ORIGINAL RESEARCH

Reduction in inpatient resource utilization and costs associated with long-acting injectable antipsychotics across different age groups of Medicaid-insured schizophrenia patients

Siddhesh A Kamat[1], Steve Offord[1], John Docherty[1], Jay Lin[2], Anna Eramo[3], Ross A Baker[4], Benjamin Gutierrez[1*], Craig Karson[5]

[1]Otsuka America Pharmaceutical, Inc., Princeton, NJ, USA; [2]Novosys Health, Flemington, NJ, USA; [3]Lundbeck, Deerfield, IL, USA
[4]Otsuka Pharmaceutical Development and Commercialization, Inc., Princeton, NJ, USA; [5]CNK Consulting Group LLC, Delray Beach, FL, USA
[*]Current affiliation is GlaxoSmithKline, King of Prussia, PA, USA

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Correspondence

Siddhesh Kamat, MS, MBA, Health Economics & Outcomes Research, Otsuka America Pharmaceutical, Inc., Princeton, NJ, 08540, USA. Siddhesh.Kamat@otsuka-us.com

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Abbreviations

CCI, Charlson Comorbidity Index; LAI, long-acting injectable; SD, standard deviation

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*Current affiliation is GlaxoSmithKline, King of Prussia, PA, USA

Abstract

Objective: Evaluate utilization of inpatient healthcare resources and associated costs after 12 months of treatment using long-acting injectable (LAI) antipsychotic medications among a large sample of Medicaid-insured patients categorized by different age groups.

Method: Adult patients with schizophrenia were identified from the Thomson Reuters MarketScan Research database (1/1/2006–12/31/2010) before initiation of treatment using LAI antipsychotic agents. Utilization of inpatient healthcare resources and associated direct medical costs were compared for 12-month baseline and 12-month follow-up periods.

Results: Among 3,094 Medicaid-insured patients with schizophrenia initiating treatment with LAIs, the mean number of all-cause hospitalizations and hospitalization days were reduced by 24% and 31% (p<0.0001) compared with baseline, respectively, with similar significant reductions among all age groups (18–30, 31–40, 41–50, and 51–60 years). During 12-month follow-up with LAIs, mean reductions in all-cause costs were $4,369 (18–30 years, p<0.0001), $3,681 (31–40 years, p<0.0001), $2,051 (41–50 years, p=0.1332), and $4,492 (51–60 years, p=0.0107). Subanalyses separating first-generation and second-generation medication groups resulted in mean reduction in all-cause costs of $3,561 and $3,645, respectively.

Conclusions: Results from this large cohort study provide naturalistic real-world evidence of the utility of LAIs in patients with schizophrenia and suggest that these agents may help to reduce the risk of relapse across all age groups (especially among younger patients). Given that relapse prevention is the ultimate goal of antipsychotic treatment, results from this large Medicaid patient population establish the value of LAIs for the management of schizophrenia.

Keywords: utilization of inpatient healthcare resources, inpatient costs, long-acting injectable agents, schizophrenia, mirror study, first-generation, second-generation, naturalistic study.

Introduction

Schizophrenia is a burden for patients and society. An estimated 1.1% of adults (2.6 million) in the USA are diagnosed with schizophrenia (one-year prevalence based on data from the 2010 census) with onset in early adulthood [1,2]. The overall cost of schizophrenia in the USA was estimated to be $22.7 billion in 2002 based on direct healthcare costs (drug acquisition; care in inpatient, outpatient, and long-term settings) for patients with schizophrenia, which was equivalent to $46.7 billion in 2012 (adjusted for inflation using the US Consumer Price Index Medical Care Category) [3].

Antipsychotic therapy remains the cornerstone of schizophrenia management. However, in the naturalistic real-world setting, adherence to antipsychotic agents given via the oral route is often low. Up to 74% of patients are non-adherent to prescribed oral antipsychotic agents [4].

Non-adherence to oral antipsychotics is associated with an increased risk of schizophrenia relapse as well as hospitalizations and associated costs [5–7]. Even short gaps in medication intake have been shown to increase the risk of relapse [8]. Early-intervention strategies are associated with successful treatment outcomes [9]. Discontinuation of antipsychotic therapy by patients with first-episode schizophrenia and schizoaffective disorder has been reported to carry the strongest correlation of risk factors for relapse [10], and is the biggest predictive factor of relapse after a first episode of psychosis [11].

Long-acting injectable (LAI) formulations of antipsychotic agents ('depot antipsychotics') were developed with the primary aim of improving treatment adherence in patients with schizophrenia. LAIs provide sustained drug coverage due to the drug-formulation benefits of long-acting dosage forms. In addition, patients treated with LAIs must visit the clinic every 1–6 weeks [12] where interactions with healthcare professionals can facilitate persistence and adherence to treatment, thereby reducing the risk of future relapses and hospitalizations [13].

Guidelines, such as those set by the American Psychiatric Association and the World Federation of Societies of Biological Psychiatry [14–19], support use of LAIs for patients with schizophrenia. However, in the naturalistic real-world setting, the effectiveness of LAIs compared with that of oral treatments is controversial. Controlled clinical studies have demonstrated that LAIs are at parity with oral treatments in terms of efficacy [20]. Specifically, a recent non-inferiority trial investigated three second-generation antipsychotic agents compared with an oral antipsychotic. The investigators found the oral antipsychotic to be non-inferior in both the 18-month intent-to-treat analysis and additional subanalyses [21]. Also, the Preventing Relapse Oral Antipsychotics Compared to Injectables Evaluating Efficacy (PROACTIVE) study showed that differences between treatment use of LAIs and oral second-generation agents in time to first relapse and hospitalization were not significant [22]. In addition, a meta-analysis of randomized trials revealed that second-generation LAIs were similar to oral medications in terms of relapse prevention, though first-generation LAIs were superior to oral medications [23]. That study stated that randomized controlled trials are less representative of real-world patients, and that studies in real-world patients are needed to make a true comparison. Given that treatment non-adherence is most evident in the naturalistic real-world setting, results from controlled clinical studies may not be the most important consideration in understanding the value of LAIs in the management of schizophrenia. Several systematic reviews and meta-analyses of studies of LAIs compared with oral treatments have indicated that study design and practice setting play important parts, especially with regard to medication adherence, and that these naturalistic and/or mirror studies favor LAIs over oral therapies in terms of effectiveness and adherence [24–26].

Naturalistic and/or mirror studies demonstrate the benefits of use of LAIs, including reduction of the risk of schizophrenia relapse, resource utilization, and cost. Use of LAIs has been shown to reduce the frequency of re-hospitalizations for patients with schizophrenia compared with oral formulations of the same treatment [27]. All-cause hospitalizations and schizophrenia-related hospitalizations were reduced by 41% and 56%, respectively, among patients who initiated therapy using LAIs in community mental health centers and Veterans Health Administration hospitals in the USA [28]. Utilization of inpatient healthcare resources and schizophrenia relapses declined significantly after patients initiated therapy using LAIs within the Veterans Health Administration [29], and the prevalence of hospitalization and related costs declined in commercially insured patients who initiated therapy using LAIs [12]. Two recent reports describe an improvement in patient outcomes based on fewer hospitalizations and relapses, and an associated reduction in healthcare costs for patients with schizophrenia who initiated therapy using LAI antipsychotic therapy [30,31]. Collectively, these data support use of LAIs as an important treatment option for patients with schizophrenia.

Medicaid is the largest payer of mental health services in the USA. It provides critical access to health and behavioral care for individuals with mental illnesses [32]. More than half of Medicaid beneficiaries are diagnosed with a mental illness, including schizophrenia and bipolar disorder [33], thereby underscoring the importance of understanding disease burden and best treatment options for patients reliant upon Medicaid.

Studies in commercially insured and Medicaid-insured patients suggest that LAIs are used more often among older patients, and also document the effectiveness of LAIs over a six-month timeframe [31]. However, data are limited on the effectiveness of LAIs among different age categories (especially younger patients) and the long-term benefits of LAIs observed over 12 months.

To advance our understanding of the effectiveness of LAIs in reducing hospitalizations among patients with schizophrenia in the USA, we evaluated utilization of inpatient healthcare resources and direct medical costs before and after initiation of use of LAIs among one of the largest available databases of Medicaid-insured patients with schizophrenia. The value of initiating LAIs for patients across different age categories was also assessed to evaluate treatment-related unmet need among younger patients.

Methods

Data source and study design

This was a retrospective study of Medicaid-insured patients who initiated therapy using LAIs. Patients (aged 18–60 years)

with at least one inpatient claim or two outpatient claims on separate dates with a primary or secondary diagnosis of schizophrenia (ICD-9-CM codes 295.0X, 295.1X, 295.2X, 295.3X, 295.5X, 295.6X, 295.8X, 295.9X) before initiation of treatment with LAI antipsychotic agents (index event) were identified for inclusion from the Thomson Reuters MarketScan Research database (1/1/2006–12/31/2010). It is a proprietary US research database providing fully integrated, de-identified patient data (inpatient, outpatient, drug, laboratory, health and productivity management; health-risk assessment; benefit design) from commercial, Medicare supplemental, and Medicaid populations. The index date was the date of initiation of LAIs. Patients were required to have 12 months of continuous enrolment in medical and pharmacy health plans before (baseline period) and after (follow-up period) initiation of LAI antipsychotic agents to ensure a balanced comparison in the two study periods. Utilization of inpatient healthcare resources and associated actual direct medical costs were compared for baseline and follow-up periods. The follow-up period for all endpoints was 12 months.

To assess the effectiveness of LAIs among different-aged patients with schizophrenia, patients from the full study group were divided into four age categories: 18–30, 31–40, 41–50, and 51–60 years.

Patient and treatment-related characteristics of interest

Baseline characteristics. Demographic/clinical characteristics and comorbidities assessed by the Charlson Comorbidity Index (CCI) [34], as well as utilization of healthcare resources and associated costs, were reported. Inpatient costs were acquired from the MarketScan Research database representing the payment amount recorded in the claims database.

Outcomes of interest over the follow-up period. The change in the number of all-cause hospitalizations, the change in the number of all-cause inpatient days, and direct inpatient costs were reported.

Statistical analyses

Descriptive statistics were used to evaluate differences for baseline and follow-up with p-values provided by chi-squared test, analysis of variance, and Student's t-tests (when appropriate). Statistical analyses were carried out using SAS* 9.2 software; p=0.05 was considered significant. Repeated measures in the study design provided additional statistical power to the overall analyses.

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*SAS Institute, Inc., Cary, NC, USA.

Results

Demographics and clinical characteristics

A total of 3,094 Medicaid-insured patients with schizophrenia who initiated treatment using LAIs were included in these analyses. Baseline demographic and clinical characteristics are summarized in Table 1. Overall, the mean age was 38.7 years. Most patients were male (55.0%) and were African–American (58.3%) or Caucasian (32.5%). The most common LAI antipsychotic therapies initiated (index drugs) were haloperidol and risperidone (41.8% and 38.6%, respectively; Table 1).

Comorbidities and concomitant medications

Most patients had a CCI score of 0 (total mean score of 0.8; Table 1), which suggested a low comorbidity burden and

Table 1. Demographics and clinical characteristics of patients at baseline.

Variable	Full study group (N=3,094)	
Continuous variables		
	Mean	SD
Age[a], years	38.7	12.0
Charlson Comorbidity Index	0.79	1.33
	N	%
Charlson Comorbidity Index group		
0	1,816	58.7
1–2	1,002	32.4
3–4	198	6.4
≥5	78	2.5
Categorical variables	N	%
Sex		
Male	1,702	55.0
Female	1,392	45.0
Race		
Caucasian	1,006	32.5
African–American	1,803	58.3
Hispanic	42	1.4
Other/unknown	243	7.9
Index drug, n (%)		
Fluphenazine	395	12.8
Haloperidol	1,294	41.8
Paliperidone	212	6.9
Risperidone	1,193	38.6

[a]Cutoff for patient age was >60 years.

Table 2. Descriptive analyses of comorbid conditions and concomitant medications during the 12-month baseline period.

Variable	Full study group N=3,094	
Condition, n (%)	n	%
Diabetes mellitus	641	20.7
Chronic pulmonary disease	612	19.8
Cardiovascular disease	205	6.6
Liver disease	123	4.0
Cerebrovascular disease	76	2.5
Dementia	52	1.7
Peptic ulcer disease	71	2.3
Renal disease	59	1.9
Cancer	33	1.1
Rheumatic disease	21	0.7
Medication type, n (%)		
Antidepressant	1,660	53.7
Anticonvulsant	1,550	50.1
Analgesic/antipyretic	1,364	44.1
Anxiolytic/sedative/hypnotic	715	23.1
Antihyperlipidemic	546	17.6
Antimanic	247	8.0
Hypotensive agent	161	5.2

low risk of mortality [34]. As expected, younger patients had lower mean CCI scores: 0.4 for patients aged 18–30 years, 0.7 for 31–40 years, 0.9 for 41–50 years, and 1.3 for 51–60 years. Comorbidities were assessed using the CCI during the 12-month baseline period and are summarized in Table 2. The most common comorbid conditions were diabetes mellitus (20.7%) and chronic pulmonary disease (19.8%). Concomitant medications taken during the 12-month baseline period are also summarized in Table 2.

Utilization of healthcare resources

Compared with baseline, initiation of therapy using LAI antipsychotic agents resulted in significant reductions in utilization of all-cause inpatient resources during 12-month follow-up regardless of age.

For the full study group, the mean number of all-cause hospitalizations before and after initiation of therapy using LAI antipsychotic agents was reduced significantly by 24.2%, from 1.28 (standard deviation [SD] 2.19) to 0.97 (SD 1.97); p<0.0001 (Figure 1a). Specific age-group analyses of the full study group also showed that the mean number of all-cause hospitalizations before and after initiation of therapy using
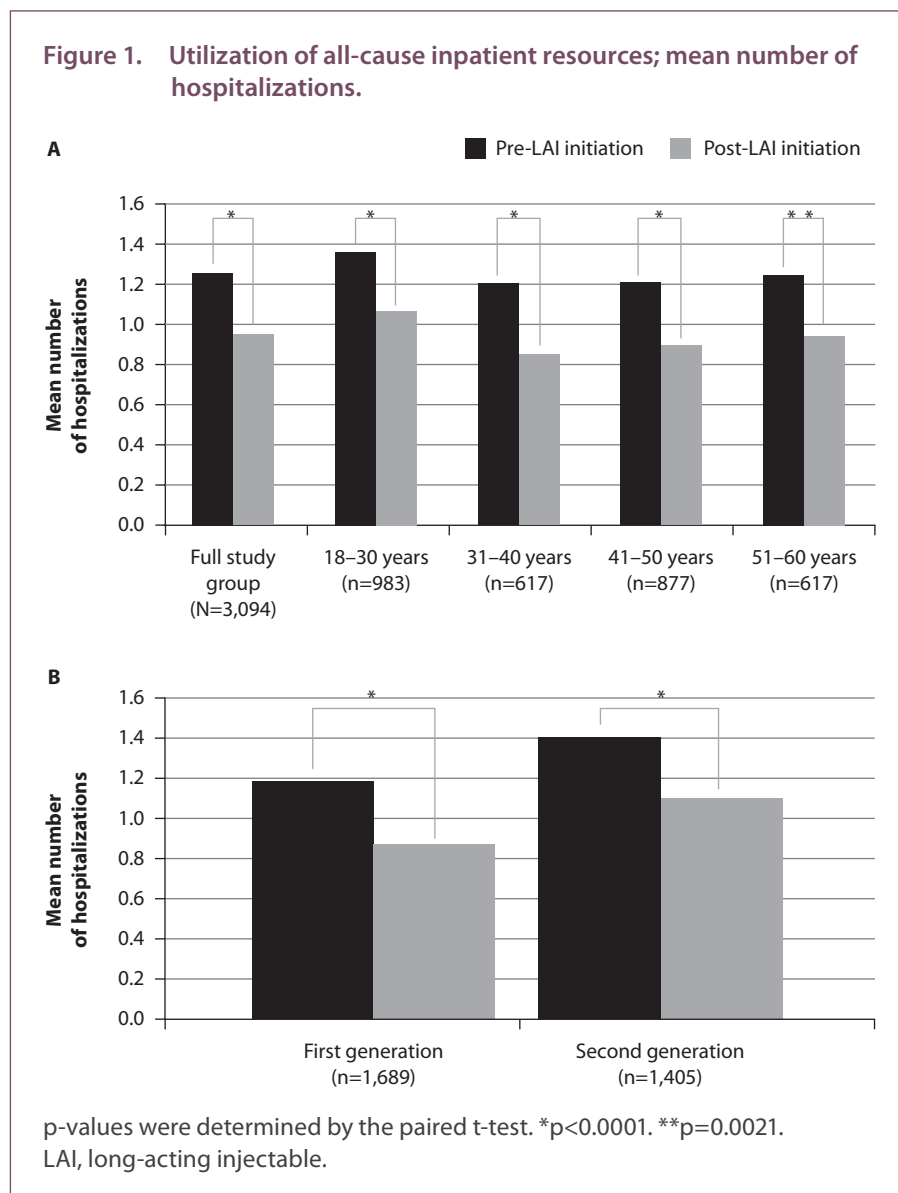
LAI antipsychotic agents was reduced significantly. The mean number of hospitalizations was reduced by 21.7%, from 1.38 (SD 2.13) to 1.08 (SD 2.26); p<0.0001 (18–30 years); 29.5%, from 1.22 (SD 1.91) to 0.86 (SD 1.74); p<0.0001 (31–40 years); 26.0%, from 1.23 (SD 2.24) to 0.91 (SD 1.93); p<0.0001 (41–50 years); and 23.8%, from 1.26 (SD 2.45) to 0.96 (SD 1.72); p=0.0021 (51–60 years). Subanalyses separating first-generation and second-generation medication groups showed similar reductions for the overall age group (Figure 1b) and individual age groups (data not shown). In subanalyses of data for mental health-related hospitalizations, the mean number of hospitalizations was also reduced significantly by 24.2%, from 1.24 (SD 2.07) to 0.94 (SD 1.93).

The mean number of hospitalization days before and after initiation of therapy using LAI antipsychotic agents was reduced significantly by 31.0%, from 11.52 (SD 20.33) to 7.95 (SD 19.72) days; p<0.0001 (Figure 2a). The mean number of hospitalization days was also reduced by 32.4%, from 13.10 (SD 23.37) to 8.85 (SD 22.16); p<0.0001 (18–30 years); by 38.9%, from 10.36 (SD 18.00) to 6.33 (SD 14.15); p<0.0001 (31–40 years); by 25.5%, from 10.34 (SD 18.43) to 7.70 (SD 20.08); p=0.0001 (41–50 years); and by 28.4%, from 11.85 (SD 19.73) to 8.48 (SD 19.79); p=0.0003 (51–60 years). Subanalyses separating first-generation and second-generation medication groups showed similar reductions for the overall age group (Figure 2b) and individual age groups (data not shown). In subanalyses of the data for mental health-related hospitalizations, the total length of stay was reduced by 31.6% from 11.35 (SD 20.07) to 7.76 (SD 19.40). As for full-study data, age-group data had similar reductions.

Annual healthcare costs

As a result of the decline in the mean number of hospitalizations and hospitalization days for inpatients, hospital costs were collectively significantly lower during 12-month follow-up compared with baseline for most ages, with the exception of patients aged 41–50 years (Figure 3).

Mean reduction in all-cause costs for the full study group was $3,599 (p<0.0001) during 12-month follow-up compared with baseline. For specific age groups, mean reductions in all-cause costs were $4,369 (18–30 years; p<0.0001), $3,681 (31–40 years; p<0.0001), $2,051 (41–50 years; p=0.1332), and $4,492 (51–60 years; p=0.0107) during 12-month follow-up compared with baseline. Annual healthcare costs were also assessed in the subanalyses separating first-generation and second-generation medication groups, and demonstrated similar results (Figure 3b); mean reduction in all-cause costs for the first-generation medication group was $3,561, and was $3,645 for the second-generation medication group. In subanalyses focusing on mental health-related hospitalizations, the mean reduction in total costs was $3,587 (p<0.0001), and for the specific age groups was $4,270 (18–30 years; p<0.0001), $3,846 (31–40 years;
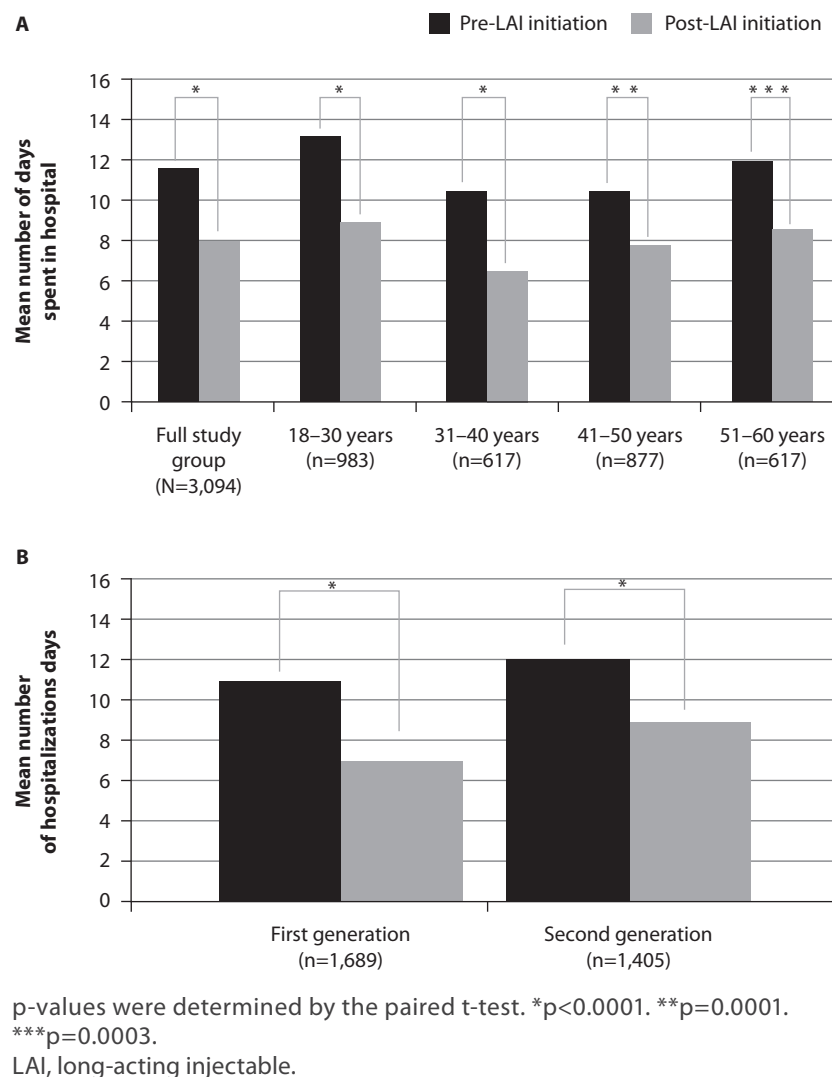
Figure 1. Utilization of all-cause inpatient resources; mean number of hospitalizations.

p-values were determined by the paired t-test. *p<0.0001. **p=0.0021.
LAI, long-acting injectable.

p<0.0001), $2,154 (41–50 years; p=0.0878), and $4,275 (51–60 years; p=0.0090) during 12-month follow-up compared with baseline.

Discussion

Observational studies have provided naturalistic real-world evidence that therapy using LAI antipsychotic agents can improve management of schizophrenia. Such study designs are more representative of the population of schizophrenia patients. They also provide information on treatment patterns and resource utilization observed in these patients in routine clinical practice. This retrospective mirror study involving >3,000 Medicaid-insured patients with schizophrenia in the USA is one of the largest cohorts studied to evaluate outcomes associated with LAIs over a 12-month follow-up period. Results showed that compared with baseline, during the 12-month follow-up after initiation of treatment using LAI antipsychotic agents,

a reduction in healthcare utilization and associated annual healthcare costs was clearly evident. Utilization of all-cause inpatient healthcare and costs for the full study group were reduced significantly during the 12-month follow-up after initiation of treatment using LAI antipsychotic agents compared with baseline. Specific age-group analyses of the full study population indicate that LAIs are as effective in younger patient groups as they are for older patients.

Our findings on the reduction in the utilization of healthcare resources and costs are consistent with previous analyses of US claims documenting reductions among patients with schizophrenia who initiated treatment of LAIs in the naturalistic real-world setting [12,30,31]. While consistent with the overall reduction in utilization of healthcare resources, the magnitude of cost savings was higher in earlier studies, possibly due to smaller cohorts and shorter time horizons [12] or inclusion of commercial populations [31]. Differences in cost savings between the present study and those reported

Figure 2. Utilization of all-cause inpatient resources; mean number of hospitalization days.

p-values were determined by the paired t-test. *p<0.0001. **p=0.0001. ***p=0.0003.
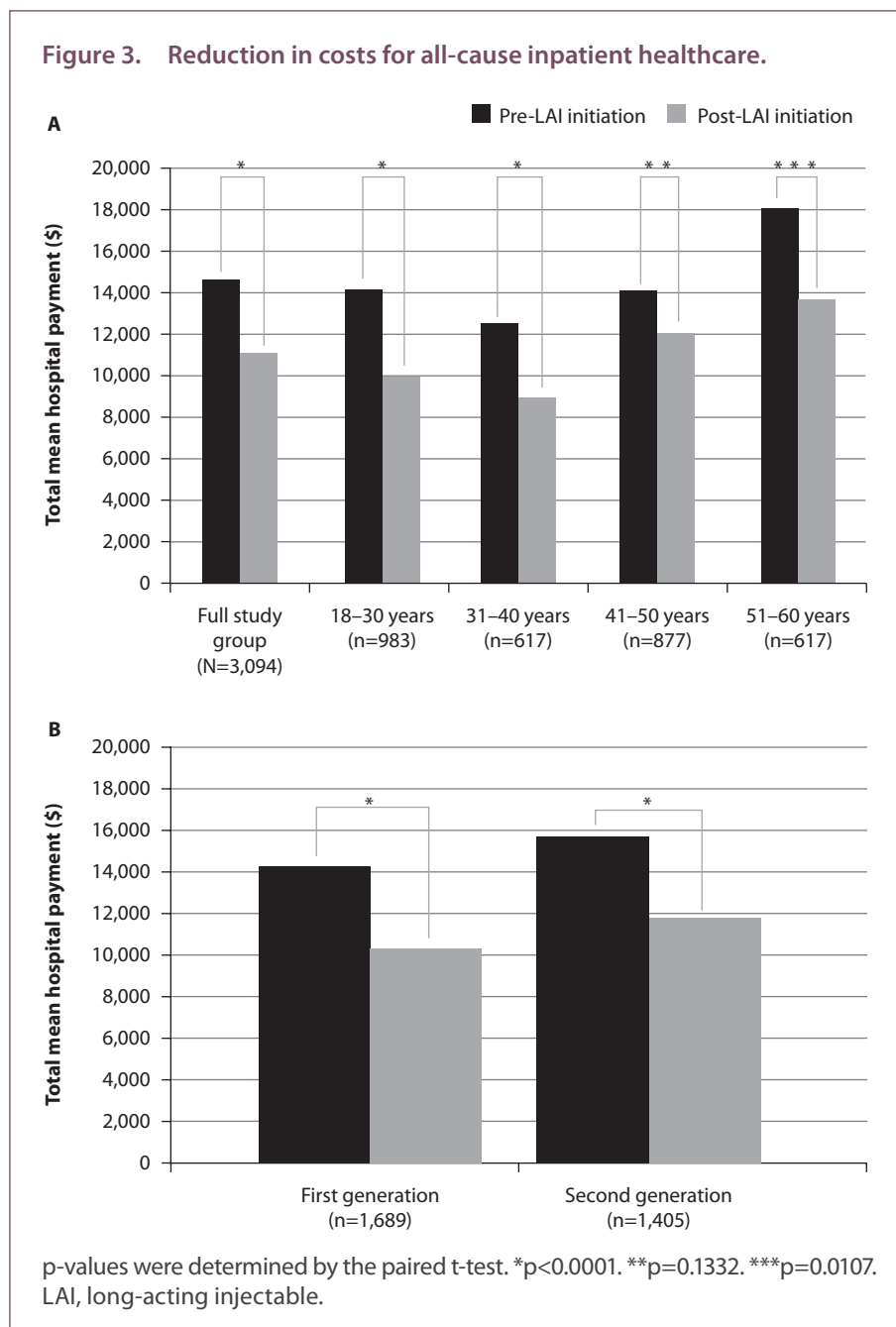LAI, long-acting injectable.

by Bera and colleagues [30] in a similar study of Medicaid-insured patients with schizophrenia may be due to the variable follow-up period in the Bera study after initiation of LAIs, which ended when the patient was disenroled from Medicaid coverage, or at the end of the study period, whichever came first. For patients who were not taking antipsychotic medications at baseline (n=821; Figure 1), reductions in resource utilization and healthcare costs may be because patients are receiving LAIs and because of initiating treatment with antipsychotic agents.

The comprehensive body of evidence from naturalistic and mirror studies should be considered in addition to controlled clinical studies that indicate that LAIs are at parity in terms of effectiveness compared with oral treatments [20]. Non-adherence to treatment is more likely in the naturalistic real-world setting than in clinical trials. Hence, it may be more appropriate to consider the results from these naturalistic and mirror studies instead of extrapolating findings on adherence and effectiveness from clinical studies to the naturalistic real-world setting. Evidence suggests that patients in the real-world setting are less likely to engage with physicians and health-service providers [24,25]. No clinical studies have shown that oral therapies are better than LAIs in terms of effectiveness, suggesting that LAIs may be considered for use based on the preferences of physicians, patients, or caregivers.

Research design is different in randomized controlled trials compared with naturalistic and mirror studies. While both are valid approaches, it can be argued that naturalistic and mirror studies offer more appropriate conditions for evaluation of the benefits of LAIs. However, conducting such studies presents a unique set of methodological challenges because, in the real world, LAIs are used among patients with more severe schizophrenia. Multivariable analyses and statistical matching

Figure 3.   Reduction in costs for all-cause inpatient healthcare.

p-values were determined by the paired t-test. *p<0.0001. **p=0.1332. ***p=0.0107. LAI, long-acting injectable.

methods may not be sufficient to account for the inherent differences in clinical factors and disease severity between patients initiating treatment with LAIs or oral therapies. Hence, mirror-study designs that evaluate the reduction in rates and costs of psychiatric hospitalization before and after initiation of treatment using LAIs have high utility for understanding the value of LAIs in the naturalistic real-world setting.

In our analyses, younger patients had low adherence to oral agents during baseline. LAIs have been associated with the same favorable reduction in utilization of inpatient resources and costs across all age groups. Hence, these data provide naturalistic real-world evidence suggesting that prescribers

may consider use of LAIs even in younger patients with schizophrenia. In such patients, prevention may have the greatest long-term impact in terms of patient outcomes and reduced utilization of healthcare resources.

Limitations

The baseline compared with the follow-up study design lacks a comparable control patient population and regression to the mean. The effects of regression to the mean have been explored via age-category analyses, which show consistency in the finding that reduction in resource use and cost is similar across the four age groups. In addition, the fact that the baseline period may have contained a possible 'index'

hospitalization may have confounded the results. Furthermore, adherence was not assessed in the follow-up period, and so there was no control for adherence in the study. Some patients may have not continued administration of LAIs in the follow-up period, which may have affected the results. However, limiting the patient population to only those with high adherence would be too restrictive on the analyses and would enrich the sample with a specific population.

The LAI antipsychotic agents evaluated in this study included typical and atypical types, and the efficacy, safety, and outcomes may differ by class. Further study is needed to evaluate the outcomes of patients with schizophrenia treated with a particular LAI antipsychotic agent.

The MarketScan Medicaid database comprises claims submitted by healthcare providers. Such claims are subject to possible coding errors, coding for the purpose of exclusion rather than the actual disease, and undercoding (either by the healthcare provider or due to the limitations imposed by the database). Also, obtaining complete medical histories based on data from Medicaid claims is difficult. Changes in the status of Medicaid eligibility, disenrollment, and the likelihood of multiple insurance plans for some individuals may have confounded the results of this study. In addition, the MarketScan Medicaid database is based on a large convenience sample. The sample is not random, so it may contain biases or fail to generalize well to other populations, particularly those who have alternate healthcare coverage, such as commercial insurance.

Conclusions

This is one of the largest mirror studies of Medicaid-insured patients with schizophrenia. It showed a significant reduction in all-cause hospitalizations and overall healthcare costs during the 12-month follow-up after initiation of treatment with LAI antipsychotic medications. Age-specific analyses also suggest that use of LAIs in younger patients with schizophrenia may be beneficial for the prevention of relapse and for reducing costs. These results provide naturalistic real-world evidence of the utility of LAI antipsychotic medications in the treatment of schizophrenia.

Contributions

Drs. Gutierrez, Baker, Offord, Lin, and Karson contributed to the conception and design of this study. Contributions to statistical analyses were made by Mr. Kamat and Dr. Lin; supervisory contributions were made by Mr. Kamat and Dr. Offord; and contributions related to administrative, technical or material support were made by Dr. Lin. All authors contributed to the analysis and interpretation of the data as well as the writing, review, and revision of the manuscript.

Potential conflicts of interest

Funding declaration

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