Electronic Supplementary Material

Article Title: A Retrospective Cohort Study of Acute Kidney Injury Risk Associated with Antipsychotics

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Appendices

eAppendix 1 Diagnoses Codes

Supplementary eTable 1 Diagnoses codes used in the study to identify patients and target outcomes

Diagnoses	ICD-9 Codes
Schizophrenia	295.X
Bipolar disorder	296.4-296.8
Acute kidney injury[a]	584.5-584.9
Hypotension[a]	458.X
Acute urinary retention[a]	788.2
Neuroleptic malignant syndrome/ rhabdomyolysis[a]	333.92, 728.88
Pneumonia[a]	480.X-486.X, 770.0

a: Converted from ICD-10 codes in order to be compliant with existing studies.

Reference: http://www.icd10data.com/Convert

eAppendix 2 Covariates

Supplementary eTable 2 Covariates used in regressions

Demographic
Age categories (10 year intervals)
Sex
Medicare Advantage vs. Commercial
Diagnoses in prior 6 months
Prior occurrence of target events
Infectious diseases
Neoplasms
Endocrine disorders
Diabetes
Obesity
Diseases of the blood and blood-forming organs
Dementias
Alcohol-induced mental disorders
Drug-induced mental disorders
Transient mental disorders due to conditions classified elsewhere
Persistent mental disorders due to conditions classified elsewhere
Simple type schizophrenia
Paranoid type schizophrenia
Schizophreniform disorder
Schizoaffective disorder
Other specified types of schizophrenia
Major depressive disorder single episode
Bipolar I disorder-single manic episode, Manic disorder recurrent episode
Bipolar I disorder, most recent episode (or current) manic
Bipolar I disorder, most recent episode (or current) depressed
Bipolar I disorder, most recent episode (or current) mixed
Bipolar I disorder, most recent episode (or current) unspecified
Other and unspecified bipolar disorders
Other and unspecified episodic mood disorder
Delusional disorders
Other nonorganic psychoses
Anxiety states
Obsessive-compulsive disorders
Dysthymic disorder
Neurasthenia, Depersonalization disorder, Hypochondriasis, Somatoform disorders, Unspecified nonpsychotic mental disorder
Personality disorders
Alcohol dependence syndrome
Drug dependence
Other nonpsychotic mental disorders
Diseases of the nervous system and sense organs
Acute myocardial infarction

Angina pectoris
Conduction disorders, cardiac dysrhythmias
Heart failure
Other cardiovascular diseases
Diseases of the respiratory system
Diseases of the digestive system
Diseases of the genitourinary system
Diseases of the skin and subcutaneous tissue
Diseases of the musculoskeletal system and connective tissue
Congenital Anomalies
Injury And Poisoning
External Causes Of Injury And Poisoning
Blood sugar test and monitor
Lab tests for blood sugar
Blood sugar monitoring equipment
Use of other classes of drugs in prior 6 months
Hypnotics
Antiparkinson agents
Anxiolytics
Antiepileptic drugs/ anti-seizure medications
Mood stabilizer
Anticonvulsants
Antidepressants
Primary Extrapyramidal symptoms drugs
Secondary Extrapyramidal symptoms drugs
Antidiabetics
Antihyperlipidemic agents
Other medical services
Long-term care facility
Assisted living facility
Inpatient admission
Emergency department visit
Treatment history and current episode characteristics
Whether the patient restarted an antipsychotic used before, switched from another antipsychotic, or augmented with an additional antipsychotic
The number of treatment episodes a patient had
Used depot antipsychotic
Monotherapy vs poly therapy (any overlap of time with the use of another antipsychotic)
Number of different types of previously used antipsychotics
Dose categories
Within target range (reference)
Below target range
Above target range

eAppendix 3 Instrumental Variables (IVs)

Ideally, IVs should be correlated with the endogenous treatment variable, but not correlated with the outcomes except through predicting the treatment variable[1] such that they are orthogonal to the unobserved heterogeneity. Therefore, whether the IVs are strongly correlated with the treatment choice and whether they are not directly correlated with the outcomes were tested.

Because the analytic file is episode-based, an individual can have one or more observations. Given the multiple-episode structure of our analytic data file, it is possible to exploit the panel data nature in IV models. Specifically, Anderson & Hsiao[2] and Arellano & Bond[2] proposed to use lag values (or differenced lag values) of dependent variables as IVs in first-difference model of dynamic panel. In estimating the equation

$$y_{it} - y_{i,t-1} = \gamma(y_{i,t-1} - y_{i,t-2}) + (x_{it} - x_{i,t-1})'\beta + (\epsilon_{it} - \epsilon_{i,t-1}),$$

$\Delta y_{i,t-2} = (y_{i,t-2} - y_{i,t-3})$ can be used to instrument $(y_{i,t-1} - y_{i,t-2})$ if $y_{i,t-2}$ is uncorrelated with $\epsilon_{it} - \epsilon_{i,t-1}$. Kawatkar et al.[3] extended this theory to use first and second lag values of observed treatment as IVs for the current treatment in estimating costs associated with disease modifying antirheumatic drugs. The justification for the correlation between the IVs and the current treatment was that physician treatment decision was made after observing the patient's experience and outcomes based on the patient's past treatment choice.[3] We used the lagged treatment approach in the current study. The first and second lag values of antipsychotic treatment as IVs for contemporary antipsychotic treatment. Although physicians make decisions based on prior treatment experience of patients, they likely use information on treatment response and well-known adverse events such as EPS, metabolic side effects, and prolactin elevation.[4] Variation in treatment across time is less likely to be caused by uncommon and scantly documented events. Therefore, the lag values

of treatment should explain the current treatment, yet not having direct impact on the target events in the current episode. As a result of using the lag values of treatment as IVs, the first and the second episodes of each patient were not included in IV-Cox regressions.

Prescriber specialty indicators were also used as IVs in our analysis. Physicians of different specialties likely have different practice patterns and therefore have different preferences for treatment,[5] yet physician specialties should have minimum direct correlation with target side effects in the current study. Specialties were categorized into: 1) psychiatry/mental health; 2) family medicine, primary care, and general internal medicine; and 3) all other specialties.

The sample used in IV analyses was not exactly the same as base-case non-IV Cox regressions because the first and the second episodes of an individual did not have up to two lags of treatment. Results of IV analysis are described in eAppendix 3.1 and Supplementary eTable 3.1. Additionally, eAppendix 4 and Supplementary eTable 4 list the IV results of atypical antipsychotics compared to typical antipsychotics.

Cox models are nonlinear models. Therefore, conventional IV estimators including two-stage least squares (2SLS) and general method of moments (GMM) cannot be used here. IV-Cox models in this study used two-stage residual inclusion (2SRI). Terza et al. showed that 2SRI generates consistent estimates in nonlinear models when IVs satisfy the rank condition and the order condition.[6] The first stage in the current 2SRI analyses was a multinomial logit model.[7] More details of first stage statistics are discussed in eAppendix 3.2. In the second stage, residuals from the multinomial logit model were calculated using observed choice and predicted probability of each choice and were taken into the Cox regressions as additional regressors. Standard errors of coefficients were obtained with

bootstrapping for 2SRI-Cox models. Testing the joint significance of the residuals in the Cox regressions is equivalent to Hausman tests of endogeneity in the linear setting.[7] Currently, there are no over-identification tests in 2SRI regressions. Therefore, the exogeneity of IVs was tested indirectly. Specifically, proxy risk factors including pre-index costs, pre-index Charlson Comorbidity Index, an indicator for pre-index hospitalization, an indicator for pre-index emergency department visit, and the occurrence of each target event in the prior 6-month period was regressed on the IVs conditional on other covariates to examine the correlation between the target events and the IVs (eAppendix 3.3). It was expected that the lag values of treatment were not statistically significant predictors of prior 6-month event occurrence.

eAppendix 3.1 IV results

The first-stage residuals were jointly statistically significant in the 2SRI-IV regression of AKI. According to the 2SRI-IV results (Supplementary eTable 3.1), aripiprazole (HR: 1.893, 95% CI: 1.149-3.119), olanzapine (HR: 1.964, 95% CI: 1.182-3.261), quetiapine (HR: 2.377, 95% CI: 1.472-3.837), and risperidone (HR: 1.759, 95% CI: 1.119-2.765) were associated with significantly higher risks of AKI compared to haloperidol, whereas other drugs were not associated with significantly different risks of AKI. Also, the study antipsychotics were not associated with different hypotension risks in the 2SRI-IV Cox regression, and the residuals were not statistically significant. In addition, the 2SRI-IV Cox regression of acute urinary retention did not identify different risks across drugs, and the first-stage residuals were statistically insignificant in the second stage of 2SRI-IV Cox regression, indicating a lack of endogeneity. More, estimates from the 2SRI-

IV Cox regression of neuroleptic malignant syndrome/rhabdomyolysis were not statistically significant, and the first-stage residuals were not significant in the 2SRI-IV regression. Last but not least, no endogeneity was identified in the IV analysis of pneumonia because the first-stage residuals were statistically insignificant in the second stage of the 2SRI-IV Cox regression. All estimates in the IV analysis of pneumonia were insignificant.

eAppendix 3.2 First-stage Statistics

The first stage regression for 2-stage residual inclusion (2SRI)-IV regressions was a multinomial logit regression. Therefore, the traditional way of using F-statistic as evidence of the strength of IVs is not applicable. In fact, consensus on how the strength of IVs should be determined in nonlinear regressions is still absent in literature. In the following tables, we first show the results of the multinomial logit regression. Then, we show the results of a series of binary linear probability models (LPMs) for each of the drugs and the F-statistics for each of the LPM regressions.

As shown in Supplementary eTable 3.2.1, The IVs were statistically significant predictors of the drug choice in the current episode. Also, the pseudo-R^2 of the multinomial logit regression was 0.384. McFadden suggested that a pseudo-R^2 between 0.2-0.4 is evidence of very good fitting.[8]

Supplementary eTable 3.2.2 lists the results of the binary LPMs. Bootstrapped standard errors with 200 repeats were used for this set of analyses. Traditionally, an F-statistic value greater than 10 is considered as the threshold of non-weak IVs.[9] In the current LPMs, the F-statistics were substantially greater than 10.

eAppendix 3.3 Exogeneity of IVs

Exogeneity of IVs cannot be directly tested in nonlinear regressions. In fact, tests for this purpose, known as overidentification tests, are hardly gold standards even though they exist in a linear setting.[10] As mentioned in the method section of main text, proxy risk factors in the prior 6-month period was regressed on the IVs using linear models to examine the correlation between the target events and the IVs conditional on other covariates. Bootstrapped standard errors with 200 repeats were used. Instrumental variables should not be correlated with proxy risk factors conditional on observed covariates.[11] Absence of correlation is indirect evidence of the exogeneity of IVs. The results are displayed in Supplementary eTable 3.3.1, Supplementary eTable 3.3.2, Supplementary eTable 3.3.3, and Supplementary eTable 3.3.4. Overall, lags of treatment were not statistically significant correlated with prior occurrence of target events. Indicators of prescriber specialties were statistically significantly but very weakly correlated with prior occurrence of target events. Therefore, we did not find plausible evidence that the IVs were associated with the outcomes in ways other than through affecting the treatment.

eAppendix 3 References

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Supplementary eTable 3.1 Instrumental variable analysis using 2-stage residual inclusion Cox regressions: hospitalization with acute kidney injury (AKI) or events that may cause AKI

	Acute kidney injury	Hypotension	Acute urinary retention	Neuroleptic malignant syndrome / rhabdomyolysis	Pneumonia
N sample	126,589	126,590	126,602	126,608	126,590
N events	1,396	1,094	519	363	1,716
aripiprazole	1.893* [1.149,3.119]	1.164 [0.661,2.049]	1.375 [0.636,2.976]	0.715 [0.264,1.933]	1.287 [0.830,1.996]
fluphenazine	0.773 [0.402,1.488]	1.189 [0.595,2.375]	1.463 [0.614,3.483]	1.337 [0.462,3.873]	1.147 [0.681,1.931]
olanzapine	1.964** [1.182,3.261]	1.419 [0.795,2.532]	0.819 [0.363,1.849]	2.364 [0.958,5.835]	1.330 [0.849,2.082]
quetiapine	2.377*** [1.472,3.837]	1.548 [0.900,2.662]	1.174 [0.560,2.464]	2.033 [0.841,4.914]	1.336 [0.875,2.041]
risperidone	1.759* [1.119,2.765]	1.420 [0.846,2.384]	1.260 [0.625,2.539]	1.764 [0.767,4.053]	1.154 [0.770,1.730]
ziprasidone	1.671 [0.953,2.930]	1.706 [0.931,3.129]	1.374 [0.585,3.223]	1.938 [0.715,5.251]	1.120 [0.686,1.830]
Test of exogeneity[a]	p=0.0493	p=0.7810	p=0.3003	p=0.2770	p=0.8740

Exponentiated coefficients; 95% confidence intervals in brackets. Baseline comparator: haloperidol.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

a: H0: each of the residual equals 0. Rejection of this hypothesis means endogeneity of treatment choice cannot be ignored and instrumental variable estimates should be used.

Supplementary eTable 3.2. 1 First-stage multinomial logit regression results

	Aripiprazole	Fluphenazine	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Specialty: psychiatry	1.187***	1.017	1.102**	1.097**	1.197***	1.168***
Specialty: family medicine, primary care, general internal medicine	1.042	0.600***	1.288***	1.428***	1.295***	0.851**
lag 1 aripiprazole	72.50***	12.04***	7.363***	11.24***	8.297***	9.107***
lag 1 fluphenazine	11.13***	286.2***	11.26***	9.866***	10.57***	9.006***
lag 1 olanzapine	9.174***	11.78***	51.47***	6.413***	6.786***	7.130***
lag 1 quetiapine	13.57***	11.03***	6.810***	37.72***	9.422***	9.929***
lag 1 risperidone	9.259***	10.53***	6.175***	7.992***	41.51***	7.271***
lag 1 ziprasidone	10.08***	8.996***	6.641***	8.652***	7.187***	62.37***
lag 2 aripiprazole	15.92***	4.127***	4.948***	5.808***	5.477***	5.866***
lag 2 fluphenazine	3.776***	35.38***	4.181***	3.860***	3.865***	3.683***
lag 2 olanzapine	5.452***	4.435***	16.73***	5.574***	5.051***	5.310***
lag 2 quetiapine	5.789***	4.300***	5.008***	12.87***	5.044***	5.444***
lag 2 risperidone	5.235***	4.561***	5.114***	5.328***	11.80***	5.091***

lag 2 ziprasidone	6.481***	4.778***	5.647***	5.988***	5.473***	20.08***
N	126,612	126,612	126,612	126,612	126,612	126,612

Exponentiated coefficients. Baseline comparator of specialties: other specialties. Baseline comparators of lags of treatment: haloperidol.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Supplementary eTable 3.2. 2 Binary linear probability models of drug choices on IVs

	Aripiprazole	Fluphenazine	Haloperidol	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Specialty: psychiatry	0.00616***	-0.00186*	-0.00640***	-0.000481	-0.00705**	0.00695***	0.00268
Specialty: family medicine, primary care, general internal medicine	-0.0138***	-0.00944***	-0.00930***	0.00647**	0.0338***	0.00804**	-0.0157***
lag 1 aripiprazole	0.475***	0.00456**	-0.452***	-0.0158***	0.0137**	-0.0189***	-0.00624*
lag 1 fluphenazine	-0.000644	0.504***	-0.465***	-0.00261	-0.0179*	-0.00853	-0.00952*
lag 1 olanzapine	0.0112**	0.00771***	-0.442***	0.467***	-0.0280***	-0.0120*	-0.00381
lag 1 quetiapine	0.0228***	0.00356*	-0.451***	-0.0185***	0.444***	-0.00160	0.000853
lag 1 risperidone	0.00421	0.00386*	-0.447***	-0.0179***	-0.0129**	0.477***	-0.00684*
lag 1 ziprasidone	0.0133**	0.00306	-0.442***	-0.0103**	0.0113	-0.00830	0.433***
lag 2 aripiprazole	0.223***	-0.00377*	-0.280***	0.00884*	0.0196***	0.0206***	0.0119***
lag 2 fluphenazine	-0.0100	0.307***	-0.272***	-0.00430	-0.00758	-0.0104	-0.00274
lag 2 olanzapine	0.00773	-0.00336	-0.282***	0.221***	0.0336***	0.0147**	0.00856*

lag 2 quetiapine	0.00449	-0.00268	-0.280***	0.0106**	0.255***	0.00684	0.00631*
lag 2 risperidone	0.00913*	-0.000814	-0.279***	0.0149***	0.0268***	0.220***	0.00904**
lag 2 ziprasidone	0.0156***	-0.00153	-0.285***	0.0128**	0.0224***	0.0152**	0.221***
N	126,612	126,612	126,612	126,612	126,612	126,612	126,612
F-statistic	3012.1	1132.0	1694.6	1847.1	5019.1	3677.9	1231.1

Baseline comparator of specialties: other specialties. Baseline comparators of lags of treatment: haloperidol.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Supplementary eTable 3.3.1 Linear regressions of pre-index costs, Charlson Comorbidity Index (CCI), indicator of hospitalization, and indicator of emergency department visit on first lag of treatment, second lag of treatment, and specialty indicators

	Pre-index costs	Pre-index CCI	Pre-index hospitalization indicator	Pre-index emergency department visit indicator
lag 1 aripiprazole	316.0	0.00702	-0.00147	-0.0104*
lag 1 fluphenazine	348.9	-0.00869	-0.00456	0.00462
lag 1 olanzapine	520.9*	0.0220	0.00436	-0.000903
lag 1 quetiapine	478.7*	0.0192	0.00880	0.00485
lag 1 risperidone	360.5	-0.0175	0.00413	0.000742
lag 1 ziprasidone	523.5*	-0.00251	0.00131	-0.00644
lag 2 aripiprazole	229.8	0.0169	0.00276	-0.00763
lag 2 fluphenazine	-16.95	0.00965	-0.00477	-0.00421
lag 2 olanzapine	220.3	0.0248	0.000380	-0.00456
lag 2 quetiapine	158.0	0.0163	0.00350	-0.000454
lag 2 risperidone	-135.2	0.00778	0.00379	-0.000296
lag 2 ziprasidone	274.2	0.0130	0.000381	-0.00305
Specialty: psychiatry	-866.1***	-0.0424***	-0.0190***	-0.0245***
Specialty: family medicine, primary care, general internal medicine	-357.9**	-0.0145	-0.00502	-0.0179***
N	126,612	126,612	126,612	126,612

Supplementary eTable 3.3. 2 Regressions of target events in prior 6-month period on indicators of prescriber specialties

	Acute coronary syndrome / ischemic stroke	Ventricular arrhythmia	Acute kidney injury	Hypotension	Acute urinary retention	Neuroleptic malignant syndrome / rhabdomyolysis	Pneumonia
Specialty: psychiatry	-0.000748	-0.000254	0.000356	0.000165	-0.000349	-0.0000977	0.000277
Specialty: family medicine, primary care, general internal medicine	-0.000671	0.000138	0.00492***	0.00201	-0.000243	0.000584	0.00412**
N	126,612	126,612	126,612	126,612	126,612	126,612	126,612

Baseline comparator: other specialties.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Supplementary eTable 3.3. 3 Regressions of target events in prior 6-month period on indicators of first lag of treatment

	Acute coronary syndrome / ischemic stroke	Ventricular arrhythmia	Acute kidney injury	Hypotension	Acute urinary retention	Neuroleptic malignant syndrome / rhabdomyolysis	Pneumonia
lag 1 aripiprazole	0.00146	-0.000579	0.000431	0.000750	-0.0000880	0.0000686	0.00280*
lag 1 fluphenazine	0.00219	-0.000958	-0.00198	0.00158	-0.00162	0.00106	-0.000331
lag 1 olanzapine	-0.0000722	-0.000966	0.00299	0.00441**	-0.00168	0.00165	0.00223
lag 1 quetiapine	0.000400	-0.000541	0.000688	0.00158	-0.000804	0.00101	-0.000296
lag 1 risperidone	-0.000129	0.000228	0.00193	0.000791	-0.000625	0.000767	0.000663
lag 1 ziprasidone	0.000957	-0.000585	0.00270	0.00187	0.000543	0.00157	-0.000665
N	126,612	126,612	126,612	126,612	126,612	126,612	126,612

Baseline comparators of lags of treatment: haloperidol.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Supplementary eTable 3.3. 4 Regressions of target events in prior 6-month period on indicators of second lag of treatment

	Acute coronary syndrome / ischemic stroke	Ventricular arrhythmia	Acute kidney injury	Hypotension	Acute urinary retention	Neuroleptic malignant syndrome / rhabdomyolysis	Pneumonia
lag 2 aripiprazole	0.00219	-0.000213	0.00154	0.000247	-0.000906	0.000162	0.00203
lag 2 fluphenazine	0.00212	--0.000514	-0.00174	0.00174	-0.00170	0.000835	0.00153
lag 2 olanzapine	0.000958	-0.000534	0.00244	0.00292	-0.00118	0.00238*	0.000683
lag 2 quetiapine	0.00165	-0.000560	0.00135	0.000371	-0.000995	0.000994	-0.000411
lag 2 risperidone	0.000374	0.0000859	0.00313*	0.00113	-0.000676	0.00109	0.00165
lag 2 ziprasidone	0.00210	-0.000342	0.00154	0.000852	-0.000779	0.000954	-0.000607
N	126,612	126,612	126,612	126,612	126,612	126,612	126,612

Baseline comparators of lags of treatment: haloperidol.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

eAppendix 4 IV analyses of atypical antipsychotics compared to typical antipsychotics

According to results shown in Supplementary eTable 4, endogeneity not only existed across specific drug groups, but also existed between the larger groups of atypical antipsychotics and typical antipsychotics. Atypical antipsychotics were associated with a higher risk of acute kidney injury (AKI) in both base-case regressions and 2SRI-IV regressions.

Supplementary eTable 4 Instrumental variable analysis using 2-stage residual inclusion regressions compared with base-case: hospitalization with acute kidney injury (AKI) or events that may cause AKI-- Atypical vs. Typical

	Acute kidney injury	Hypotension	Acute urinary retention	Neuroleptic malignant syndrome / rhabdomyolysis	Pneumonia
			Base-case Cox regressions		
Atypical indicator	1.313** [1.083,1.591]	1.055 [0.858,1.297]	0.834 [0.636,1.094]	1.425 [0.988,2.055]	1.148 [0.966,1.364]
N	172,283	172,285	172,297	172,307	172,280
			2SRI-IV regressions		
Atypical indicator	2.041*** [1.339,3.113]	1.267 [0.806,1.991]	1.166 [0.630,2.159]	1.442 [0.711,2.926]	1.136 [0.796,1.622]
Test of exogeneity	P=0.004	P=0.455	P=0.356	P=0.849	P=0.744
N	126,589	126,590	126,602	126,608	126,590

Exponentiated coefficients; 95% confidence intervals in brackets. Baseline comparator: typical antipsychotics.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Supplementary eTable 5 Weibull regressions: hospitalization with acute kidney injury (AKI) or events that may cause AKI

	Acute kidney injury	Hypotension	Acute urinary retention	Neuroleptic malignant syndrome / rhabdomyolysis	Pneumonia
aripiprazole	1.180 [0.930,1.497]	0.885 [0.674,1.162]	0.846 [0.595,1.203]	0.866 [0.530,1.415]	1.101 [0.887,1.367]
fluphenazine	0.724 [0.479,1.093]	1.158 [0.778,1.724]	0.964 [0.569,1.634]	0.889 [0.431,1.832]	0.922 [0.655,1.299]
olanzapine	1.355* [1.066,1.722]	1.081 [0.822,1.420]	0.768 [0.533,1.107]	1.278 [0.796,2.052]	1.322* [1.064,1.643]
quetiapine	1.361** [1.090,1.697]	1.301* [1.017,1.666]	0.886 [0.642,1.224]	1.602* [1.042,2.464]	1.189 [0.971,1.455]
risperidone	1.153 [0.928,1.433]	1.037 [0.810,1.327]	0.793 [0.575,1.093]	1.505 [0.989,2.291]	1.060 [0.867,1.296]
ziprasidone	1.349* [1.044,1.744]	1.290 [0.973,1.712]	0.942 [0.642,1.381]	1.295 [0.782,2.145]	1.065 [0.840,1.352]
N	172,283	172,285	172,297	172,307	172,280

Exponentiated coefficients; 95% confidence intervals in brackets. Baseline comparator: haloperidol.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Supplementary eTable 6 Cox regressions: hospitalization, ED visits, or urgent care visits with acute kidney injury (AKI) or events that may cause AKI

	Acute kidney injury	Hypotension	Acute urinary retention	Neuroleptic malignant syndrome / rhabdomyolysis	Pneumonia
aripiprazole	1.185 [0.936,1.500]	0.854 [0.667,1.094]	0.863 [0.615,1.212]	0.823 [0.514,1.320]	1.091 [0.893,1.334]
fluphenazine	0.787 [0.530,1.170]	1.035 [0.711,1.507]	1.062 [0.646,1.744]	0.900 [0.452,1.792]	0.909 [0.661,1.250]
olanzapine	1.365* [1.076,1.731]	1.034 [0.806,1.327]	0.764 [0.537,1.088]	1.133 [0.715,1.795]	1.284* [1.049,1.571]
quetiapine	1.401** [1.125,1.745]	1.226 [0.979,1.536]	0.900 [0.658,1.231]	1.533* [1.014,2.316]	1.177 [0.975,1.421]
risperidone	1.175 [0.948,1.457]	1.000 [0.799,1.252]	0.779 [0.570,1.065]	1.454 [0.972,2.174]	1.048 [0.870,1.263]
ziprasidone	1.350* [1.047,1.741]	1.165 [0.898,1.513]	0.945 [0.653,1.368]	1.242 [0.764,2.018]	1.028 [0.823,1.283]
N	172,282	172,279	172,296	172,307	172,272

Exponentiated coefficients; 95% confidence intervals in brackets. Baseline comparator: haloperidol.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Supplementary eTable 7 Cox regressions using episodes without overlap: hospitalization with acute kidney injury (AKI) or events that may cause AKI

	Acute kidney injury	Hypotension	Acute urinary retention	Neuroleptic malignant syndrome / rhabdomyolysis	Pneumonia
aripiprazole	1.511* [1.056,2.163]	0.970 [0.644,1.462]	0.887 [0.509,1.547]	0.569 [0.297,1.091]	1.296 [0.936,1.793]
fluphenazine	0.733 [0.384,1.397]	1.018 [0.533,1.945]	2.204* [1.053,4.610]	1.185 [0.487,2.882]	0.788 [0.452,1.375]
olanzapine	1.848*** [1.291,2.647]	1.430 [0.952,2.148]	0.834 [0.467,1.490]	0.800 [0.424,1.509]	1.607** [1.158,2.229]
quetiapine	1.786*** [1.270,2.512]	1.654** [1.132,2.417]	1.036 [0.616,1.745]	1.275 [0.728,2.233]	1.398* [1.024,1.909]
risperidone	1.450* [1.035,2.032]	1.223 [0.836,1.788]	0.889 [0.526,1.503]	1.132 [0.652,1.964]	1.235 [0.906,1.683]
ziprasidone	1.896** [1.293,2.781]	1.382 [0.892,2.139]	1.176 [0.647,2.137]	0.846 [0.419,1.708]	1.166 [0.812,1.676]
N	71,579	71,579	71,584	71,588	71,579

Exponentiated coefficients; 95% confidence intervals in brackets. Baseline comparator: haloperidol.

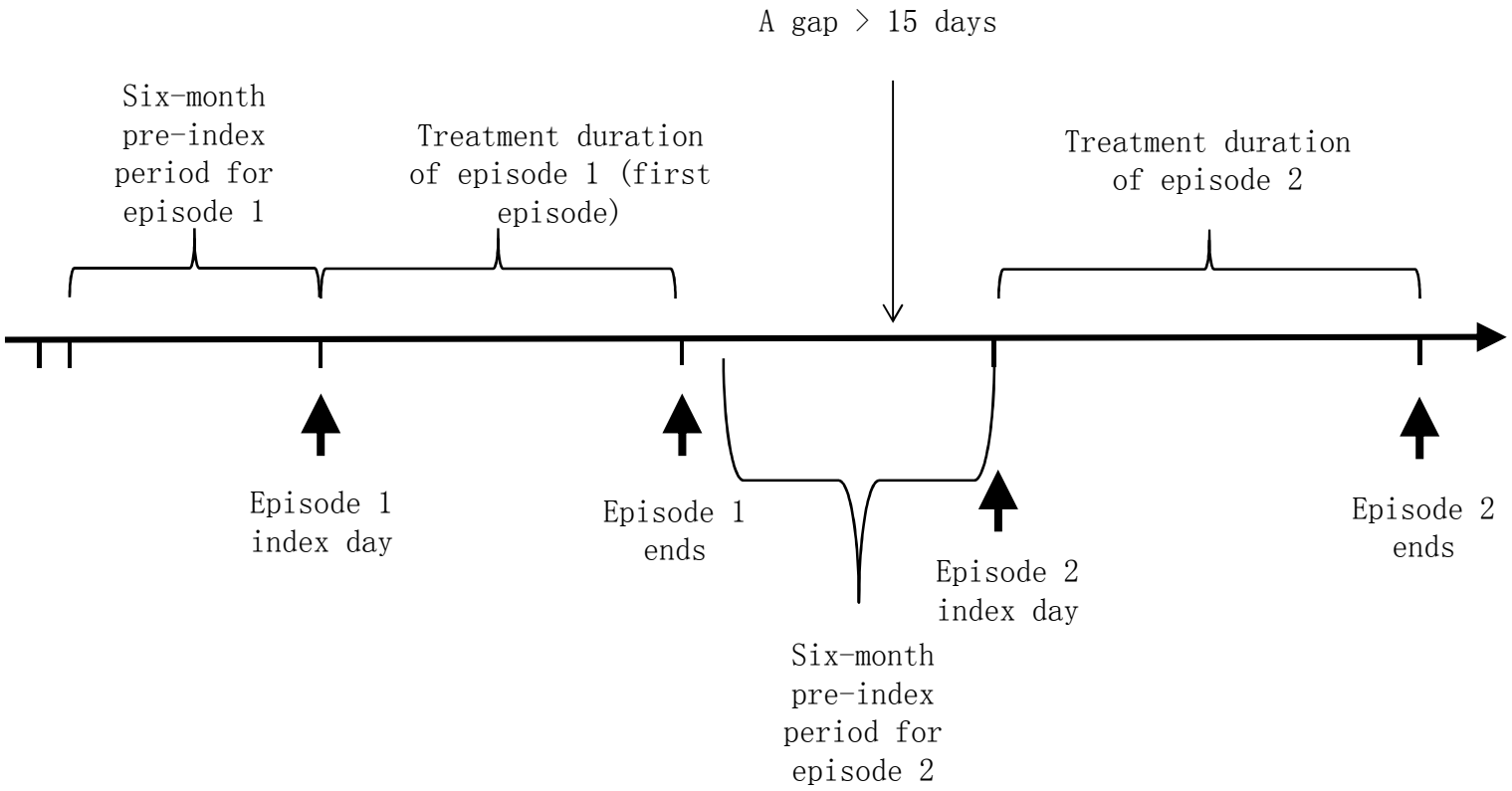
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Supplementary eTable 8 Competing risk model: hospitalization with acute kidney injury (AKI) or events that may cause AKI

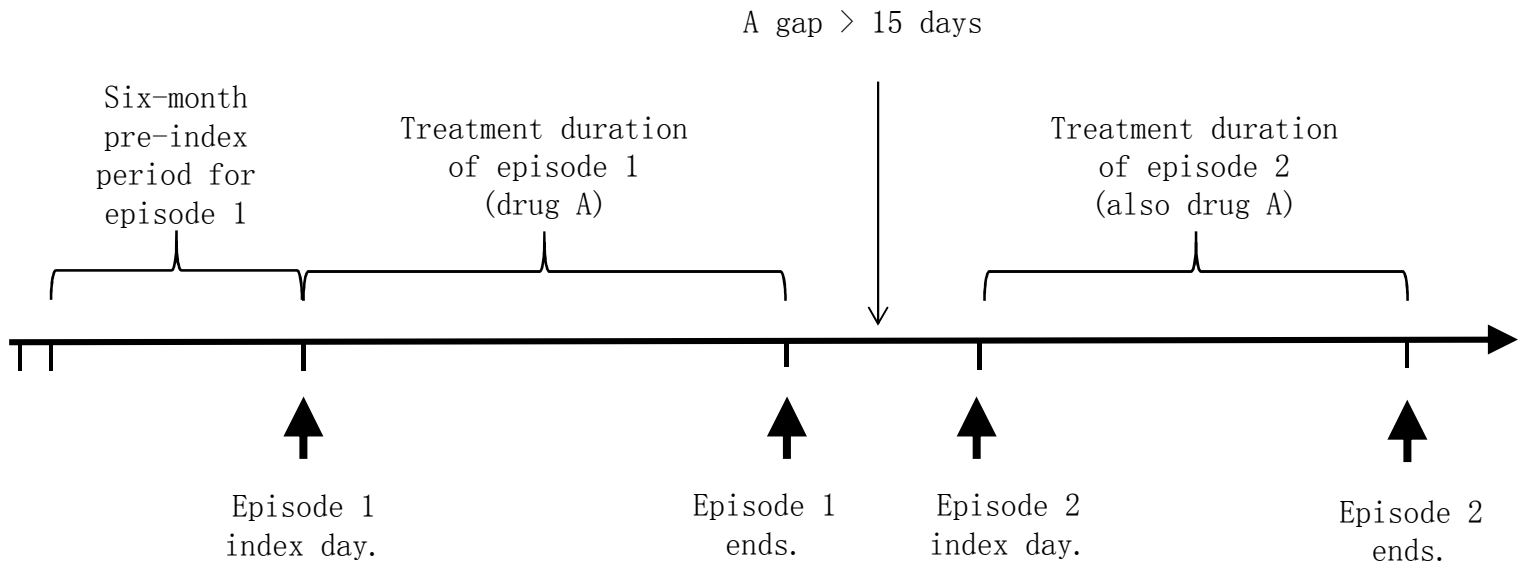
	Acute kidney injury	Hypotension	Acute urinary retention	Neuroleptic malignant syndrome / rhabdomyolysis	Pneumonia
aripiprazole	1.141 [0.899,1.448]	0.849 [0.647,1.115]	0.824 [0.579,1.173]	0.833 [0.510,1.363]	1.069 [0.861,1.327]
fluphenazine	0.739 [0.489,1.116]	1.167 [0.784,1.734]	0.977 [0.576,1.657]	0.896 [0.435,1.847]	0.938 [0.665,1.321]
olanzapine	1.366* [1.075,1.736]	1.077 [0.820,1.416]	0.773 [0.536,1.114]	1.279 [0.796,2.056]	1.331* [1.071,1.654]
quetiapine	1.379** [1.105,1.721]	1.313* [1.026,1.681]	0.900 [0.651,1.243]	1.613* [1.047,2.483]	1.208 [0.986,1.480]
risperidone	1.173 [0.944,1.457]	1.049 [0.820,1.343]	0.807 [0.585,1.113]	1.532* [1.005,2.334]	1.079 [0.883,1.320]
ziprasidone	1.343* [1.039,1.735]	1.288 [0.971,1.709]	0.948 [0.646,1.390]	1.292 [0.780,2.140]	1.069 [0.843,1.357]
N	172,283	172,285	172,297	172,307	172,280

Exponentiated coefficients; 95% confidence intervals in brackets. Baseline comparator: haloperidol.

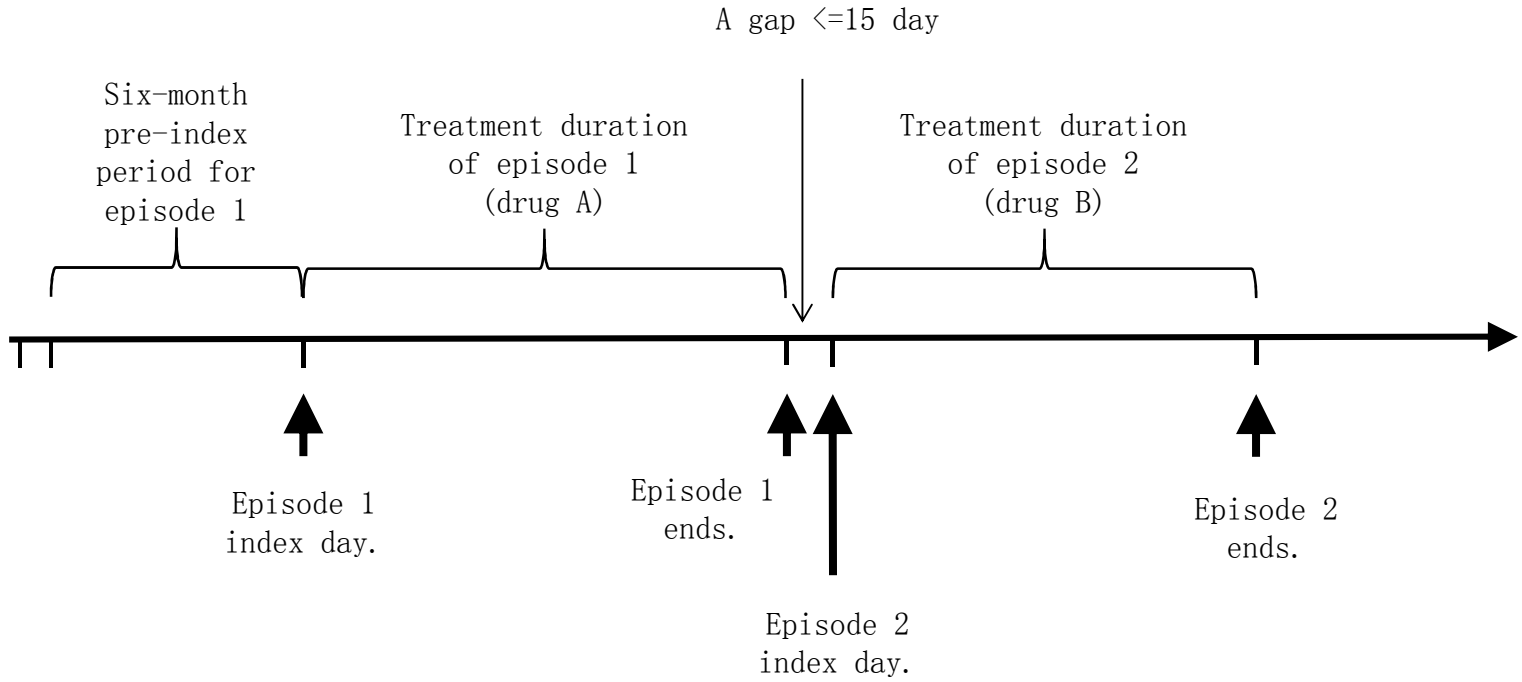
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$



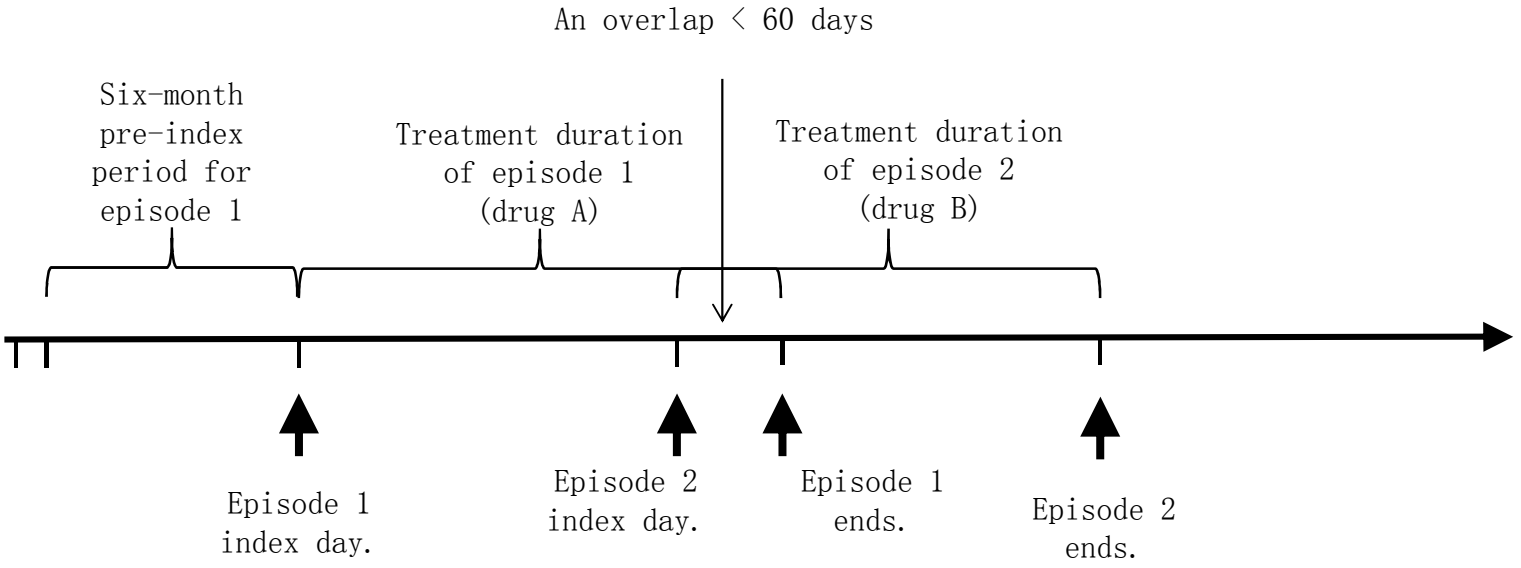
Supplementary eFigure 1. A basic illustration of episodes.



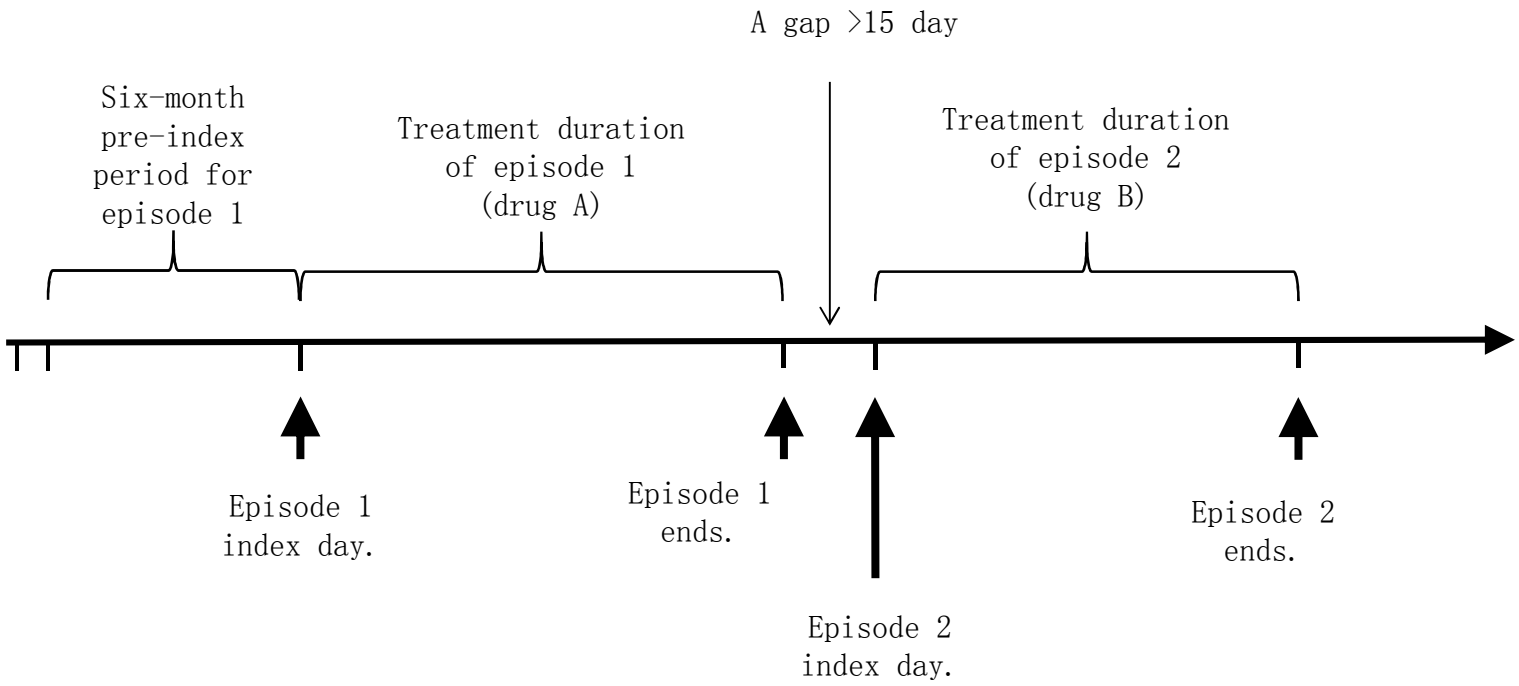
Supplementary eFigure 2. An illustration of restart episodes. Episode 2 is a restart episode.



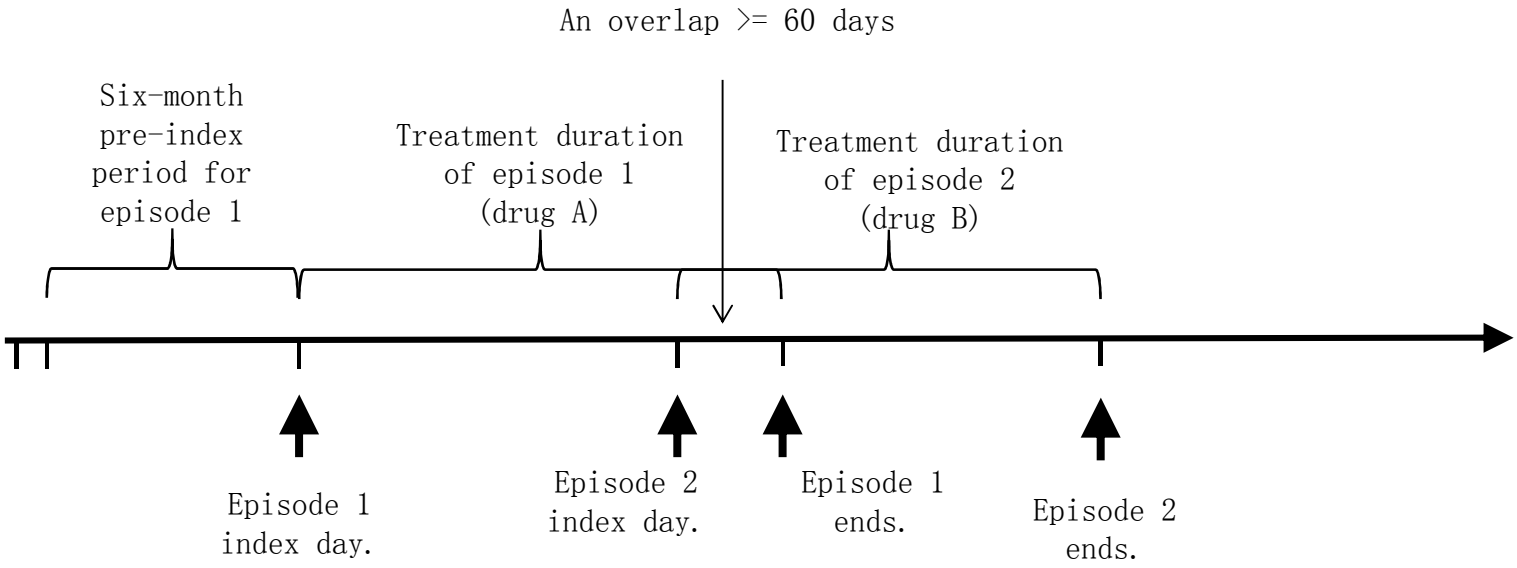
Supplementary eFigure 3. An illustration of switching episodes. Episode 2 is a switching episode because it was initiated within 15 days after the termination of the previous episode and it involved a different index drug.



Supplementary eFigure 4. Another scenario of switching episodes. Episode 2 is a switching episode. This is because it was initiated before the termination of the previous episode and it involved a different index drug, yet the previous episode terminated less than 60 days after the initiation of episode 2.



Supplementary eFigure 5. An illustration of delayed switching episodes. Episode 2 is a delayed switching episode because it was initiated later than 60 days after the termination of the previous episode and it involved a different index drug.



Supplementary eFigure 6. An illustration of augmentation episodes. Episode 2 is an augmentation episode because it had a $\geq$ 60-day overlap with the previous episode and it involved a different index drug.