

Disease relapse and adverse events during the combination use of clozapine and long-acting injectable antipsychotics and during the clozapine monotherapy



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Background

Clozapine is often considered the most effective antipsychotic, especially for people with treatment-resistant schizophrenia. However, approximately two thirds of the individuals fail to respond to clozapine. Long-acting injectables antipsychotics (LAIA) have been developed to improve patients' adherence and it has been proven that the use of LAIAs is associated with a reduced risk of disease relapse and hospitalizations, without an increased risk of adverse effects. Therefore, adding LAIAs to clozapine could be an alternative in clinical practice, particularly for people with clozapine-resistant schizophrenia. However, few studies have investigated the effectiveness and safety of the combination use of clozapine and LAIA.

Methods

- Database:** Clinical Data Analysis and Reporting System (CDARS) in Hong Kong
- Patients:** People diagnosed with schizophrenia (ICD-9: 295) between 1993-2019 and prescribed LAIAs and clozapine during 2004-2019.
- Exposures:** The combination use of clozapine and long-acting injectable antipsychotics (CLO+LAIA) versus clozapine monotherapy (CLO-mono)
- Primary outcomes:** Hospitalization for schizophrenia
- Secondary outcomes:** Extrapyramidal symptoms
- Study design and statistical analysis:** This is a population-based study. Rate of hospitalizations for schizophrenia and extrapyramidal symptoms during the full treatment periods of CLO+LAIA and CLO-mono were reported. The rate beyond the first 90 days of each treatment was further assessed to reduce potential indication bias and to measure the rate of outcomes during subsequent treatment periods.

Results

- Of the 70,396 individuals with schizophrenia (mean [SD] age, 44.2 [15.8] years; male, 47.2%), 5704 (mean [SD] age, 35.9 [12.1] years; male, 49.0%) were prescribed clozapine and 2745 (mean [SD] age, 36.5 [11.4] years; male, 49.0%) were prescribed both clozapine and LAIA during the observation period. The rate of hospitalizations for schizophrenia and extrapyramidal symptoms was 45.90 and 12.05 per 100 person-years during the CLO+LAIA treatment period, while the rate was 30.27 and 5.98 per 100 person-years during the CLO-mono treatment period, respectively. After excluding the first 90 days of each treatment period. The rate of hospitalizations for schizophrenia and extrapyramidal symptoms was 33.34 and 3.66 per 100 person-years during the CLO+LAIA treatment period, while the rate was 27.03 and 4.18 per 100 person-years during the CLO-mono treatment period, respectively.

Objectives

To assess the rate of hospitalizations for schizophrenia and extrapyramidal symptoms during the combination use of clozapine and long-acting injectable antipsychotics (CLO+LAIA) and during the clozapine monotherapy (CLO-mono) among people with schizophrenia.

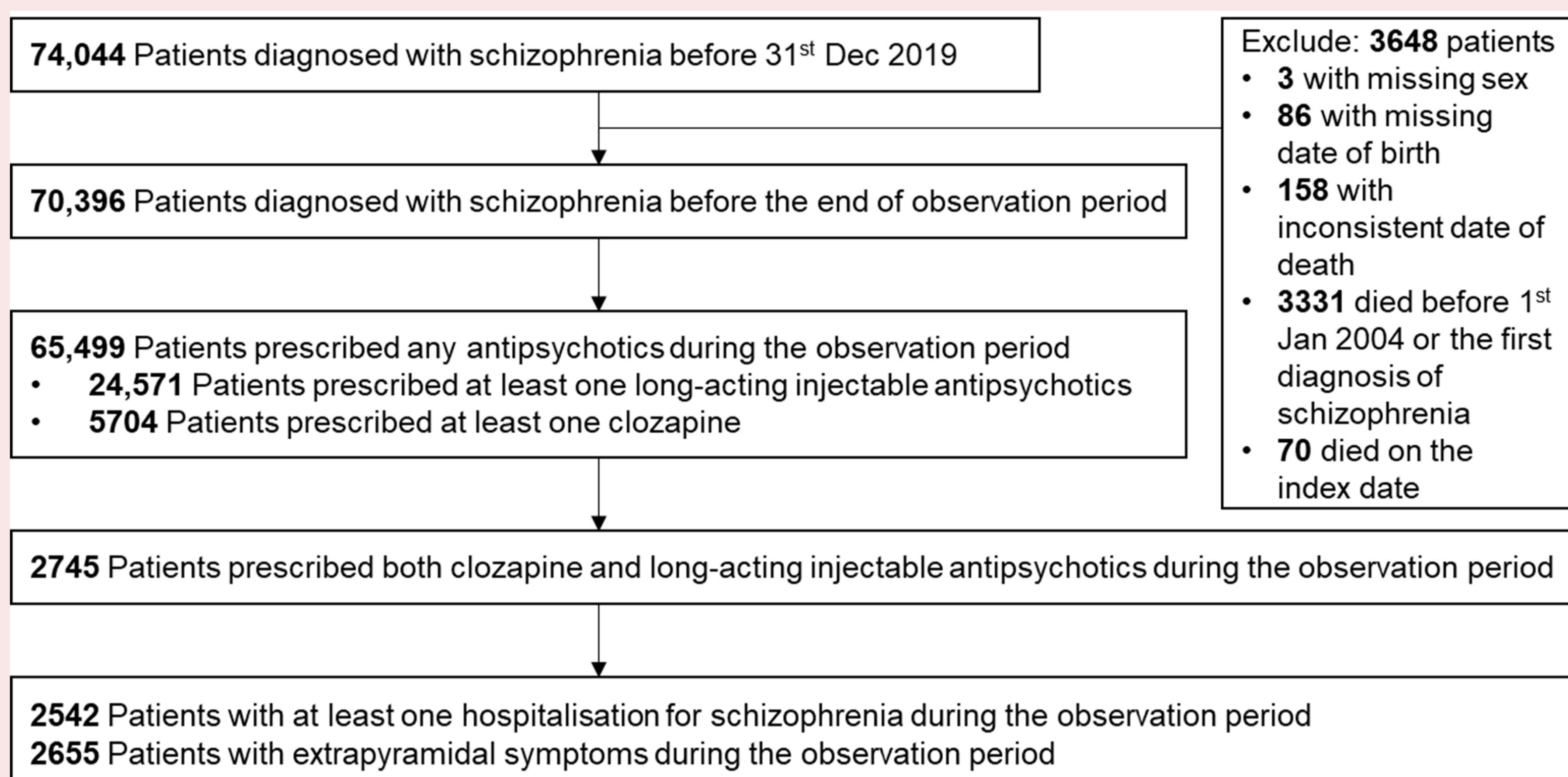


Figure 1. Patient identification

Table 1. Patient characteristics

Characteristics	Initial cohort of people with schizophrenia (N=70,396)	People prescribed LAIAs (N=24,571)	People prescribed clozapine (N=5704)	People prescribed both clozapine and LAIAs (N=2745)	Patients with at least one of the following outcome event No. (%) (N=2745)	
					Hospitalizations for schizophrenia (n=2542)	Extrapyramidal symptoms (n=2655)
Sex						
Male	33,196 (47.2)	12,750 (51.9)	2793 (49.0)	1346 (49.0)	1231 (48.4)	1297 (48.9)
Age, mean (SD), y						
At the 1 st schizophrenia diagnosis	42.0 (15.7)	39.2 (12.7)	32.8 (11.7)	33.0 (11.0)	32.9 (10.9)	32.9 (10.9)
At cohort entry	44.2 (15.8)	41.9 (12.8)	35.9 (12.1)	36.5 (11.4)	36.3 (11.4)	36.4 (11.3)
At time of event	NA	NA	NA	NA	43.4 (12.6)	40.0 (12.4)
Death						
Number of patients	12,493 (17.8)	3830 (15.6)	593 (10.4)	257 (9.4)	238 (9.4)	250 (9.4)
Age of death, mean (SD), y	66.1 (16.7)	59.6 (14.9)	54.9 (13.0)	54.7 (11.8)	54.8 (11.7)	54.5 (11.9)

Table 2. Rate of outcome events

Outcome events	Clozapine + LAIA			Clozapine monotherapy		
	No of event	Person-years	Incidence/100 person-years	No of event	Person-years	Incidence/100 person-years
Full treatment period						
Hospitalization for schizophrenia	362	788.75	45.90	2592	8562.7	30.27
Extrapyramidal symptoms	121	1004.4	12.05	605	10109.38	5.98
Subsequent treatment period*						
Hospitalization for schizophrenia	219	656.92	33.34	2139	7913.57	27.03
Extrapyramidal symptoms	28	765.77	3.66	373	8929.95	4.18

*Beyond the first 90 days in each treatment period. #Adjusted for age and season

Conclusions

The CLO+LAIA treatment appears not to reduce the risk of disease relapse and adverse events than CLO-mono treatments. However, further research is needed to make a detailed comparison between CLO+LAIA and CLO-mono treatments.