Use of secondary real-world data from the United States to fulfill European Medicines Agency post-authorisation requirement

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Abstract

- **Objectives:** The European Medicines Agency (EMA) may require a post-authorisation safety study (PASS), and in some cases secondary real-world data (RWD) may be appropriate for use. It can be challenging to obtain secondary data in Europe; however, there is precedent on using secondary RWD from the United States (US) to fulfil PASS requirements. Our objective is to provide an example of using such data to fulfil an EMA PASS requirement.
- **Methods:** A comparative, retrospective cohort study in commercially- and Medicaid-insured patients from the MarketScan® databases was conducted. Patients newly-prescribed lurasidone for schizophrenia (lurasidone cohort) were compared to patients newly-prescribed other atypical antipsychotics (OAAs; OAA cohort) for the treatment of schizophrenia. Patients from the lurasidone cohort were matched to the OAA cohort by propensity scores on age, gender, Charlson comorbidity index, payer type, number of pre-index hospitalizations, and chlorpromazine dose equivalence. The primary outcomes included important identified and potential risks of lurasidone and OAAs.
- **Results:** A total of 1,440 patients in the lurasidone cohort were matched to an OAA patient: mean (standard deviation [SD]) age (lurasidone: 39.8 [15.37]; OAA: 41.9 [18.65]), males (lurasidone: 56.0%; OAA: 48.6%), and Medicaid-insured (lurasidone: 77.6%; OAA: 81.4%) were similar. The mean (SD) daily dose of lurasidone at index was 52.9 mg (30.64) (chlorpromazine equivalence 330.7 mg [191.50]), which was greater than any other OAA (median: 227.2 mg; range: 126.7-310.8 mg). Incidence rates of important identified and potential risks were not significantly different, except drug interactions (lurasidone: 0.038, OAA: 0.059; P=0.031) and third-trimester pregnancy exposure (lurasidone: 0.030, OAA: 0.005; P=0.005), respectively.
- **Conclusion:** This study adds to the precedent of using secondary RWD from the US to fulfil an EMA PASS requirement. Among insured patients in the US diagnosed with schizophrenia, incidence rates for important identified and potential risks were similar between patients initiating lurasidone and OAAs.

Introduction

- The European Medicines Agency (EMA) may require a post-authorisation safety study (PASS), and in some cases secondary real-world data (RWD) may be appropriate for use
- It can be challenging to obtain secondary data in Europe; however, there is precedent on using secondary RWD from the United States (US) to fulfill PASS requirements
- This study focused on the EMA PASS requirement for lurasidone, which involved evaluating the safety profile of lurasidone for the treatment of schizophrenia in a real-world setting
- Lurasidone is a second-generation oral atypical antipsychotic (OAA) and was approved for use by the EMA for the treatment of schizophrenia in March 2014
- The side effects associated with lurasidone treatment are similar to that of other second-generation atypical antipsychotics
- In this study, the original marketing authorisation holder (MAH) intended to use data from a prospective study in the United Kingdom to fulfill the EMA PASS requirement; however, the required sample size would have taken several years to recruit
- Considering the challenges with the prospective study, the MAH proposed a new submission for the PASS that utilized administrative medical and pharmacy claims data from the US to meet the EMA requirements

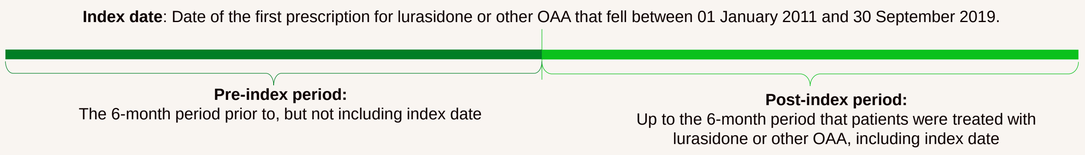
Objectives

- Our objective is to provide an example of using US administrative claims data to fulfill an EMA PASS requirement
- The primary objective of the PASS was to compare the incidence of important identified risks and important potential risks in patients treated with lurasidone to patients treated with other second generation OAAs

Methods

- A comparative, retrospective cohort study was conducted
- Data from commercially- and Medicaid-insured patients in the MarketScan® administrative claims database was analysed
- Patients of all ages were included if they had a schizophrenia diagnosis between 01 January 2010 and 30 September 2019
- The lurasidone cohort included those patients with their first prescription for lurasidone between 01 January 2011 and 30 September 2019
- The OAA cohort included those patients with their first prescription for an OAA between 01 January 2011 and 30 September 2019
- OAAs included:
  - Aripiprazole
  - Olanzapine
  - Paliperidone
  - Quetiapine
  - Risperidone
  - Ziprasidone
- The full study time period spanned from 01 January 2010 through 30 September 2019

Figure 1. Study time periods



- Additionally, each cohort required the following inclusion/exclusion criteria:
  - Diagnosis for schizophrenia in the study time period
  - Continuous medical and pharmacy health insurance coverage in the pre-index period
  - No pharmacy or medical claim for lurasidone or any other atypical or typical antipsychotic medication during the pre-index period
  - No pharmacy or medical claim for any other atypical or typical antipsychotic medication on the index date
  - No diagnosis for bi-polar disorder during the study period
- Patients in the lurasidone cohort were compared to patients in the OAA cohort for the treatment of schizophrenia by matching on propensity scores based on age, gender, Charlson comorbidity index (CCI), payer type, number of pre-index hospitalisations, and chlorpromazine dose equivalence
- Study outcomes included important identified and potential risks during the post-index period
- Important identified risks included:
  - Drug interactions with strong cytochrome P 450 3A4 inhibitors or P 450 3A4 inducers
  - Extrapyramidal symptoms: dystonia, akathisia, parkinsonism, and tardive dyskinesia
  - Neuroleptic malignant syndrome
- Important potential risks included:
  - Agranulocytosis
  - Metabolic profile: hyperglycaemia, weight increase, dyslipidaemia
  - Rhabdomyolysis
  - Seizures
  - Suicidality
  - Third trimester exposure during pregnancy
  - Use with severe or moderate renal impairment
  - Use with severe or moderate hepatic impairment
- Descriptive summary statistics were calculated for continuous variables: mean, median, standard deviation (SD), minimum, and maximum
- Counts and percentages were calculated for categorical variables
- For the important identified risks and important potential risks, the incidence rate and 95% CI were evaluated using Poisson regression, which modeled the occurrence of the outcome on cohort group, with the natural log of the person time at risk included as an offset
- Differences in demographic and pre-index clinical characteristics were examined between the two cohorts using standardised differences (StDiff); differences were considered meaningful if the absolute StDiff was >0.20

Results

- Among 497,408 patients with schizophrenia, a total of 1,447 patients in the lurasidone cohort and 34,512 patients in the OAA cohort met all eligibility criteria **(Figure 2)**
- A total of 1,440 of the 1,447 (99.5%) patients in the lurasidone cohort were successfully matched to an OAA cohort patient **(Figure 2)**
- Over one-third of the OAA cohort was comprised of patients receiving risperidone (37.6%) followed by quetiapine (21.9%), olanzapine (16.6%), aripiprazole (16.5%), ziprasidone (4.0%), and paliperidone (3.4%) **(Figure 3)**

Figure 2. Attrition in lurasidone and OAA cohorts

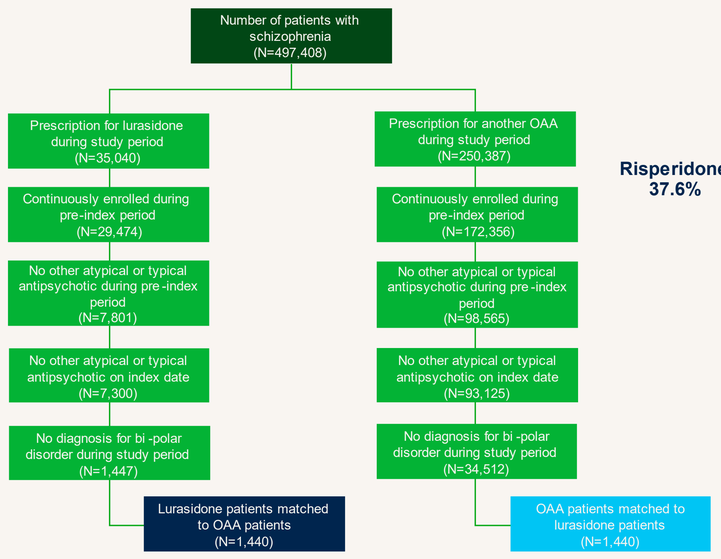
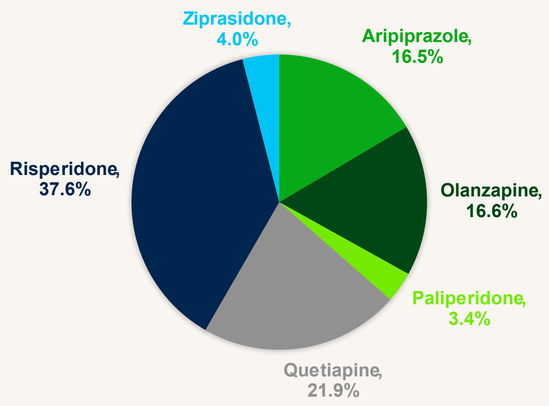


Figure 3. Distribution of OAAs (N=34,512)



Results (continued)

- Comparison of lurasidone and OAA cohorts before matching:
  - Age, proportion of males, and CCI scores were similar between lurasidone and OAA patients prior to match (absolute StDiff = 0.0913, 0.0751, and 0.1578 respectively) **(Table 1)**
  - The lurasidone cohort had a higher proportion of Medicaid patients (77.7% vs 65.6%), lower number of pre-index hospitalizations (0.24 vs 0.44), and higher chlorpromazine equivalence dose at index (330.7 vs 215.0); all absolute StDiff > 0.20 **(Table 1)**
  - Mean (SD) daily dose of lurasidone at index was 52.9 mg (30.64) (chlorpromazine equivalence 330.7 mg [191.50]), which was greater than any other OAA (median: 227.2 mg; range: 126.7-310.8 mg) **(Figure 4)**
- Comparisons of lurasidone and OAA cohorts after matching:
  - All absolute StDiff were < 0.20 except for mean CCI (absolute std diff = 0.3704) **(Table 1)**
  - Mean (SD) age (lurasidone: 39.8 [15.37]; OAA: 41.9 [18.65]), males (lurasidone: 56.0%; OAA: 48.6%), and Medicaid-insured (lurasidone: 77.6%; OAA: 81.4%) were similar **(Table 1)**

Table 1. Demographic and clinical characteristics in the unmatched and matched cohorts

	Unmatched			Matched		
Characteristic	**Lurasidone cohort (N=1,447)**	**OAA cohort (N=34,512)**	**StDiff**	**Lurasidone cohort (N=1,440)**	**OAA cohort (N=1,440)**	**StDiff**
Age, years, mean (SD)	39.9 (15.396)	41.5 (19.742)	-0.0913	39.8 (15.373)	41.9 (18.646)	-0.1241
Male, n (%)	809 (55.9)	20,575 (59.6)	-0.0751	806 (56.0)	700 (48.6)	0.1478
Payer type, n (%)			-0.2727			0.0930
Commercial	322 (22.3)	11,882 (34.4)		322 (22.4)	268 (18.6)	
Medicaid	1,125 (77.7)	22,630 (65.6)		1,118 (77.6)	1,172 (81.4)	
Charlson comorbidity index score, mean (SD)	0.60 (1.174)	0.82 (1.591)	-0.1578	0.60 (1.168)	1.15 (1.726)	-0.3704
Number of hospitalizations in the pre-index period, mean (SD)	0.24 (0.579)	0.44 (0.780)	-0.2885	0.24 (0.581)	0.33 (0.608)	-0.1472
Chlorpromazine equivalence dose at index						
n	1,440	33,623		1,440	1,440	
mean (SD)	330.7 (191.50)	215.0 (186.93)	0.6114	330.7 (191.50)	339.3 (238.39)	-0.0396
median	250.0	150.0		250.0	300.0	
range	8.3 - 1,000.0	0.8 - 1,200.0		8.3 - 1,000.0	12.5 - 1,200.0	

Figure 4. Prescribed treatment dosing for oral atypical antipsychotics in the unmatched cohorts

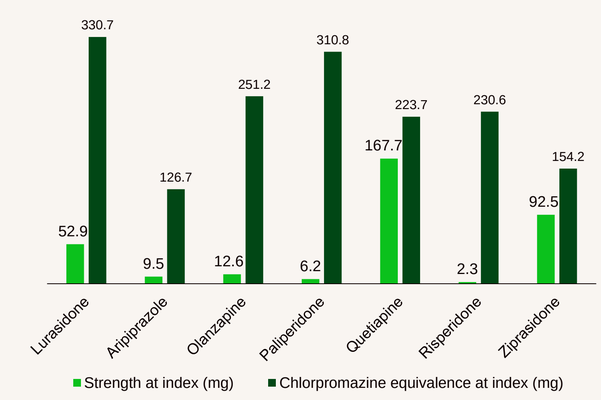


Figure 5. Adjusted incidence rates of important identified risks

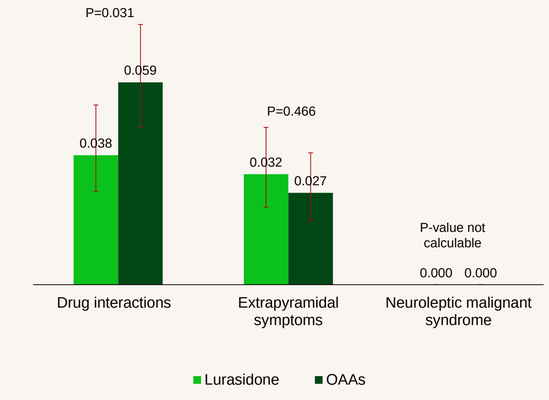
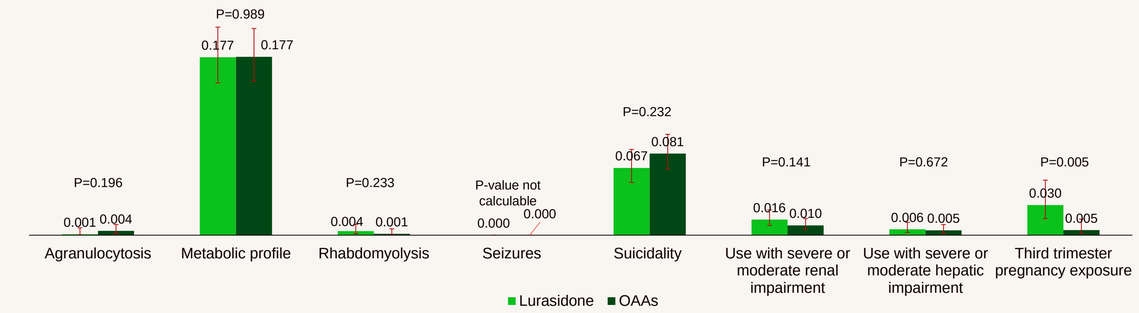


Figure 6. Adjusted incidence rate of important potential risks



Results (continued)

- Among important identified risks **(Figure 5)**:
  - Drug interactions was significantly more common in the OAA cohort (lurasidone: 0.038, OAA: 0.059; P=0.031)
  - Extrapyramidal symptoms was not significantly different (lurasidone: 0.032, OAA: 0.027; P=0.466)
  - There were no events of neuroleptic malignant syndrome in either cohort
- Among important potential risks **(Figure 6)**:
  - The adjusted rate of third-trimester pregnancy exposure was significantly more common in the lurasidone cohort (lurasidone: 0.030, OAA: 0.005; P=0.005)
  - Metabolic profile was the most common for both cohorts (lurasidone: 0.177, OAA: 0.177; P=0.989) followed by suicidality (lurasidone: 0.067, OAA: 0.081; P=0.232)
  - All other events were associated with very low adjusted rates

Conclusions

- This study further adds to the precedent of using secondary RWD (i.e., administrative claims) from the US to fulfill an EMA PASS
- Among insured patients in the US diagnosed with schizophrenia, incidence rates for important identified and potential risks were similar between patients initiating lurasidone and OAAs

Notes:

1. Abbreviations: CCI, Charlson Comorbidity Index, CI, confidence interval; EMA, European Medicines Agency; MAH, marketing authorisation holder; OAA, other atypical antipsychotic; PASS, post authorization safety study; SD, standard deviation; StDiff, standardized difference; US, United States
2. Data sources: MarketScan® Commercial Claims and Encounters and Medicaid databases

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