)	1.0 (3.8)	1.2 (6.3)	0.2 (1.2)	0.6 (2.5)
p value	0.333	0.353	0.695	0.165	0.500	0.491	0.750	0.303	0.164	0.006
Costs, €										
Pre-index	590 (2165)	1223 (4762)	1136 (3621)	355 (1019)	946 (2981)	622 (1232)	81 (282)	602 (2336)	376 (1425)	457 (1323)
Post-index	563 (1972)	1126 (2564)	868 (2555)	950 (2883)	423 (1269)	834 (1926)	615 (2617)	441 (1864)	221 (1115)	240 (853)
p value	0.447	0.519	0.936	0.060	0.500	0.521	0.625	0.078	0.461	0.027
Non-psychiatric outpatient stay, mean (SD)										
Number of hospitalizations										
Pre-index	0.1 (0.4)	0.1 (0.3)	0.1 (0.3)	0.1 (0.6)	0.1 (0.3)	0.1 (0.4)	0.2 (0.6)	0.1 (0.5)	0.0 (0.2)	0.1 (0.4)
Post-index	0.1 (0.5)	0.0 (0.0)	0.0 (0.2)	0.1 (0.6)	0.0 (0.0)	0.1 (0.5)	0.3 (1.0)	0.2 (0.7)	0.0 (0.1)	0.1 (0.5)
p value	0.690	1	0.500	0.424	0.500	0.836	0.500	0.300	0.625	0.633
Days hospitalized										
Pre-index	0.5 (5.5)	0.1 (0.3)	0.1 (0.3)	0.1 (0.7)	0.5 (2.1)	0.1 (0.4)	1.7 (7.9)	0.9 (6.5)	0.1 (0.6)	0.9 (8.6)
Post-index	1.7 (17.5)	0.0 (0.0)	0.0 (0.2)	0.6 (5.3)	0.0 (0.0)	0.3 (1.5)	12.0 (57.1)	4.1 (24.7)	0.0 (0.1)	1.7 (17.9)
p value	0.412	1	0.500	0.395	0.500	0.594	0.500	0.268	0.500	0.848

Table 3 (continued)

Parameter	First-generation antipsychotics						Second-generation antipsychotics			
	Overall (n=850)	Fluphenazine (n=35)	Haloperidol (n=96)	Flupentixol (n=129)	Zuclopenthixol (n=19)	Fluspirilene (n=76)	Olanzapine (n=23)	Risperidone (n=176)	Aripiprazole (n=66)	Paliperidone (n=230)
Costs, €										
Pre-index	14.2 (79.5)	5.3 (31.4)	7.0 (38.3)	13.8 (93.2)	15.8 (51.9)	20.2 (86.7)	21.3 (72.8)	19.6 (109)	8.5 (45.6)	13.6 (70.3)
Post-index	14.1 (83.3)	0.0 (0.0)	4.1 (32.1)	12.8 (62.9)	0.0 (0.0)	17.9 (68.6)	61.5 (240)	26.0 (113)	1.6 (13.0)	10.7 (75.4)
p value	0.932	1	0.438	0.787	0.500	0.922	0.500	0.389	0.375	0.194
Psychiatric inpatient stay, mean (SD)										
Number of hospitalizations										
Pre-index	1.3 (1.6)	0.9 (1.3)	0.8 (1.4)	1.1 (1.8)	0.9 (1.4)	0.2 (0.6)	2.6 (2.6)	1.6 (1.8)	1.3 (1.5)	1.6 (1.5)
Post-index	0.6 (1.3)	0.8 (2.1)	0.3 (0.8)	0.7 (1.5)	0.7 (1.0)	0.2 (0.5)	1.3 (3.0)	0.8 (1.3)	0.7 (1.3)	0.7 (1.2)
p value	<0.001	0.306	<0.001	0.003	0.500	0.944	<0.001	<0.001	<0.001	<0.001
Days hospitalized										
Pre-index	47.0 (59.4)	36.7 (63.2)	37.1 (67.5)	39.1 (57.2)	32.3 (69.5)	5.6 (20.2)	71.2 (56.5)	56.1 (60.4)	50.7 (52.2)	61.7 (57.9)
Post-index	18.5 (38.6)	16.0 (39.8)	8.2 (22.5)	16.3 (31.6)	34.0 (58.6)	4.8 (15.4)	22.0 (45.5)	24.4 (41.9)	26.5 (56.5)	20.6 (39.2)
p value	<0.001	0.027	<0.001	<0.001	0.496	0.821	<0.001	<0.001	<0.001	<0.001
Costs, €										
Pre-index	11,069 (14,165)	8790 (14,720)	9113 (16,785)	9258 (13,723)	8374 (18,312)	1048 (3595)	16,553 (13,352)	12,885 (13,997)	12,519 (13,501)	14,426 (13,593)
Post-index	4436 (9466)	3889 (9558)	2053 (5819)	3936 (7675)	8611 (15,173)	1273 (4379)	4749 (10,175)	6075 (11,128)	5789 (12,840)	4823 (9266)
p value	<0.001	0.035	<0.001	<0.001	0.570	0.433	<0.001	<0.001	<0.001	<0.001
Psychiatric outpatient stay, mean (SD)										
Number of hospitalizations										
Pre-index	1.0 (1.5)	0.9 (1.6)	0.9 (1.7)	1.1 (1.6)	1.0 (1.8)	0.2 (0.8)	1.0 (1.1)	1.1 (1.6)	1.3 (1.6)	1.2 (1.5)
Post-index	1.4 (1.8)	1.2 (2.0)	0.8 (1.5)	1.3 (1.8)	1.1 (1.7)	0.1 (0.6)	2.3 (1.9)	1.7 (1.9)	1.9 (1.8)	1.7 (1.8)
p value	<0.001	0.178	0.154	0.127	1	0.250	<0.001	<0.001	0.009	<0.001
Days hospitalized										
Pre-index	24.2 (64.5)	28.9 (87.9)	24.0 (81.5)	33.2 (78.3)	22.1 (54.9)	3.6 (23.3)	17.3 (27.7)	25.5 (66.8)	27.1 (50.8)	24.5 (57.2)
Post-index	37.6 (80.7)	53.8 (109.0)	25.7 (72.8)	33.0 (72.9)	22.2 (61.9)	1.8 (11.8)	84.2 (121.5)	44.1 (86.4)	56.8 (82.8)	40.6 (82.8)
p value	<0.001	0.256	0.351	0.909	0.688	0.438	0.010	0.001	<0.001	<0.001
Costs, €										
Pre-index	236 (522)	265 (659)	215 (637)	311 (784)	233 (462)	31.3 (125)	164 (221)	269 (556)	263 (334)	240 (349)
Post-index	342 (614)	453 (1356)	171 (439)	315 (605)	190 (322)	48.3 (259)	656 (1005)	424 (639)	443 (489)	396 (518)
p value	<0.001	0.685	0.126	0.462	0.688	0.688	0.003	<0.001	0.001	<0.001

SD standard deviation

Table 4 Change in hospitalizations and costs from pre-index to post-index period (hospitalization model 2)

Parameter	First-generation antipsychotics						Second-generation antipsychotics			
	Overall (n=850)	Fluphenazine (n=35)	Haloperidol (n=96)	Flupentixol (n=129)	Zuclopenthixol (n=19)	Fluspirilene (n=76)	Olanzapine (n=23)	Risperidone (n=176)	Aripiprazole (n=66)	Paliperidone (n=230)
All hospitalizations, mean (SD)										
Number of hospitalizations										
Pre-index	2.3 (2.4)	2.0 (2.4)	1.9 (2.2)	2.2 (2.6)	2.1 (2.3)	0.8 (1.2)	3.2 (3.1)	2.7 (2.7)	2.3 (2.3)	2.7 (2.3)
Post-index	2.3 (2.4)	2.5 (3.3)	1.3 (1.7)	2.4 (2.7)	1.9 (2.3)	0.9 (1.1)	4.0 (3.8)	2.8 (2.4)	2.7 (2.2)	2.6 (2.3)
p value	0.487	0.376	0.003	0.382	0.496	0.545	0.126	0.557	0.060	0.706
Days hospitalized										
Pre-index	58.9 (74.5)	58.3 (91.7)	55.9 (89.4)	57.7 (81.4)	40.8 (64.0)	10.0 (32.4)	70.9 (61.9)	66.5 (72.1)	56.5 (60.2)	72.4 (72.3)
Post-index	59.2 (88.4)	73.1 (109.7)	35.7 (73.9)	52.1 (80.7)	57.2 (80.1)	9.6 (19.6)	119.2 (116.5)	73.9 (95.7)	83.6 (92.3)	63.4 (89.9)
p value	0.111	0.370	0.004	0.215	0.092	0.148	0.300	0.890	0.014	0.010
Costs, €										
Pre-index	10,276 (13,373)	10,121 (15,531)	9874 (17,349)	8063 (12,322)	6794 (10,512)	1698 (3924)	14,877 (13,603)	11,811 (12,591)	9797 (11,444)	13,335 (13,640)
Post-index	5355 (9744)	5468 (10,894)	3096 (6300)	5214 (8582)	9224 (15,186)	2173 (4701)	6082 (10,658)	6966 (11,156)	6453 (12,899)	5470 (9433)
p value	<0.001	0.085	<0.001	0.054	0.380	0.132	<0.001	<0.001	0.009	<0.001
Non-psychiatric inpatient stay, mean (SD)										
Number of hospitalizations										
Pre-index	0.2 (0.6)	0.4 (0.9)	0.3 (0.6)	0.2 (0.5)	0.2 (0.6)	0.3 (0.6)	0.1 (0.3)	0.2 (0.7)	0.1 (0.4)	0.2 (0.6)
Post-index	0.2 (0.6)	0.5 (1.0)	0.3 (0.6)	0.3 (0.7)	0.2 (0.5)	0.4 (0.8)	0.2 (0.6)	0.2 (0.5)	0.1 (0.4)	0.1 (0.5)
p value	0.346	0.512	0.734	0.149	1	0.426	0.500	0.083	0.672	0.007
Days hospitalized										
Pre-index	1.6 (6.4)	2.1 (6.3)	2.7 (8.0)	1.0 (3.3)	1.5 (4.6)	1.9 (4.8)	0.3 (0.9)	1.8 (8.7)	1.3 (5.3)	1.5 (6.0)
Post-index	1.4 (5.2)	3.4 (8.6)	1.8 (4.7)	2.2 (6.7)	1.0 (3.5)	2.7 (6.4)	1.0 (3.8)	1.2 (6.3)	0.2 (1.2)	0.6 (2.5)
p value	0.346	0.353	0.695	0.165	0.500	0.446	0.750	0.303	0.164	0.006
Costs, €										
Pre-index	587 (2163)	1223 (4762)	1136 (3621)	355 (1019)	946 (2981)	604 (1196)	81.4 (282)	602 (2336)	376 (1425)	457 (1323)
Post-index	563 (1972)	1126 (2564)	868 (2555)	950 (2883)	423 (1269)	834 (1926)	615 (2617)	441 (1864)	221 (1115)	240 (853)
p value	0.458	0.519	0.936	0.060	0.500	0.521	0.625	0.078	0.461	0.027
Non-psychiatric outpatient stay, mean (SD)										
Number of hospitalizations										
Pre-index	0.1 (0.4)	0.1 (0.3)	0.1 (0.3)	0.1 (0.6)	0.1 (0.3)	0.1 (0.4)	0.1 (0.5)	0.1 (0.4)	0.0 (0.2)	0.1 (0.4)
Post-index	0.1 (0.5)	0.0 (0.0)	0.0 (0.0)	0.1 (0.6)	0.0 (0.0)	0.1 (0.5)	0.3 (1.0)	0.2 (0.7)	0.0 (0.1)	0.1 (0.5)
p value	0.471	1	0.500	0.383	0.500	0.836	0.500	0.210	0.625	0.817
Days hospitalized										
Pre-index	0.4 (5.1)	0.1 (0.3)	0.1 (0.3)	0.1 (0.6)	0.5 (2.1)	0.1 (0.4)	0.1 (0.5)	0.6 (5.2)	0.1 (0.6)	0.9 (8.6)
Post-index	1.7 (17.5)	0.0 (0.0)	0.0 (0.2)	0.6 (5.3)	0.0 (0.0)	0.3 (1.5)	12.0 (57.1)	4.1 (24.7)	0.0 (0.1)	1.7 (17.9)
p value	0.212	1	0.500	0.395	0.500	0.594	0.500	0.086	0.500	0.848

Table 4 (continued)

Parameter	First-generation antipsychotics						Second-generation antipsychotics			
	Overall (n=850)	Fluphenazine (n=35)	Haloperidol (n=96)	Flupentixol (n=129)	Zuclopenthixol (n=19)	Fluspirilene (n=76)	Olanzapine (n=23)	Risperidone (n=176)	Aripiprazole (n=66)	Paliperidone (n=230)
Costs, €										
Pre-index	13.3 (78.3)	5.3 (31.4)	7.0 (38.3)	12.6 (92.3)	15.8 (51.9)	20.2 (86.7)	12.2 (42.6)	18.1 (108)	8.5 (45.6)	12.8 (69.4)
Post-index	14.1 (83.3)	0.0 (0.0)	4.1 (32.1)	12.8 (62.9)	0.0 (0.0)	17.9 (68.6)	61.5 (239)	26.0 (113)	1.6 (13.0)	10.7 (75.4)
p value	0.819	1	0.438	0.711	0.500	0.922	0.500	0.326	0.375	0.359
Psychiatric inpatient stay, mean (SD)										
Number of hospitalizations										
Pre-index	1.2 (1.6)	0.9 (1.3)	0.8 (1.4)	1.0 (1.8)	0.8 (1.3)	0.2 (0.6)	2.4 (2.6)	1.5 (1.8)	1.1 (1.5)	1.4 (1.5)
Post-index	0.6 (1.3)	0.8 (2.1)	0.3 (0.8)	0.7 (1.5)	0.7 (1.0)	0.2 (0.5)	1.3 (3.0)	0.8 (1.3)	0.7 (1.3)	0.7 (1.2)
p value	<0.001	0.354	<0.001	0.036	0.500	0.944	0.002	<0.001	0.017	<0.001
Days hospitalized										
Pre-index	40.3 (55.2)	35.9 (61.3)	34.9 (66.8)	31.0 (50.2)	20.9 (36.8)	5.6 (20.2)	63.7 (58.9)	47.8 (52.8)	37.9 (47.5)	54.0 (57.8)
Post-index	18.5 (38.6)	16.0 (39.8)	8.2 (22.5)	16.3 (31.6)	34.0 (58.6)	4.8 (15.4)	22.0 (45.5)	24.4 (41.9)	26.5 (56.5)	20.6 (39.2)
p value	<0.001	0.027	<0.001	0.003	0.156	0.821	<0.001	<0.001	0.035	<0.001
Costs, €										
Pre-index	9497 (13,138)	8684 (14,473)	8567 (16,601)	7,437 (12,246)	5610 (10,309)	1048 (3595)	14,700 (13,613)	10,999 (12,313)	9216 (11,447)	12,688 (13,591)
Post-index	4436 (9466)	3889 (9558)	2,053 (5819)	3936 (7675)	8611 (15,173)	1273 (4379)	4,749 (10,175)	6075 (11,128)	5788 (12,840)	4823 (9266)
p value	<0.001	0.035	<0.001	0.004	0.164	0.433	<0.001	<0.001	0.017	<0.001
Psychiatric outpatient stay, mean (SD)										
Number of hospitalizations										
Pre-index	0.8 (1.4)	0.6 (1.3)	0.7 (1.5)	0.9 (1.5)	0.9 (1.6)	0.2 (0.7)	0.6 (1.1)	0.9 (1.4)	1.1 (1.5)	0.9 (1.3)
Post-index	1.4 (1.8)	1.2 (2.0)	0.8 (1.5)	1.3 (1.8)	1.1 (1.7)	0.1 (0.6)	2.3 (1.9)	1.7 (1.9)	1.9 (1.8)	1.7 (1.8)
p value	<0.001	0.037	0.841	0.006	0.813	0.750	<0.001	<0.001	<0.001	<0.001
Days hospitalized										
Pre-index	16.6 (50.5)	20.3 (69.1)	18.2 (64.5)	25.6 (63.8)	17.8 (44.9)	2.4 (15.7)	6.7 (16.1)	16.3 (51.1)	17.2 (38.8)	16.0 (43.8)
Post-index	37.6 (80.7)	53.8 (109.0)	25.7 (72.8)	33.0 (72.9)	22.2 (61.9)	1.8 (11.8)	84.2 (121.5)	44.1 (86.4)	56.8 (82.8)	40.6 (82.8)
p value	<0.001	0.376	0.883	0.024	1	1	<0.001	<0.001	<0.001	<0.001
Costs, €										
Pre-index	178 (431)	208 (557)	164 (450)	258 (680)	221 (455)	25.3 (102)	83.0 (217)	192 (459)	196 (297)	176 (281)
Post-index	342 (614)	453 (1356)	171 (439)	315 (605)	190 (322)	48.3 (259)	656 (1,005)	424 (639)	443 (489)	396 (518)
p value	<0.001	0.376	0.883	0.024	1	1	0.001	<0.001	<0.001	<0.001

SD standard deviation

Table 5 Change in ambulatory healthcare resource utilization and costs from pre-index to post-index period

Parameter	First-generation antipsychotics						Second-generation antipsychotics			
	Overall (n=850)	Fluphenazine (n=35)	Haloperidol (n=96)	Flupentixol (n=129)	Zuclopenthixol (n=19)	Fluspirilene (n=76)	Olanzapine (n=23)	Risperidone (n=176)	Aripiprazole (n=66)	Paliperidone (n=230)
Number of visits, mean (SD)										
Pre-index	19.4 (17.7)	19.0 (16.5)	22.9 (19.0)	21.1 (15.6)	19.6 (17.3)	30.9 (19.4)	10.8 (10.1)	18.0 (18.9)	14.6 (14.1)	16.5 (16.4)
Post-index	26.0 (29.1)	22.5 (14.7)	25.4 (18.8)	27.9 (28.4)	24.5 (15.6)	39.3 (23.7)	15.8 (11.1)	25.0 (30.5)	17.8 (16.3)	25.4 (37.7)
p value	<0.001	0.111	0.012	<0.001	0.032	<0.001	0.060	<0.001	0.012	<0.001
Number of visits by specialists, mean (SD)										
General practitioner										
Pre-index	7.9 (9.7)	8.2 (11.6)	9.0 (9.0)	8.2 (8.3)	6.6 (5.8)	13.5 (10.2)	4.8 (6.4)	7.1 (10.8)	5.8 (6.2)	7.1 (10.2)
Post-index	10.5 (16.6)	10.2 (10.8)	10.0 (9.4)	10.3 (8.6)	9.3 (8.8)	16.6 (12.4)	8.0 (7.7)	11.8 (23.9)	5.9 (7.3)	9.4 (19.7)
p value	<0.001	0.026	0.156	0.003	0.044	0.001	0.018	<0.001	0.903	<0.001
Neurology and psychiatry										
Pre-index	5.2 (6.7)	5.8 (6.0)	6.9 (6.8)	6.0 (6.2)	5.6 (6.4)	6.3 (7.8)	3.9 (4.9)	4.7 (7.4)	3.8 (5.3)	4.3 (6.3)
Post-index	7.9 (11.6)	7.1 (6.6)	8.7 (7.5)	8.7 (8.6)	9.7 (7.7)	9.4 (10.3)	4.3 (5.4)	7.4 (10.1)	5.5 (7.1)	8.0 (16.9)
p value	<0.001	0.161	0.001	<0.001	0.001	<0.001	0.349	<0.001	0.003	<0.001
Ophthalmology										
Pre-index	0.3 (0.9)	0.4 (0.7)	0.6 (1.5)	0.4 (1.1)	0.3 (1.2)	0.5 (1.5)	0.2 (0.7)	0.2 (0.6)	0.2 (0.4)	0.2 (0.5)
Post-index	0.3 (1.0)	0.4 (0.8)	0.5 (1.7)	0.4 (1.1)	0.2 (0.7)	0.6 (1.5)	0.5 (1.8)	0.2 (0.6)	0.3 (0.7)	0.2 (0.6)
p value	0.947	0.973	0.238	0.794	0.750	0.823	1	0.913	0.264	0.854
Orthopedics										
Pre-index	0.5 (1.8)	0.5 (1.7)	0.7 (2.2)	0.7 (2.4)	0.3 (1.1)	1.4 (3.1)	0.0 (0.0)	0.5 (1.5)	0.4 (1.8)	0.2 (0.9)
Post-index	0.6 (1.9)	0.2 (0.6)	0.8 (2.1)	0.8 (2.4)	0.6 (1.7)	1.4 (3.6)	0.0 (0.2)	0.5 (1.7)	0.3 (1.0)	0.3 (1.1)
p value	0.333	0.586	0.888	0.530	0.250	0.624	1	0.747	0.992	0.025
Gynecology										
Pre-index	0.6 (1.8)	0.3 (0.8)	0.6 (1.6)	0.7 (1.4)	0.4 (1.0)	1.4 (3.0)	0.0 (0.0)	0.5 (1.7)	0.7 (1.9)	0.6 (1.9)
Post-index	0.7 (1.7)	0.2 (0.5)	0.5 (1.2)	0.8 (1.7)	0.7 (1.6)	1.4 (2.8)	0.1 (0.4)	0.5 (1.8)	0.7 (1.5)	0.6 (1.5)
p value	0.253	0.219	0.511	0.134	0.500	0.937	1	0.535	0.943	0.352
Otorhinolaryngology										
Pre-index	0.4 (1.2)	0.1 (0.4)	0.5 (1.0)	0.3 (0.8)	0.2 (0.6)	1.1 (2.1)	0.2 (0.7)	0.5 (1.4)	0.2 (0.6)	0.3 (1.2)
Post-index	0.4 (1.4)	0.3 (0.6)	0.4 (1.1)	0.4 (1.2)	0.1 (0.3)	1.2 (2.8)	0.0 (0.0)	0.3 (0.9)	0.3 (0.7)	0.4 (1.4)
p value	0.549	0.176	0.314	0.831	0.750	0.984	0.500	0.186	0.357	0.953
Dermatologist										
Pre-index	0.3 (1.0)	0.4 (0.8)	0.3 (1.1)	0.3 (0.8)	0.2 (0.6)	0.5 (1.2)	0.1 (0.3)	0.4 (1.0)	0.3 (0.8)	0.4 (1.2)
Post-index	0.4 (1.4)	0.4 (1.0)	0.3 (1.2)	0.4 (1.8)	0.1 (0.2)	0.8 (2.4)	0.2 (0.7)	0.4 (1.2)	0.2 (0.6)	0.4 (1.4)
p value	0.396	0.938	0.992	0.950	0.500	0.443	1	0.621	0.588	0.416

Table 5 (continued)

Parameter	First-generation antipsychotics						Second-generation antipsychotics			
	Overall (n=850)	Fluphenazine (n=35)	Haloperidol (n=96)	Flupentixol (n=129)	Zuclopenthixol (n=19)	Fluspirilene (n=76)	Olanzapine (n=23)	Risperidone (n=176)	Aripiprazole (n=66)	Paliperidone (n=230)
Internist										
Pre-index	0.1 (0.8)	0.0 (0.0)	0.4 (1.3)	0.2 (0.8)	0.0 (0.0)	0.3 (1.4)	0.0 (0.0)	0.1 (0.6)	0.1 (0.5)	0.1 (0.4)
Post-index	0.2 (1.2)	0.5 (2.4)	0.4 (1.4)	0.2 (1.0)	0.4 (1.6)	0.4 (1.5)	0.0 (0.2)	0.1 (0.6)	0.2 (0.9)	0.2 (1.3)
p value	0.069	0.500	0.902	0.657	0.500	0.630	1	0.587	0.531	0.081
Laboratory Medicine										
Pre-index	0.8 (1.7)	1.1 (1.6)	0.6 (1.3)	0.8 (1.3)	1.2 (1.8)	0.9 (1.5)	0.4 (0.9)	0.8 (1.7)	0.7 (1.4)	0.9 (2.1)
Post-index	1.1 (2.4)	0.9 (1.5)	1.2 (4.5)	1.1 (2.2)	1.3 (1.5)	1.2 (1.6)	1.0 (1.5)	1.1 (2.0)	0.6 (1.1)	1.1 (2.3)
p value	0.002	0.407	0.316	0.106	0.558	0.099	0.107	0.066	0.536	0.103
Radiology										
Pre-index	0.3 (0.7)	0.2 (0.5)	0.2 (0.4)	0.2 (0.6)	0.4 (1.2)	0.6 (1.1)	0.0 (0.0)	0.3 (0.7)	0.2 (0.5)	0.2 (0.6)
Post-index	0.2 (0.7)	0.1 (0.2)	0.2 (0.6)	0.3 (0.7)	0.2 (0.5)	0.7 (1.2)	0.2 (0.7)	0.2 (0.6)	0.3 (1.0)	0.1 (0.5)
p value	0.405	0.234	0.862	0.712	0.500	0.989	0.500	0.503	0.709	0.216
Urology										
Pre-index	0.3 (1.5)	0.3 (0.8)	0.9 (3.4)	0.3 (1.2)	0.6 (2.8)	0.4 (1.1)	0.2 (0.8)	0.2 (1.3)	0.1 (0.5)	0.1 (0.4)
Post-index	0.3 (1.7)	0.2 (0.8)	0.7 (2.6)	0.3 (1.3)	0.9 (3.9)	0.4 (1.0)	0.0 (0.0)	0.2 (1.2)	0.0 (0.2)	0.3 (2.1)
p value	0.761	0.375	0.037	0.841	0.500	0.967	1	0.363	0.250	0.230
Psychological psychotherapist										
Pre-index	0.4 (2.5)	0.0 (0.0)	0.1 (0.8)	0.4 (2.1)	0.0 (0.0)	0.6 (2.3)	0.0 (0.0)	0.4 (2.9)	0.7 (3.2)	0.5 (3.1)
Post-index	0.8 (4.2)	0.0 (0.0)	0.1 (0.9)	0.6 (2.9)	0.0 (0.0)	1.2 (4.2)	0.0 (0.0)	0.6 (3.7)	1.6 (6.3)	1.1 (5.6)
p value	0.010	1	0.500	0.977	1	0.186	1	0.895	0.102	0.065
Other										
Pre-index	1.3 (3.7)	1.0 (3.1)	1.4 (2.6)	1.3 (3.1)	3.3 (9.5)	2.1 (3.3)	0.3 (1.0)	1.4 (5.4)	1.0 (2.9)	1.0 (2.3)
Post-index	1.2 (2.9)	1.0 (2.0)	1.0 (2.0)	1.1 (2.2)	0.7 (1.1)	3.1 (5.7)	0.6 (1.0)	0.9 (1.8)	1.7 (4.0)	1.1 (2.6)
p value	0.903	0.630	0.039	0.549	0.138	0.063	0.459	0.174	0.046	0.644
Unknown										
Pre-index	0.8 (2.2)	0.7 (2.2)	0.8 (1.4)	1.1 (3.8)	0.4 (1.2)	1.1 (1.7)	0.7 (1.5)	0.9 (2.1)	0.6 (1.2)	0.7 (1.8)
Post-index	1.4 (15.1)	1.0 (2.7)	0.6 (1.3)	2.4 (21.3)	0.4 (0.8)	1.0 (1.7)	0.8 (1.6)	0.8 (1.7)	0.4 (0.8)	2.2 (24.1)
p value	0.019	0.213	0.246	0.131	1	0.485	0.734	0.176	0.200	0.294
Costs, € mean (SD)										
Pre-index	581 (563)	546 (457)	664 (524)	648 (591)	708 (851)	874 (614)	328 (314)	522 (553)	495 (532)	501 (528)
Post-index	739 (703)	657 (369)	731 (478)	795 (614)	698 (470)	1096 (698)	496 (339)	659 (719)	668 (855)	714 (812)
p value	<0.001	0.137	0.013	<0.001	0.332	<0.001	0.035	<0.001	0.062	<0.001

SD standard deviation

significant changes were observed only in the olanzapine, risperidone, and paliperidone groups ($p < 0.05$ for all). No significant changes were observed in the mean number and duration of sickness benefit periods and sickness benefit costs (Table 6).

3.2.5 Employment, Aids, and Associated Costs

Across the pre- and post-index periods, the overall number of unemployed patients (26.3% vs 27.1%) and mean length of unemployment (2.4 months) were similar. Compared to typical antipsychotic users, a greater number of atypical antipsychotic LAI users were unemployed (11.9% vs 34.5%) and for a longer duration (1.1 vs 3.2 months). Comparison of the number of patients who switched from unemployment to employment and vice versa also showed similar results (Supplementary Table 6).

Overall, fewer patients required aids in the post-index period compared with pre-index (0.6% vs 1.2%). The mean number of aids and associated costs significantly decreased from the pre-index to post-index ($p < 0.05$ for all; Supplementary Table 7).

3.2.6 Therapies

Overall, the mean number of times biperiden; lorazepam; and psychiatric interview, consulting (single treatment) was used was greater in the post-index period compared with pre-index (0.6 vs 0.4, 0.6 vs 0.4, and 4.7 vs 3.1; $p < 0.001$ for all). Elaborate diagnostics usage decreased significantly from pre-index to post-index (0.1 vs 0.0, $p < 0.001$). The overall mean number of times standard and intensive adult treatment was used also decreased significantly from pre-index to post-index (2.7 vs 1.3 and 1.6 vs 0.7, $p < 0.001$ for all). All the atypical antipsychotics showed a significant decrease compared with less than half of the typical antipsychotics. Similar reductions from pre-index to post-index period was observed for treatment area usage. Supplementary Table 8 shows the above results and changes in the number of patients utilizing the services.

3.2.7 Total Costs

As total costs include the associated costs of hospitalizations, total costs were also affected by the two models. Figure 3 depicts the total costs as a composite of individual costs for models 1 and 2, respectively. In model 1, the overall mean total costs reduced significantly from pre-index to post-index (€13,776 vs €10,418; $p < 0.001$). Group-wise, significant cost reduction was observed for haloperidol (€12,131 vs €4971; $p = 0.009$), flupentixol (€11,571 vs €7504; $p = 0.014$), risperidone (€15,725 vs 12,973; $p = 0.049$), and paliperidone palmitate (€17,166 vs €13,499; $p = 0.001$); with haloperidol

showing the greatest reduction (2.4-fold). Compared to pre-index costs, the post-index costs increased for fluspirilene users (€3906 vs €4914; $p = 0.005$). In model 2, only haloperidol showed a significant decrease (€11,534 vs €4971; $p = 0.024$) while fluspirilene showed a significant increase (€3882 vs €4914; $p = 0.004$) in total costs.

3.3 Beneficial Characteristics for LAI Initiation

More non-psychiatric ($p = 0.008$) and psychiatric ($p < 0.001$) inpatient stays during the pre-index period were present in patients who benefitted the most from cost reduction after LAI initiation (Table 7). The estimated parameter suggests that each stay in a psychiatric hospital before the index date is associated with a post-index date cost reduction of €3304 after LAI initiation.

4 Discussion

This retrospective German claims-based study assessed the impact of LAI initiation among patients with schizophrenia in terms of HRU and costs. Multiple typical and atypical antipsychotic LAIs were evaluated. The number and duration of hospitalizations decreased after LAI initiation during the post-index period. Although LAI initiation increased medication costs, antipsychotic costs, and ambulatory visit costs, the corresponding decrease in hospitalization costs resulted in decreased total costs.

Switching to LAI decreased the number and duration of hospitalizations by 12% and 19%, respectively. The reduction was mainly driven by a decrease in psychiatric inpatient stays. These results are consistent with other mirror-image studies conducted in cohorts of less than 200 patients [30–32], a cohort of almost 2000 patients [33], and a meta-analysis of 15 mirror-image studies [34] that showed a significant decrease in hospitalization after patients switched to LAI. Particularly strong evidence was reported in a Spanish 10-year mirror-image study conducted in more than 300 patients that linked LAI administration with significant reductions in number of hospitalized patients and number of hospitalizations due to relapse [35]. Several real-world non-mirror-image studies also reported lower hospitalization on usage of LAIs compared with OAPs [14, 36–40].

Switching to LAIs in the current study resulted in total annual savings of €3358 (model 1) and €1726 (model 2), consequent to the psychiatric inpatient stay-driven reduction in hospitalization and resultant costs. The resultant savings are similar to another German mirror-image study wherein 119 patients were switched from an OAP to a risperidone LAI (RLAI). Here, net savings after a year of switching to RLAI were €3812 [30]. Studies in other populations have also reported savings after LAI initiation. Two Canadian

Table 6 Change in sick leave and sickness benefit from pre-index to post-index period

Parameter	First-generation antipsychotics						Second-generation antipsychotics			
	Overall (n=850)	Fluphenazine (n=35)	Haloperidol (n=96)	Flupentixol (n=129)	Zuclopenthixol (n=19)	Fluspirilene (n=76)	Olanzapine (n=23)	Risperidone (n=176)	Aripiprazole (n=66)	Paliperidone (n=230)
Number of patients with sick leave periods, n (%)										
Pre-index	175 (20.6)	4 (11.4)	13 (13.5)	14 (10.9)	0 (0.0)	17 (22.4)	7 (30.4)	42 (23.9)	13 (19.7)	65 (28.3)
Post-index	150 (17.6)	1 (2.9)	11 (11.5)	11 (8.5)	1 (5.3)	18 (23.7)	4 (17.4)	35 (19.9)	14 (21.2)	55 (23.9)
p value	0.002	0.750	0.146	0.969	1	0.950	0.031	0.213	0.814	0.015
Number of sick leave periods, mean (SD)										
Pre-index	0.6 (1.6)	0.1 (0.4)	0.6 (1.6)	0.4 (1.5)	0.0 (0.0)	0.6 (1.4)	1.3 (2.9)	0.6 (1.5)	0.5 (1.2)	0.8 (1.9)
Post-index	0.5 (1.5)	0.1 (0.7)	0.3 (1.1)	0.4 (2.1)	0.1 (0.2)	0.6 (1.4)	0.4 (1.0)	0.5 (1.2)	0.4 (1.1)	0.7 (1.9)
p value	0.006	0.125	0.146	0.969	1	0.950	0.031	0.213	0.814	0.015
Duration of sick leave periods, mean (SD)										
Pre-index	20.6 (57.0)	8.7 (33.0)	13.8 (51.4)	11.1 (43.3)	0.0 (0.0)	11.0 (34.7)	25.7 (43.7)	29.2 (71.7)	26.1 (65.2)	26.6 (61.5)
Post-index	16.9 (55.8)	0.9 (5.2)	6.0 (21.5)	8.1 (35.6)	19.2 (83.7)	21.7 (61.2)	13.0 (50.0)	19.9 (66.5)	21.3 (61.5)	24.0 (63.0)
p value	0.006	0.125	0.203	0.224	1	0.143	0.297	0.019	0.528	0.379
Number of patients with sickness benefit periods, n (%)										
Pre-index	116 (13.6)	1 (2.9)	5 (5.2)	9 (7.0)	0 (0.0)	10 (13.2)	6 (26.1)	33 (18.8)	10 (15.2)	42 (18.3)
Post-index	99 (11.6)	0 (0.0)	3 (3.1)	7 (5.4)	1 (5.3)	11 (14.5)	3 (13.0)	26 (14.8)	9 (13.6)	39 (17.0)
p value	0.082	1	0.375	0.781	1	0.346	0.063	0.123	0.500	0.550
Number of sickness benefit periods, mean (SD)										
Pre-index	0.3 (0.9)	0.0 (0.2)	0.1 (0.7)	0.2 (1.2)	0.0 (0.0)	0.3 (1.0)	0.6 (1.6)	0.4 (1.0)	0.2 (0.6)	0.3 (0.8)
Post-index	0.2 (1.0)	0.0 (0.0)	0.1 (0.6)	0.2 (1.8)	0.1 (0.2)	0.4 (1.2)	0.2 (0.5)	0.3 (0.9)	0.2 (0.5)	0.3 (0.8)
p value	0.082	1	0.375	0.781	1	0.346	0.063	0.123	0.500	0.550
Duration of sickness benefit periods, mean (SD)										
Pre-index	13.6 (47.2)	0.5 (2.9)	9.2 (45.6)	6.6 (34.3)	0.0 (0.0)	7.6 (31.8)	13.3 (25.4)	21.7 (60.0)	18.1 (56.0)	16.9 (50.6)
Post-index	13.3 (50.4)	0.0 (0.0)	2.7 (15.3)	5.0 (27.5)	19.2 (83.7)	18.3 (55.7)	12.0 (49.9)	16.8 (61.2)	16.8 (56.2)	18.7 (56.4)
p value	0.614	1	0.281	0.385	1	0.065	0.563	0.144	1	0.610
Sickness benefit costs, € mean (SD)										
Pre-index	486 (2,330)	0.0 (0.0)	227 (1,766)	268 (1,744)	0.0 (0.0)	210 (1,178)	321 (938)	789 (3,152)	821 (3,150)	610 (2,435)
Post-index	492 (2,225)	0.0 (0.0)	46.5 (330)	183 (1,276)	980 (4,274)	435 (1,701)	704 (3,001)	474 (1,921)	930 (3,403)	773 (2,776)
p value	0.906	1	0.625	0.383	1	0.297	1	0.223	0.820	0.326

SD standard deviation

Fig. 3 Total annual costs (€) during the 12-month pre-index interval compared to post-index interval. Two models were used to evaluate hospitalization costs; hence, the other costs show the same value irrespective of the model. Significant differences were observed between pre-index and post-index periods for model 1 total costs ($p < 0.001$), model 1 and 2 hospitalization costs ($p < 0.001$ for both), medication and antipsychotics costs ($p < 0.001$ for both), ambulatory visit costs ($p < 0.001$), and medical aids costs ($p = 0.014$)
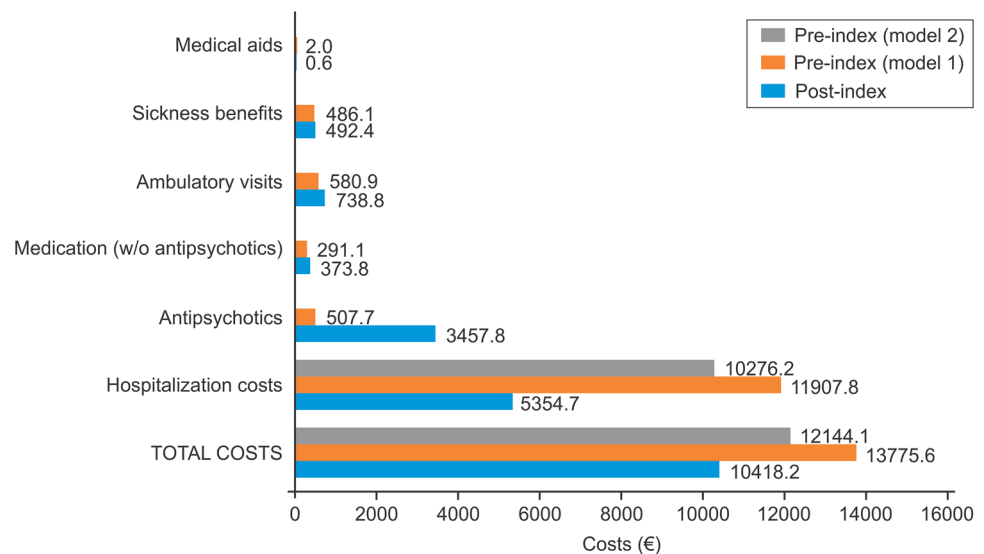
mirror-image studies evaluated the effect of LAI usage for 12 months on healthcare costs. Chawla et al [32] analyzed data of 44 patients in a community center hospital and reported pre-LAI initiation hospital costs of $1,169,600 and post-LAI initiation hospital and LAI costs to be $363,801, resulting in net savings of $18,314 per patient per year. On the other hand, Lachaine et al [33] used the Régie de l'assurance maladie du Québec database to assess data of 1992 patients and reported net savings of CAD11,292 per year. A similar analysis by Peng et al [41] in the USA showed savings of $3228 per patient after 6 months of LAI initiation in 147 patients with schizophrenia. Cost analysis using models also show the benefit of switching to LAIs. Laux et al [17] used a discrete event simulation model to compare the costs of RLAI with oral olanzapine over a 5-year period in Germany, and reported that LAI initiation reduces costs by €6096. Another German study by Zeidler et al [16] estimated the cost effectiveness of paliperidone LAI (PLAI) using a Markov decision analytic model over a 5-year period. Here, the incremental cost-effectiveness ratio (€/gained quality-adjusted life-years) of PLAI was €69,659 and €23,183 compared with oral atypical and oral typical agents, respectively. A budget impact analysis also estimated enormous savings amounting to > 8000 million yen ($68 million) for the Japanese healthcare system after the market introduction of PLAI [42]. These data represent only direct costs; the indirect costs of preventing relapse were not assessed.

Compound-wise analysis reveals that significant overall cost-reductions were associated with haloperidol (€ − 7160), and flupentixol (€ − 4068) among the first-generation antipsychotics; and with risperidone (€ − 2753), and paliperidone palmitate (€ − 3667) among the second-generation antipsychotics. However, patient populations treated with first- and second-generation antipsychotics are different from each

other as indicated by lower total pre-index costs. Those pre-index cost differences probably reflect a high degree of heterogeneity in disease severity. Therefore, comparisons across compounds should be treated with caution.

Multiple European studies have associated LAI usage with lower relapses, symptomatic improvement, increased personal recovery, and lower suicidal ideation and suicide attempts [20, 43, 44]. Interestingly, Corigliano et al [44] reported that patients in the early stages of schizophrenia (≤ 5 years of schizophrenia) seemed to benefit more from LAI initiation than chronic patients (> 5 years of schizophrenia). Similar effects were noted by Brown et al [45] on administering PLAI once a month and once every 3 months to patients with various durations of schizophrenia. Early LAI initiation was also associated with lower hospitalization and costs in the USA [46]. Although we could not observe these effects as the data were not stratified based on disease duration, future studies could certainly assess this outcome.

In current clinical practice, LAIs are often reserved for non-adherent patients, and psychiatrists themselves avoid prescribing LAIs to patients with first-episode schizophrenia [47]. While some patients prefer LAIs over OAPs due to increased relapse prevention [48] as well as better quality of life [49], others report being coerced into undergoing treatment with LAIs [50]; with pain at the injection site, misconceptions regarding LAIs, and lack of awareness also being reported as reasons for low LAI uptake [51, 52]. Bridges et al [53] recently quantified the effect of schizophrenia treatment goals on a patient's treatment plan. In this study, patients who had functional goals such as improving social relationships, increasing interest in work, and experiencing full range of emotions were more likely to prefer LAIs over OAPs. While the current study along with existing evidence suggests reduced HRU and financial burden on LAI initiation, successful treatment of schizophrenia also depends on

Table 7 Beneficial characteristics for LAI initiation

Outcome: Costs_post − Costs_pre	Estimate	*p* value
Intercept	811.3	0.7607
Age	− 48.2	0.2324
Insurance status		
0 − No compulsory insurance	− 14791.7	0.0584
1 − Compulsory insurance	− 859.2	0.5325
2 − Voluntary insurance	2068.3	0.2312
3 − Unemployed person	1368.3	0.4062
4 − Pension claimant	7355	0.1886
6 − Special group of persons	10164.1	0.0268
7 − Family member	− 1326.2	0.5469
Unknown	− 1128.8	0.5073
5 − Retired person (reference)	0	
Gender		
Male	238.8	0.8113
Female (reference)	0	
HRU during pre-index period		
Number of different agents (ATC N05A)	− 261.6	0.5219
Number of inpatient stays during pre-index period, non-psychiatric	− 2178.7	0.0077
Number of out-patient stays during pre-index period, non-psychiatric	1236.7	0.2713
Number of in-patient stays during pre-index period, psychiatric	− 3304.5	< 0.0001
Number of out-patient stays during pre-index period, psychiatric	1496.9	0.0002
Number of office visits	105.1	0.0006
Psychiatric interview, consulting		
Yes	1426.8	0.2001
No (reference)	0	
R-Square	0.17	

HRU Healthcare Resource Utilization, *LAI* long-acting injectable

the patient's comfort. Therefore, we suggest that treatment decisions should incorporate patient preference and treatment goals in addition to other clinical factors and costs.

4.1 Limitations

There are certain limitations in the current study. Since claims data were used to identify a diagnosis of schizophrenia, it is possible that misclassification or coding errors could have occurred. Moreover, claims data insufficiently reflect the severity of a disease and other influencing circumstances. Claims data were also used to identify antipsychotic utilization; however, the data only support receipt and payment and actual consumption is only presumed. Nevertheless, since LAIs are generally administered by a healthcare professional, a claim for a LAI provides confidence that the effective dose was administered to the patient. Finally, indirect costs were excluded from the analyses as this study concentrated on the payer's perspective. However, inclusion of indirect costs would most likely result in lower total costs for LAIs compared with OAPs as LAIs cause fewer relapses

and would have probably reduced loss of productivity more than OAPs.

5 Conclusion

Patients with schizophrenia who switched to treatment with LAI antipsychotics had fewer hospitalizations and clinic visits compared with their treatment period before the switch. Although treatment with LAIs increases the medication and ambulatory visit costs, the corresponding reduction in hospitalization costs results in overall total cost reduction. The average total costs considering all the LAIs together reduced by 24.4% and 14.2% as per models 1 and 2, respectively. This is one of the first claims database analysis for Germany that studied the impact of treatment initiation with LAIs on costs in a large cohort of patients with schizophrenia. In line with results from other countries, we found significant savings from a health insurance point of view that calls for a wider use of LAIs in Germany. Since treatment of schizophrenia is a long-term engagement, future research could

perform an extended follow-up and report the impact of treatment with LAIs.

Compliance with Ethical Standards

Conflict of interest Jörg Mahlich, Kerstin Olbrich, and Antonie Wimmer are employees of Janssen-Cilag. Adrian Wilk is an employee of Team Gesundheit GmbH which received funding for this study from Janssen-Cilag. Claus Wolff-Menzler has no conflict of interest to declare.

Ethics approval Not required as this study used anonymized German claims data.

Informed consent Not applicable.

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