1 **Title page**

2 Study title:

3 Antipsychotics and risk of neuroleptic malignant syndrome: a population-based cohort and case-
4 crossover study

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6 Running heading:

7 Antipsychotics and neuroleptic malignant syndrome

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9 Authors: Kim SJ Lao, PhD^{1,2}; Jiaxi Zhao, MSc¹; Joseph Edgar Blais, BScPharm¹; Lam Lam,
10 MSocSc¹; Ian CK Wong, PhD^{1,3}; Frank MC Besag, FRCP^{3,4,5}; Wing Chung Chang,
11 FHKCPsych^{6,7}; David J Castle, MD^{8,9}; Esther W Chan, PhD¹

12

13 Affiliations: ¹Centre for Safe Medication Practice and Research, Department of Pharmacology
14 and Pharmacy, The University of Hong Kong, Hong Kong SAR, China

15 ²Global Medical Affairs, Merck Research Laboratories, Shanghai, China

16 ³Research Department of Practice and Policy, UCL School of Pharmacy, London, UK

17 ⁴East London NHS Foundation Trust, Bedford, Bedfordshire, UK

18 ⁵Institute of Psychiatry, Psychology and Neuroscience, London, UK

19 ⁶Department of Psychiatry, Li Ka Shing Faculty of Medicine, The University of Hong Kong,
20 Hong Kong SAR, China

21 ⁷State Key Laboratory of Brain & Cognitive Sciences, The University of Hong Kong, Hong
22 Kong SAR, China

23 ⁸St. Vincent's Hospital, Melbourne, Victoria, Australia

24 ⁹Department of Psychiatry, University of Melbourne, Melbourne, Victoria, Australia

25

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33 Correspondence to:

34 Dr Esther W Chan

35 Associate Professor

36 Research Lead, Centre for Safe Medication Practice and Research

37 Department of Pharmacology and Pharmacy

38 Office 02-08, 2/F Laboratory Block, 21 Sassoon Road, Pokfulam

39 Li Ka Shing Faculty of Medicine

40 The University of Hong Kong

41 Hong Kong SAR, China

42 Email: ewchan@hku.hk

43 Centre: +852 2831 5110

44 Office: +852 3917 9029

45

Abstract

Background: Neuroleptic malignant syndrome (NMS) is a rare and acute adverse drug reaction associated with antipsychotic therapy. However, few data on the risk and epidemiology of NMS are available.

Objectives: To ascertain the incidence risk and all-cause mortality of NMS associated with antipsychotic use, and to assess the association of recent antipsychotic exposure and NMS.

Methods: We did a population-based study using data from the Hong Kong Hospital Authority's Clinical Data Analysis and Reporting System database. Cases had a first diagnosis of NMS between 1 January 2004 and 30 November 2017. A case-crossover analysis was used to compare antipsychotic exposure 30 days before the diagnosis of NMS (index date) and a reference period 91 to 120 days before the index date. To adjust for potential time-trends in antipsychotic exposure, we sampled from cases to match current cases and future cases, and further adjusted for select medications, and acute medical conditions.

Results: 297 647 patients were prescribed antipsychotics, and the incidence risk of NMS was 0.11%. Of the 336 cases included in the case-crossover analysis, 20 (6%) died within 30 days after the index date; only one case had NMS recorded as the primary cause of death. When compared with the reference period, cases were more frequently prescribed multiple antipsychotics (15.8% vs 26.8%; standardized mean difference [SMD] 0.27) and short-acting injectable antipsychotics (3.6% vs 13.7%; SMD 0.37) during the 30 days prior to the diagnosis of NMS. Odds ratios for antipsychotic exposure in the case-crossover, case-crossover adjusted for time-trend, and case-crossover adjusted for time-trend and potential confounders analysis were 8.00 (95% confidence interval 3.42-18.69), 5.88 (2.46-14.04), and 4.77 (1.95-11.66).

68 Conclusions: Our results suggest that recent use of antipsychotics is associated with NMS.
69 Although a case-only design inherently controls for confounding by time-invariant factors,
70 residual confounding by acute medical conditions with similar presentations to NMS cannot be
71 fully excluded.

72

73 **Key points**

- 74 • In the cohort analysis of 297 647 antipsychotic users, the incidence risk of NMS was
75 0.11%.
- 76 • Recent antipsychotic use was consistently associated with an increased risk of NMS in
77 case-crossover and analyses adjusted for changes in prevalence of antipsychotic
78 exposures over time. The increased risk was observed for a period of about 20 to 40 days
79 before the diagnosis of NMS.

Main Text

1. Introduction

Neuroleptic malignant syndrome (NMS) is a rare and potentially life-threatening adverse drug reaction. Since it was first reported in 1956, most cases have been linked to antipsychotics, although it can occur in patients receiving drugs that inhibit or deplete dopamine such as antiemetics (metoclopramide), benzodiazepines, antiepileptics, and lithium, or due to the withdrawal of dopaminergic therapy in Parkinson's disease. Estimates of the occurrence of NMS vary; the reported incidence is between 0.06% to 1.4% among patients treated with antipsychotics [1, 2]. Among patients with a psychiatric diagnosis, 0.04% experienced NMS [3] and 9.4% died within 30 days of diagnosis of NMS in patients with bipolar disorder [4]. However, the epidemiology of NMS, including its incidence risk and mortality in patients taking antipsychotics remains unclear.

Previous case reports, case series, case-control, and cohort studies describe the occurrence of NMS in association with several antipsychotics, notably haloperidol [2, 3, 5-7]. The association between antipsychotics and the risk of NMS by drug generation (first-generation antipsychotics and second-generation antipsychotics) also remains inconsistent [3, 5, 8]. The limited sample sizes of published studies have made it difficult to obtain precise estimates of the risks associated with individual antipsychotic drugs.

Acute mental health or medical conditions such as psychosis, psychomotor agitation, delirium, and dehydration are also important risk factors for NMS [4, 7, 9]. Only one previous study has adjusted for the potential confounding effect of current psychotropic medication and comorbidities of mental health disorders [4]. In addition, genetic polymorphisms affecting

pharmacodynamic or pharmacokinetic processes can influence the susceptibility to NMS [10]; previous research has not controlled for such genetic factors.

To address these issues and to eliminating confounding and selection bias by time-invariant variables we used a case-crossover study design, in which each case acts as its own control [11]. Using a 13-year population-based cohort of patients prescribed antipsychotics, our primary aim was to assess the risk of NMS associated with exposure to any antipsychotic and to ascertain the incidence risk of NMS. In an exploratory analysis, we also assessed the risk of NMS for four commonly prescribed antipsychotics in Hong Kong: haloperidol, quetiapine, olanzapine, and risperidone.

2. Methods

2.1. Data Source

We obtained data from the Clinical Data Analysis and Reporting System (CDARS), a clinical database managed by the Hong Kong Hospital Authority. The Hospital Authority provides primary, secondary, and tertiary care services to Hong Kong's seven million residents through 41 public hospitals and institutions, 47 specialist outpatient clinics, and 73 general outpatient clinics. Since 1993, CDARS has contained patient demographic and clinical data (including records of diagnosis, prescriptions, pharmacy dispensing, admission and discharge information, emergency attendance, laboratory test results, and payment method) for research and audit purposes. CDARS has been used in several epidemiological studies to investigate medication safety. High positive predictive values (PPV) have been reported for the diagnosis of myocardial infarction, arrhythmia, stroke, and trauma [12-14]. Research ethics approval was obtained from

the Institutional Review Board of The University of Hong Kong/Hospital Authority HKWC (Reference Number: UW 15-619).

2.2. Case Identification and Data Validation

New NMS cases, defined as the first diagnosis record during the study period of International Classification of Diseases, Ninth Revision Clinical Modification (ICD-9-CM) code 333.92, were identified using CDARS. We validated a subset of all cases that occurred in the Hospital Authority's Hong Kong West Cluster (HKWC), which serves 521 200 people (7% of Hong Kong's population) [15]. Access to full medical records of NMS cases in HKWC for validation was granted by IRB. One author who is a psychiatrist (WCC) retrieved and reviewed the full paper and electronic medical records to validate whether each case from HKWC met the DSM-IV criteria for NMS [16]. The assessed diagnostic criteria included hyperthermia, generalized rigidity and other associated neurological symptoms (including tremor, akinesia, dystonia, myoclonus), altered mental status characterized by delirium or altered consciousness, laboratory results (elevation of creatine kinase), and signs of automatic activation and instability. The exposure to antipsychotics and presentation of other identifiable medical causes explaining the index clinical manifestations were also considered to ascertain the diagnosis.

2.3. Cohort Study: Incidence Risk of Neuroleptic Malignant Syndrome

We previously identified a cohort of patients with any antipsychotic prescription (defined as a drug classified in British National Formulary categories 4.2.1 and 4.2.2) from 1 January 2004 to 31 December 2016 (Figure 1) [17]. Among this cohort of antipsychotic users, we estimated the incidence risk of NMS by dividing the number of new cases of NMS by the total number of antipsychotic users.

2.4. Case-Crossover Study: Risk of Neuroleptic Malignant Syndrome

2.4.1. Eligibility Criteria

To ensure we had an adequate and current sample of cases, we also identified cases from CDARS between 1 January 2017 to 30 November 2017 (Figure 1). We restricted our analysis to patients who routinely use Hospital Authority services and should thus have complete medical records in CDARS, by excluding cases who did not have a documented hospitalization, outpatient clinic visit, drug dispensing occurrence, or emergency department visit during the 180-day period preceding the index date (see section 2.4.2 for the definition of index date).

2.4.2. Study Design

The case-crossover study is a within-individual case-only design used for investigating the risk of an acute event, in which the case period (time immediately before the outcome) and reference period (time preceding the case period) are sampled from the same individual (Figure 2A). The exposure status during the case and reference periods of the same subject are compared to derive the odds ratio (OR) of the event [18, 19]. Compared with case-control studies, the case-crossover study design can inherently control for confounders which vary between subjects (such as genetic factors and socioeconomic status) but not within an individual over time, because each case serves as their own control. This study design has been applied to investigate the association between antipsychotic exposure and other acute outcomes [20, 21].

The index date (time zero) was defined as the earliest occurrence of hospital admission, outpatient clinic attendance, or emergency department visit for NMS. The case period was

defined as days 1-30 prior to the index date and reference period was defined as days 91-120 prior to the index date. The 30-day duration of the case and reference period in primary analysis was selected according to the NMS diagnostic criterion DSM-IV which states that most cases of NMS developed within 30 days of initiating the causal agent [16]. We included a 60-day buffer period between the case and reference periods to avoid the residual effects of long-acting antipsychotic injections administered during the reference period. The duration of the buffer period was selected based on the expected duration of action of long-acting antipsychotic injections and from previous studies [20, 21]. Exposure to any antipsychotic was defined as having at least one prescription of at least one day in duration during either the case or reference period. Exposure to haloperidol, olanzapine, quetiapine, and risperidone was defined similarly for exploratory outcome analysis.

2.4.3. *Adjustment for Time-Trend in Antipsychotic Exposure*

The case-crossover method assumes a constant prevalence of exposure during the study period [18], which is violated if there is a varying trend in the prevalence of antipsychotic exposure. An exposure time-trend may exist when there is varying use of the exposure at the population level or a temporal change in exposure before the detection or diagnosis of the outcome (i.e. protopathic bias or reverse causality) [19]. One scenario in which protopathic bias occurs is when a drug is prescribed to manage the early symptoms of the disease, when the disease has yet to be detected, diagnosed and recorded.

One approach to address this issue is to measure the exposure time-trend in a control group sampled from cases and adjust for it in a regression model (referred to as the case-crossover adjusted for exposure time-trend analysis). This control group consists of person-time sampled

from future cases , and is the person-time shortly before the diagnosis of NMS (Figure 2B) [19]. Due to similar medical history and occurrence of NMS to the current cases, the future case control group provides a close approximation of exposure time-trend of current cases [19]. We matched current cases with future case controls on gender, age on the index date (within 10 years), and year of NMS diagnosis at a maximum ratio of 1:10. To correctly align calendar time, each future case control was assigned the index date of the matched current case (Figure 2B).

2.5. Statistical Analysis

Characteristics, including demographics, any medical history of schizophrenia, bipolar disorder, major depressive disorder, and all other mental health conditions were assessed from the start of data availability to the start of the reference period for all cases included in the case-crossover study. We estimated 30-day all-cause mortality by dividing the number of patients who died within 30 days of the index date by the included cases.

Crude and adjusted ORs were estimated with 95% confidence intervals (CI) using a conditional logistic regression model. To account for the potential confounding of baseline medical conditions, we measured exposure to the drug classes listed in Supplementary Table 1. Considering the potential lag-time to diagnosis, we assessed medication use instead of diagnosis records to reflect any transient changes in health status. We also accounted for acute medical conditions which may require antipsychotic treatment such as catatonic-type schizophrenia, psychosis, alcohol intoxication, and delirium (Supplementary Table 1). Concurrent medications or comorbidities with statistically significant associations with the diagnosis of NMS in the univariate analysis were adjusted for in the model. Based on the results of the univariate analyses, use of hypnotics/anxiolytics, antiepileptics, proton pump inhibitors (PPI)/histamine-

receptor antagonists (H2RA), antibacterials, antivirals, and antiemetics; and presentation with acute conditions were included in the adjusted model (referred to as the case-crossover adjusted for time-trend and potential confounders analysis). Standardized mean differences were calculated for each covariate to assess the magnitude of difference in covariate exposure between the control and case period. Standardized mean differences less than 0.1 are generally considered to have a negligible difference.

Sensitivity analyses were conducted to test the robustness of the analysis and methodological assumptions. The time period immediately preceding an NMS diagnosis may capture the time-lag from disease onset to diagnosis [21]. Therefore, we introduced a lag-time period of various lengths (3, 7, and 14 days) to verify the efficiency of this method for addressing protopathic bias (Supplementary Figure 1A) [21]. We also varied the length of the case and reference periods (20 or 40 days) and the buffer period (0 or 365 days) (Supplementary Figures 1B, 1C, 1D, 1E). By using the hospital admission date as the index date, we assumed that NMS had developed before hospitalization in the primary analysis. However, NMS could have developed during hospitalization, therefore we extended the case period to include the dates of hospital admission and extended the reference period by the duration of hospital admission (Supplementary Figure 1F). To investigate the effect of antipsychotic monotherapy, we further conducted a subgroup analysis by excluding patients with overlapping prescriptions of multiple antipsychotics during the reference or case period.

PPV was calculated as the proportion of validated cases out of the total cases of NMS identified in the HKWC using a binomial exact method. Analyses were conducted independently by KSJL and JXZ using *R* (version 3.33; *R* core team).

3. Results

3.1. Case Validation, Incidence Risk, and 30-day Mortality

Figure 1 shows the identification and eligibility of patients in the study. There were 351 patients with an incident diagnosis of NMS between 1 January 2004 to 30 November 2017. After exclusion of patients without recent healthcare service use, 336 patients were included in the case-crossover analysis, and 312 patients were matched to at least one future case.

We retrieved all 41 cases in the HKWC; 34 met the definition of NMS and were considered valid. The PPV of an NMS diagnosis was calculated as 82.9% (95% CI, 67.9%-92.9%) and was considered satisfactory.

Based on cases identified from the cohort of antipsychotic users between 1 January 2004 to 31 December 2016, the incidence risk of NMS was 0.11% (328/297 647). Twenty patients died within 30 days of the index date resulting in a 30-day all-cause mortality of 6.0% (20/336). The majority of cases died within 30 days of the index date because of sepsis or pneumonia, and only one case had NMS as the primary cause of death (Supplementary Table 2).

3.2. Characteristics of Patients with Neuroleptic Malignant Syndrome

Characteristics of the 336 patients included in the case-crossover study as assessed during the reference and case periods, and standardized mean differences between are presented in Table 1. There were more likely to have a diagnosis of an acute medical condition when compared to the reference period. Emergency department attendance 24 hours prior to admission was recorded in the majority (72.1%) of cases. A shorter length of antipsychotic prescription was observed in the case compared to the control period.

Medication and diagnosis history before the start of the reference period are shown in Supplementary Table 3. Of the cases, 65.2% had a diagnosis of schizophrenia, bipolar disorder, or major depressive disorder. A similar proportion of patients were on stable antipsychotic treatment (i.e. single prescription with duration longer than 60 days).

3.3. Antipsychotic Exposure and Risk of Neuroleptic Malignant Syndrome

In the any antipsychotic analysis, 282 patients were concordant, meaning they had either a prescription for an antipsychotic or no prescription for an antipsychotic in both the control and reference periods, while 54 patients were discordant and contributed to the OR (Supplementary Table 4). Results of the primary and sensitivity analyses for any antipsychotic use are shown in Table 2. In the main analysis, after adjustment for potential confounders and exposure-time trend, recent use of any antipsychotic was significantly associated with the diagnosis of NMS. The magnitude and direction of estimates was largely consistent in all sensitivity analyses.

For individual antipsychotics, a statistically significant association was found for exposure to haloperidol (OR, 4.40; 95% CI 1.97-9.81) and quetiapine (OR, 4.32; 95% CI, 1.70-10.97), but not risperidone (OR, 2.00; 95% CI, 0.93-4.32) or olanzapine (OR, 1.23; 95% CI, 0.47-3.18) (Supplementary Table 5). Results of the sensitivity analyses were generally consistent with the

primary analysis except that there was no statistically significant association with an increased risk of NMS for quetiapine compared with non-exposure to quetiapine in the 14-day lag-time model.

4. Discussion

To our knowledge, this is the largest observational study of NMS in patients prescribed antipsychotics. Our results showed an increased probability of exposure to any antipsychotic during the 30 days prior to the diagnosis of NMS, compared with the earlier reference period.

4.1. Incidence Risk of NMS Compared to Previous Studies

The incidence risk of NMS of 0.11% in our study is higher when compared to contemporary reports [3, 4], and more closely aligns with the incidence reported in older literature of antipsychotic use [1]. We hypothesize that there may be several reasons for this finding. Our previous research has shown that about 50% of all antipsychotic prescriptions in the Hong Kong Hospital Authority between 2004 and 2014 were for first-generation antipsychotics, mainly haloperidol [22], which was associated with higher risk of NMS [2, 3, 5-7]. The proportion of first-generation antipsychotic prescription prevalence may be higher because CDARS captures both outpatient and inpatient prescriptions. Prescribers may select first-generation agents because of their greater affordability. Patients prescribed short-acting injectable antipsychotics for acute medical conditions, such as delirium or acute agitation, may be at higher risk of NMS. Finally, the study population (patients prescribed antipsychotics) were generally at potential risk of NMS. This is in contrast with other studies of patients with specific psychiatric diagnoses, some of whom may or may not be treated with antipsychotics [3].

4.2. Risk of Neuroleptic Malignant Syndrome

The case-crossover and exposure time-trend analyses were initially developed to investigate the association between a transient exposure and acute outcomes [18, 19]. By adopting these methods, we have controlled for potential confounders such as comorbidities and the severity of underlying mental disorders and chronic medical conditions. These factors have not been adjusted for in previous studies of NMS [3-5, 7, 23]. Additionally, certain genetic polymorphisms of the cytochrome enzyme CYP2D6, the dopamine receptor, and the serotonin receptor could affect the metabolism, and pharmacodynamics of antipsychotics, and may be associated with a higher risk of NMS [10, 24]. These factors were also controlled for by using a within-individual study design. In addition to the exposure-time trend adjustment, the lag-time analysis was proposed as another method to control for protopathic bias [25]. Similar results from lag-time sensitivity analyses suggested that the primary analysis is robust against potential protopathic bias.

In our exploratory outcome analysis, we also observed an increased risk of NMS associated with exposure to haloperidol and quetiapine during the case period. The risk of NMS associated with second-generation antipsychotic drugs is inconsistent in at least two case-control studies. In one case-control study using a psychiatric specialist register, second-generation antipsychotics were not associated with an increased risk of NMS (OR, 0.74; 95% CI, 0.38-1.44) [5]. In the other study, second-generation antipsychotics were associated with an increased risk of NMS (OR, 3.01; 95% CI, 1.34-6.82) [3]. A previous review also demonstrated that NMS was associated with exposure to second-generation antipsychotics [8]. However, due to the currently unknown mechanism of NMS, different NMS risk profiles by individual antipsychotics are less investigated and clarified. To the best of our knowledge, our study is the first to report the risk of

NMS associated with individual second-generation antipsychotics. In our study, among the selected second-generation antipsychotics, an increased risk of NMS was observed within 30 days for prescriptions of quetiapine. Although the point estimates of risk associated with risperidone and olanzapine exceeded one, showing a trend towards elevated risk, the analyses after adjustment were not significant. However, due to the limited sample size, we cannot rule out a potentially increased risk of NMS associated with risperidone or olanzapine.

Cases were more often prescribed short-acting antipsychotic injections, and had a recorded diagnosis of acute medical conditions for which short-acting antipsychotic treatment is indicated (e.g. delirium, acute alcohol intoxication, agitation [26], infection, and trauma [27]) during the 30-days before the diagnosis of NMS when compared to the reference period. These acute conditions are routinely managed with antipsychotic drugs such as short-acting injections of haloperidol and olanzapine [28]. NMS following exposure to antipsychotics in emergency, critical care, and trauma care settings has been reported [29-32]. Consistently, the result of the univariate analysis in our study indicated that presentation with acute conditions was a possible risk factor for NMS. Although the covariate acute medical condition was adjusted for in the regression model, the risk of NMS may be overestimated by the possibility of residual confounding of underlying acute conditions.

We observed a statistically significant difference between the proportion of multiple antipsychotic prescriptions during the reference period and the case period. Although it is challenging to define the prescribing behavior (polypharmacy regimens, drug switching, or the administration of short-acting antipsychotic injections in addition to maintenance antipsychotic therapy) represented by the observed overlapping prescription records, considering the increased risk of NMS associated with exposure to multiple antipsychotics has also been reported

previously [7], these results suggest the importance of monitoring for NMS when patients are exposed to multiple antipsychotics. Risk of NMS associated with polypharmacy should be further investigated.

4.3. Limitations

Our study has several limitations. Only a proportion of NMS cases were validated to the full medical record. Future studies with a larger validation sample are warranted. Due to the unclear pathophysiologic mechanisms underlying NMS, the possibility of unmeasured or residual confounding factors cannot be excluded. Since CDARS does not include data before 1993 or medical records from the private sector, some diagnosis or prescription exposures are unmeasured. However, since the costs of antipsychotic medications are fully covered in the public sector but are self-financed in the private sector, the majority of Hong Kong residents in need of antipsychotics would access medications from the public sector and would therefore be captured in CDARS. As with other pharmacoepidemiological studies, adherence to the prescribed drugs is unknown. Medication adherence could introduce misclassification bias in cases when the treatment period is long and when patients are required to take medication outside the hospital. However, most cases of NMS were diagnosed in inpatient and emergency settings (98.3%) and the observation period was relatively short. It is unlikely that medication non-adherence would have affected our results. Due to the difficulties in diagnosing NMS and the under-recognition of NMS, CDARS likely only includes more severe or obvious cases. Therefore, the representativeness of the study might be limited to patients with more severe NMS. Incidence risk and 30-day all-cause mortality of NMS might be underestimated. Moreover, changes in incidence of NMS over time and the association between the severity of NMS and risk of mortality were not assessed. Finally, the case-crossover method was selected to

361 investigate the risk of an acute event but it may not be able to capture a risk factor in a prolonged
362 time period. We adjusted for potential time varying covariates, but potential risk factors
363 including severity of chronic medical conditions, dosage, or withdrawal of treatment were not
364 measured or adjusted in this study.

5. Conclusion

Our results suggest that recent use of any antipsychotic within a one-month window is associated with NMS. Based on these findings, when prescribing antipsychotics, clinicians should consider the risk of inducing NMS in the acute phase after medication initiation, along with the risk of other adverse effects. Studies with a larger sample size are warranted to replicate these findings and to investigate the risk of NMS associated with individual antipsychotic agents.

371 Table 1. Characteristics of Cases of Neuroleptic Malignant Syndrome, Antipsychotic Exposure,
372 Other Medication Exposure, and Diagnosis of Acute Medical Conditions during the Case and
373 Reference Periods

374 Table 2. Odds Ratios of Exposure to Antipsychotics during the Case Period versus Reference
375 Period in Patients Prescribed Antipsychotics with Neuroleptic Malignant Syndrome

376 Figure 1. Flow Diagram of Neuroleptic Malignant Syndrome Case Identification and Patient
377 Inclusion in the Case-crossover and Case-crossover Adjusted for Time-Trend Analyses

378 Figure 2. Graphical Presentation of the Case-crossover and Matching of Current Cases to Future
379 Cases for Adjustment of Antipsychotic Exposure Time-trend Analyses

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Characteristic	Reference period	Case period	Standardized mean difference
	No. (%) (n=336)	No. (%) (n=336)	
Male	210 (62.5)		—
Age, mean (SD), years	49.7 (17.4)		—
Antipsychotic exposure			
Any antipsychotic	260 (77.4)	302 (89.9)	0.34
<i>First-generation</i>	146 (43.5)	181 (53.9)	0.21
Haloperidol	48 (14.3)	92 (27.4)	0.33
Chlorpromazine	45 (13.4)	47 (14.0)	0.02
Sulpiride	25 (7.4)	29 (8.6)	0.04
<i>Second-generation</i>	145 (43.2)	194 (57.7)	0.30
Quetiapine	46 (13.7)	78 (23.2)	0.25
Risperidone	45 (13.4)	63 (18.8)	0.15
Olanzapine	35 (10.4)	42 (12.5)	0.07
Clozapine	19 (5.7)	24 (7.1)	0.06
Amisulpride	17 (5.1)	19 (5.7)	0.03
Aripiprazole	6 (1.8)	8 (2.4)	0.04
Ziprasidone	1 (0.3)	3 (0.9)	0.08
<i>Dosage form</i>			
Oral tablet/capsule/liquid	252 (75.0)	288 (85.7)	0.27
Long-acting injection	38 (11.3)	44 (13.1)	0.06
Short-acting injection	12 (3.6)	46 (13.7)	0.37
<i>No. of antipsychotics prescribed</i>			
0	76 (22.6)	34 (10.1)	0.34
1	207 (61.6)	212 (63.1)	0.03
≥2	53 (15.8)	90 (26.8)	0.27
Prescription length, median (IQR), days	28 (57)	8 (25)	0.35
Concurrent medication use			
Dopaminergic drugs used in Parkinson's disease	157 (46.7)	182 (54.2)	0.15
Hypnotic/anxiolytic	115 (34.2)	178 (53.0)	0.39
Antiepileptic	83 (24.7)	114 (33.9)	0.20
Antibacterial	29 (8.6)	140 (41.7)	0.82
Antidepressant	75 (22.3)	84 (25.0)	0.06
Beta blockers	57 (17.0)	69 (20.5)	0.09
PPI/H2 blocker	48 (14.3)	76 (22.6)	0.22
Calcium channel blockers	38 (11.3)	50 (14.9)	0.11
Antidiabetic	34 (10.1)	39 (11.6)	0.05
Drugs used in hypertension and heart failure	35 (10.4)	36 (10.7)	0.01
Antiplatelet	27 (8.0)	36 (10.7)	0.09
Antiemetic	21 (6.3)	33 (9.8)	0.13
Anti-manic	21 (6.3)	25 (7.4)	0.05
Lipid lowering drugs	22 (6.5)	24 (7.1)	0.02
Antiviral drugs	5 (1.5)	26 (7.7)	0.30
Oral corticosteroid	9 (2.7)	18 (5.4)	0.14
NSAIDS	9 (2.7)	16 (4.8)	0.11
Loop diuretics	9 (2.7)	10 (3.0)	0.02
Peripheral vasodilator	7 (2.1)	7 (2.1)	<0.001
Nitrate	6 (1.8)	7 (2.1)	0.02
Other diuretics	4 (1.2)	8 (2.4)	0.09
Antifungal	1 (0.3)	1 (0.3)	<0.001
Digoxin	1 (0.3)	1 (0.3)	<0.001
Antiarrhythmic	0 (0.0)	1 (0.3)	0.08
Acute medical conditions	3 (0.9)	17 (5.1)	0.25
Unspecified psychosis	2 (0.6)	14 (4.2)	0.30

Delirium	0 (0.0)	2 (0.6)	0.11
Acute alcoholic intoxication	0 (0.0)	1 (0.3)	0.08
Catatonic type schizophrenia	1 (0.3)	0 (0.0)	0.08

Abbreviations: SD, standard deviation; IQR, interquartile range; H₂, histamine-2 receptor blockers; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitors.

Table 1. Characteristics of Cases of Neuroleptic Malignant Syndrome, Antipsychotic Exposure, Other Medication Exposure, and Diagnosis of Acute Medical Conditions during the Case and Reference Periods

	OR (95% CI)		
	<i>Case-crossover</i>	<i>Case-crossover adjusted for time-trend</i>	<i>Case-crossover adjusted for time-trend and potential confounders *</i>
	(N=336)	(N=312)	(N=312)
Main analysis	8.00 (3.42, 18.69)	5.88 (2.46, 14.04)	4.77 (1.95, 11.66)
Sensitivity analyses			
<i>Lag-time period added</i>			
3-days	6.00 (2.70, 13.36)	4.46 (1.96, 10.17)	3.57 (1.53, 8.34)
7-days	4.22 (2.04, 8.73)	3.17 (1.49, 6.74)	3.18 (1.48, 6.84)
14-days	4.38 (2.03, 9.43)	3.29 (1.49, 7.27)	3.19 (1.43, 7.13)
<i>Reference and case period length</i>			
20-days	5.44 (2.68, 11.08)	4.14 (1.98, 8.66)	3.35 (1.58, 7.13)
40-days	8.33 (3.57, 19.43)	5.98 (2.51, 14.26)	5.10 (2.09, 12.45)
Extended period	8.83 (3.80, 20.55)	6.14 (2.58, 14.61)	4.04 (1.60, 10.18)
<i>Buffer period</i>			
Removal buffer period	6.40 (2.49, 16.43)	5.09 (1.94, 13.38)	4.03 (1.51, 10.73)
365-day buffer period	10.56 (5.33, 20.91)	5.75 (2.83, 11.67)	4.77 (1.95, 11.66)
<i>Monotherapy subgroup</i>	5.17 (2.16, 12.38)	3.63 (1.46, 9.00)	4.77 (1.95, 11.66)

* Adjusted for concurrent use of hypnotic/anxiolytic, antiepileptic, PPI/H₂ blocker, antibacterial, antiviral, and antiemetic drugs, and diagnosis of acute medical conditions.

In lag-time analyses, lag-time periods were added between the index date and the end of the case period. In the 20-day and 40-day reference and case period analysis, the length of each period was changed to its respective value; in the removal and 365-day buffer period analysis, the 60-day buffer period was removed and extended to 365-days; in the extended observation period analysis, the case period of patients with NMS diagnosed in inpatient setting started from 30 days before the index admission date and ended on the discharge date. The reference period was extended accordingly to equal the duration of the case period; in the monotherapy subgroup analysis, only patients on monotherapy during the reference and case period were included.

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 2. Odds Ratios of Exposure to Antipsychotics during the Case Period versus Reference Period in Patients Prescribed Antipsychotics with Neuroleptic Malignant Syndrome

Abbreviations: CDARS, Clinical Data Analysis and Reporting System; NMS, neuroleptic malignant syndrome.

Figure 1. Flow Diagram of Cohort Identification, and Patient Inclusion in the Case-crossover Analysis and the Cohort Study Analysis

408

409

410
 411 (A) Case-crossover analysis: Index date of current case is set as the first diagnosis of NMS. Case period and
 412 reference period are two 30-day period sampled from the same case. Buffer period is a 60-day period set between
 413 case period and reference period.
 414
 415 (B) Case-crossover adjusted for exposure time-trend analysis: Each current case is matched with at least one future
 416 case. Future cases controls are sampled from cases with an index date after the index date of the current case (i.e.
 417 NMS diagnosis date of the current case). Future cases are used to estimate the prevalence and time-trend of
 418 antipsychotic exposure in the sample of cases.
 419

420 Abbreviations: NMS, neuroleptic malignant syndrome.
 421

422 **Figure 2. Graphical Presentation of the Case-crossover and Matching of Current Cases to**
 423 **Future Cases for Adjustment of Antipsychotic Exposure Time-trend Analyses**
 424

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432 **Author Contributions**

433 KSJL, ICKW and EWC had the original idea for the study and contributed to the development of
434 the idea and study design. KSJL and LL conducted the literature search. KSJL wrote the first
435 draft of the study protocol. KSJL retrieved data and undertook the analysis. JZ independently
436 cross-checked all the analyses and results. KSJL, JZ, JEB, ICKW, and EWC contributed to
437 interpretation of the analyses. KSJL wrote the first draft of the paper. KSJL, JZ, ICKW, JEB, and
438 EWC critically reviewed the results and the manuscript. FMCB, WCC, and DJC reviewed the
439 data, the presentation of the paper and provided clinical input. KSJL, ICKW and EWC provided
440 oversight to all aspects of this project. KSJL and EWC are the guarantors. All authors had full
441 access to all the data in the study and take responsibility for the integrity of the data and the
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443

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449 Conflict of interest

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466 **Data Sharing**

467 No additional data available.

468

469 Table 1. Characteristics of Cases of Neuroleptic Malignant Syndrome, Antipsychotic Exposure,
 470 Other Medication Exposure, and Diagnosis of Acute Medical Conditions during the Case and
 471 Reference Periods

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479 **Supplementary materials**

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 481 Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Codes Used in This Study

482 Supplementary Table 2. Cause of Death and Characteristics, Antipsychotic Exposure, Other
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487 Supplementary Table 4. Summary of Concordant and Discordant Exposures for the 336 Cases in
 488 the Case-crossover Analysis

489 Supplementary Table 5. Odds Ratios of Neuroleptic Malignant Syndrome by Select Individual
 490 Antipsychotic

491 Supplementary Figure 1. Graphical Presentation of the Study Design of Sensitivity Analyses

492 **References**

- 493 1. Dickey W. The neuroleptic malignant syndrome. *Prog Neurobiol.* 1991;36(5):425-36.
- 494 2. Stubner S, Rustenbeck E, Grohmann R, Wagner G, Engel R, Neundorfer G, et al. Severe and
495 uncommon involuntary movement disorders due to psychotropic drugs. *Pharmacopsychiatry.* 2004;37
496 Suppl 1:S54-64.
- 497 3. Nielsen RE, Wallenstein Jensen SO, Nielsen J. Neuroleptic malignant syndrome-an 11-year
498 longitudinal case-control study. *Can J Psychiatry.* 2012;57(8):512-8.
- 499 4. Chen Y, Guo JJ, Steinbuch M, Buckley PF, Patel NC. Risk of neuroleptic malignant syndrome in
500 patients with bipolar disorder: a retrospective, population-based case-control study. *Int J Psychiatry*
501 *Med.* 2009;39(4):439-50.
- 502 5. Su YP, Chang CK, Hayes RD, Harrison S, Lee W, Broadbent M, et al. Retrospective chart review on
503 exposure to psychotropic medications associated with neuroleptic malignant syndrome. *Acta Psychiatr*
504 *Scand.* 2014;130(1):52-60.
- 505 6. Ciranni MA, Kearney TE, Olson KR. Comparing acute toxicity of first- and second-generation
506 antipsychotic drugs: a 10-year, retrospective cohort study. *J Clin Psychiatry.* 2009;70(1):122-9.
- 507 7. Viejo LF, Morales V, Punal P, Perez JL, Sancho RA. Risk factors in neuroleptic malignant
508 syndrome. A case-control study. *Acta Psychiatr Scand.* 2003;107(1):45-9.
- 509 8. Belvederi Murri M, Guaglianone A, Bugliani M, Calcagno P, Respino M, Serafini G, et al. Second-
510 generation antipsychotics and neuroleptic malignant syndrome: systematic review and case report
511 analysis. *Drugs R D.* 2015;15(1):45-62.
- 512 9. Gurrera RJ. A systematic review of sex and age factors in neuroleptic malignant syndrome
513 diagnosis frequency. *Acta Psychiatr Scand.* 2017;135(5):398-408.
- 514 10. Kawanishi C. Genetic predisposition to neuroleptic malignant syndrome : implications for
515 antipsychotic therapy. *Am J Pharmacogenomics.* 2003;3(2):89-95.
- 516 11. Maclure M, Fireman B, Nelson JC, Hua W, Shoaibi A, Paredes A, et al. When should case-only
517 designs be used for safety monitoring of medical products? *Pharmacoepidemiol Drug Saf.* 2012;21 Suppl
518 1:50-61.
- 519 12. Chan EW, Lau WC, Leung WK, Mok MT, He Y, Tong TS, et al. Prevention of dabigatran-related
520 gastrointestinal bleeding with gastroprotective agents: a population-based study. *Gastroenterology.*
521 2015;149(3):586-95 e3.
- 522 13. Man KK, Chan EW, Coghill D, Douglas I, Ip P, Leung LP, et al. Methylphenidate and the risk of
523 trauma. *Pediatrics.* 2015;135(1):40-8.
- 524 14. Wong AY, Root A, Douglas IJ, Chui CS, Chan EW, Ghebremichael-Weldeselassie Y, et al.
525 Cardiovascular outcomes associated with use of clarithromycin: population based study. *BMJ.*
526 2016;352:h6926.
- 527 15. The Government of the Hong Kong Special Administrative Region. LCQ13: Resource allocation of
528 Hospital Authority 2017 [Available from:
529 <https://www.info.gov.hk/gia/general/201712/13/P2017121300666.htm>].
- 530 16. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th ed.,
531 Text Revision): American Psychiatric Pub; 2000.
- 532 17. Lao KSJ, Wong AYS, Wong ICK, Besag FMC, Chang WC, Lee EHM, et al. Mortality risk associated
533 with haloperidol use compared with other antipsychotics: an 11-year population-based propensity-
534 score-matched cohort study. *CNS Drugs.* 2020;34(2):197-206.
- 535 18. Maclure M. The case-crossover design: a method for studying transient effects on the risk of
536 acute events. *Am J Epidemiol.* 1991;133(2):144-53.

19. Wang S, Linkletter C, Maclure M, Dore D, Mor V, Buka S, et al. Future cases as present controls to adjust for exposure trend bias in case-only studies. *Epidemiology*. 2011;22(4):568-74.
20. Wang S, Linkletter C, Dore D, Mor V, Buka S, Maclure M. Age, antipsychotics, and the risk of ischemic stroke in the Veterans Health Administration. *Stroke*. 2012;43(1):28-31.
21. Wang MT, Tsai CL, Lin CW, Yeh CB, Wang YH, Lin HL. Association between antipsychotic agents and risk of acute respiratory failure in patients with chronic obstructive pulmonary disease. *JAMA psychiatry*. 2017;74(3):252-60.
22. Lao KSJ, Tam AWY, Wong ICK, Besag FMC, Man KKC, Chui CSL, et al. Prescribing trends and indications of antipsychotic medication in Hong Kong from 2004 to 2014: General and vulnerable patient groups. *Pharmacoepidemiol Drug Saf*. 2017;26(11):1387-94.
23. Berardi D, Amore M, Keck PE, Jr., Troia M, Dell'Atti M. Clinical and pharmacologic risk factors for neuroleptic malignant syndrome: a case-control study. *Biol Psychiatry*. 1998;44(8):748-54.
24. Butwicka A, Krystyna S, Retka W, Wolanczyk T. Neuroleptic malignant syndrome in an adolescent with CYP2D6 deficiency. *Eur J Pediatr*. 2014;173(12):1639-42.
25. Tamim H, Monfared AA, LeLorier J. Application of lag-time into exposure definitions to control for protopathic bias. *Pharmacoepidemiol Drug Saf*. 2007;16(3):250-8.
26. Knott JC, Bennett D, Rawet J, Taylor DM. Epidemiology of unarmed threats in the emergency department. *Emerg Med Australas*. 2005;17(4):351-8.
27. Battaglia J. Pharmacological management of acute agitation. *Drugs*. 2005;65(9):1207-22.
28. Baker SN. Management of acute agitation in the emergency department. *Adv Emerg Nurs J*. 2012;34(4):306-18; quiz 19-20.
29. Bellamy CJ, Kane-Gill SL, Falcione BA, Seybert AL. Neuroleptic malignant syndrome in traumatic brain injury patients treated with haloperidol. *J Trauma*. 2009;66(3):954-8.
30. Dixit D, Shrestha P, Adelman M. Neuroleptic malignant syndrome associated with haloperidol use in critical care setting: should haloperidol still be considered the drug of choice for the management of delirium in the critical care setting? *BMJ Case Rep*. 2013;2013.
31. Morita T, Shishido H, Tei Y, Inoue S, Nagayama K. Neuroleptic malignant syndrome after haloperidol and fentanyl infusion in a patient with cancer with severe mineral imbalance. *J Palliat Med*. 2004;7(6):861-4.
32. Rock W, Elias M, Lev A, Saliba WR. Haloperidol-induced neuroleptic malignant syndrome complicated by hyperosmolar hyperglycemic state. *Am J Emerg Med*. 2009;27(8):1018 e1-3.

1 **Supplementary Material**

2 **Antipsychotics and risk of neuroleptic malignant syndrome: population-based**
3 **cohort and case-crossover study**

4 Kim SJ Lao, PhD^{1,2}; Jiayi Zhao, MSc¹; Lam Lam, MSocSc¹; Joseph Edgar Blais,
5 BScPharm¹; Ian CK Wong, PhD^{1, 3}; Frank MC Besag, FRCP^{3, 4, 5}; Wing Chung
6 Chang, FHKCPsych^{6, 7}; David J Castle, MD^{8, 9}; Esther W Chan, PhD¹

7
8 ¹Centre for Safe Medication Practice and Research, Department of Pharmacology and
9 Pharmacy, The University of Hong Kong, Hong Kong SAR, China

10 ²Research Department of Practice and Policy, UCL School of Pharmacy, London, UK

11 ³East London NHS Foundation Trust, Bedfordshire, UK

12 ⁴Institute of Psychiatry, Psychology and Neuroscience, London, UK

13 ⁵Department of Psychiatry, Li Ka Shing Faculty of Medicine, The University of Hong
14 Kong, Hong Kong SAR, China

15 ⁶State Key Laboratory of Brain & Cognitive Sciences, The University of Hong Kong,
16 Hong Kong SAR, China

17 ⁷St. Vincent's Hospital, Melbourne, Australia

18 ⁸Department of Psychiatry, University of Melbourne, Melbourne, Australia

19

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30 336 Cases in the Case-crossover Analysis

31 Supplementary Table 5. Odds Ratios of Neuroleptic Malignant Syndrome by Select
32 Individual Antipsychotic

33 Supplementary Figure 1. Graphical Presentation of the Study Design of Sensitivity
34 Analyses

BNF	Description
Antipsychotic	
4.2.1	Antipsychotic drugs
4.2.2	Antipsychotic depot injections
Antidepressant	
4.3.1	Tricyclic and related antidepressant drugs
4.3.2	Monoamine-oxidase inhibitors
4.3.3	Selective serotonin re-uptake inhibitors
4.3.4	Other antidepressant drugs
Hypnotic and anxiolytics	
4.1.1	Hypnotics
4.1.2	Anxiolytics
4.1.3	Barbiturates
Antiepileptic	
4.8.1	Control of the epilepsies
4.8.2	Drugs used in status epilepticus
4.8.3	Febrile convulsions
Anti-manic	
4.2.3	Drugs used for mania and hypomania
Antidiabetic	
6.1.1	Insulins
6.1.2	Antidiabetic drugs
6.1.3	Diabetic ketoacidosis
6.1.4	Treatment of hypoglycemia
6.1.5	Treatment of diabetic nephropathy and neuropathy
6.1.6	Diagnostic and monitoring devices for diabetes mellitus
Drug used in hypertension and heart failure	
2.5.1	Vasodilator antihypertensive drugs
2.5.2	Centrally acting antihypertensive drugs
2.5.3	Adrenergic neurone blocking drugs
2.5.4	Alpha-adrenoceptor blocking drugs
2.5.5	Drugs affecting the renin-angiotensin system
Antiplatelet	
2.9	Antiplatelet drugs
Calcium channel blocker	
2.6.2	Calcium channel blockers

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BNF	Description
Diuretic	
2.2.1	Thiazides and related diuretics
2.2.2	Loop diuretics
2.2.3	Potassium-sparing diuretics and aldosterone antagonists
2.2.4	Potassium-sparing diuretics with other diuretics
2.2.5	Osmotic diuretics
2.2.6	Mercurial diuretics
2.2.7	Carbonic anhydrase inhibitors
2.2.8	Diuretics with potassium
Beta blocker	
2.4	Beta-adrenoceptor blocking drugs
Antiarrhythmic	
2.3.2	Drugs for arrhythmias
Digoxin	
2.1.1	Cardiac glycosides
Nitrates	
2.6.1	Nitrates
Peripheral vasodilator	
2.6.4	Peripheral vasodilators and related drugs
Lipid regulating drugs	
2.12	Lipid regulating drugs
Oral corticosteroid	
3.2	Corticosteroids
6.3	Corticosteroids
Non-steroidal anti-inflammatory drugs	
10.1.1	Non-steroidal anti-inflammatory drugs
Proton pump inhibitors	
1.3.5	Proton pump inhibitors
Histamine-2 receptor blocker	
1.3.1	H2-receptor antagonists

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BNF	Description
Antibacterial	
5.1.1	Penicillins
5.1.2	Cephalosporins, carbapenems, and other beta-lactams
5.1.3	Tetracyclines
5.1.4	Aminoglycosides
5.1.5	Macrolides
5.1.6	Clindamycin
5.1.7	Some other antibacterials
5.1.8	Sulfonamides and trimethoprim
5.1.9	Antituberculosis drugs
5.1.10	Antileprotic drugs
5.1.11	Metronidazole and tinidazole
5.1.12	Quinolones
5.1.13	Urinary-tract infections
Antifungal	
5.2.1	Triazole antifungals
5.2.2	Imidazole antifungals
5.2.3	Polyene antifungals
5.2.4	Echinocandin antifungals
5.2.5	Other antifungals
Antiviral	
5.3.1	HIV infection
5.3.2	Herpesvirus infections
5.3.3	Viral hepatitis
5.3.4	Influenza
5.3.5	Respiratory syncytial virus
Dopaminergic drugs used in Parkinson's disease	
4.9.1	Dopaminergic drugs used in Parkinson's disease
Antiemetic (drug name)	
Domperidone	
Prochlorperazine	
Promethazine	

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40

ICD-9-CM	Description
Schizophrenia	
295	Schizophrenic disorders
Bipolar disorder	
296.0	Bipolar I disorder, single manic episode
296.4	Bipolar I disorder, most recent episode (or current) manic
296.5	Bipolar I disorder, most recent episode (or current) depressed
296.6	Bipolar I disorder, most recent episode (or current) mixed
296.7	Bipolar I disorder, most recent episode (or current) unspecified
296.8	Other and unspecified bipolar disorders
Other psychoses	
296.1	Manic disorder recurrent episode
296.9	Other and unspecified episodic mood disorder
298	Other nonorganic psychoses
299	Pervasive developmental disorders
Major depressive disorder	
296.2	Major depressive disorder single episode
296.3	Major depressive disorder recurrent episode
Dementia	
290	Dementias
Anxiety disorder	
300	Anxiety, dissociative and somatoform disorders
Delusional disorder	
297	Delusional disorders
Personality disorder	
301	Personality disorders
Post-traumatic stress disorder	
309.81	Posttraumatic stress disorder
Sleep disorder	
292.85	Drug induced sleep disorders
307.40	Nonorganic sleep disorder, unspecified
327	Organic sleep disorders
780.57	Unspecified sleep apnea

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ICD-9-CM	Description
Acute conditions	
312	Disturbance of conduct not elsewhere classified
307.9	Other and unspecified special symptoms or syndromes, not elsewhere classified
295.2	Catatonic type schizophrenia
298.9	Unspecified psychosis (including confusion)
303.0	Alcohol dependence syndrome
293.0	Delirium due to conditions classified elsewhere
293.1	Subacute delirium
294.11	Dementia in conditions classified elsewhere with behavioral disturbance
Suicide	
E950	Suicide and self-inflicted poisoning by solid or liquid substances
E951	Suicide and self-inflicted poisoning by gases in domestic use
E952	Suicide and self-inflicted poisoning by other gases and vapors
E953	Suicide and self-inflicted injury by hanging strangulation and suffocation
E954	Suicide and self-inflicted injury by submersion [drowning]
E955	Suicide and self-inflicted injury by firearms air guns and explosives
E956	Suicide and self-inflicted injury by cutting and piercing
E957	Suicide and self-inflicted injuries by jumping from high place
E958	Suicide and self-inflicted injury by other and unspecified means
E959	Late effects of self-inflicted injury

Supplementary Table 1. British National Formulary (BNF) and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Codes Used in This Study

Demographic characteristic	Value (n=20)	
Male, n (%)	10 (50.0)	
Age, mean (SD), years	59.6 (20.7)	
≤40, n (%)	4 (20.0)	
41-60, n (%)	5 (25.0)	
≥61, n (%)	11 (55.0)	
Main cause of death	ICD-10 code	No. (%)
Pneumonia, unspecified	J189	8 (40.0)
Sepsis, unspecified	A419	4 (20.0)
Neuroleptic malignant syndrome	G210	1 (5.0)
Cerebrovascular accident, unspecified	I679	1 (5.0)
Furuncle/carbuncle, not otherwise specified	L029	1 (5.0)
Poison, other opioids	T402	1 (5.0)
Missing value	NA	3 (15.0)
Medication characteristics	Reference period	Case period
	No. (%)	No. (%)
	(n=20)	(n=20)
Antipsychotic exposure		
Any antipsychotic	15 (75.0)	16 (80.0)
<i>First-generation</i>	10 (50.0)	11 (55.0)
Haloperidol	3 (15.0)	5 (25.0)
Chlorpromazine	3 (15.0)	3 (15.0)
Sulpiride	1 (5.0)	2 (10.0)
<i>Second-generation</i>	6 (30.0)	8 (40.0)
Quetiapine	3 (15.0)	3 (15.0)
Risperidone	3 (15.0)	5 (25.0)
Olanzapine	0 (0.0)	0 (0.0)
Clozapine	0 (0.0)	0 (0.0)
Amisulpride	1 (5.0)	1 (5.0)
Aripiprazole	0 (0.0)	0 (0.0)
Ziprasidone	0 (0.0)	0 (0.0)
<i>Dosage form</i>		
Oral tablet/capsule/liquid	15 (75.0)	16 (80.0)
Long-acting injection	1 (5.0)	1 (5.0)
Short-acting injection	0 (0.0)	2 (10.0)
<i>No. of antipsychotics prescribed</i>		
0	8 (40.0)	6 (30.0)

1	10 (50.0)	9 (45.0)
≥2	2 (10.0)	5 (25.5)
Concurrent medication use		
Dopaminergic drugs used in Parkinson's disease	7 (35.0)	11 (55.0)
Hypnotic/anxiolytic	7 (35.0)	10 (50.0)
Antiepileptic	1 (5.0)	1 (5.0)
Antibacterial	4 (20.0)	12 (60.0)
Antiemetic	2 (10.0)	3 (15.0)
Anti-manic	0 (0.0)	0 (0.0)
Antiviral drugs	0 (0.0)	1 (0.0)
Antifungal	0 (0.0)	0 (0.0)
Acute medical conditions	0 (0.0)	0 (0.0)

Abbreviation: SD, standard deviation. Diagnoses and medications were assessed from the start of data availability (1 January 2003) until day 121 before the index date.

Supplementary Table 2. Cause of Death and Characteristics, Antipsychotic Exposure, Other Medication Exposure, and Diagnosis of Acute Medical Conditions of the 20 Cases Who Died Within 30 Days of NMS Diagnosis

Characteristic	No. (%)	
	(n = 336)	
Male	210	(62.5)
Age, mean (SD), years	49.7	(17.4)
<i>Diagnosis history</i>		
Mental health condition	291	(86.6)
Schizophrenia, bipolar disorder or major depressive disorder	219	(65.2)
Schizophrenia	177	(52.7)
Bipolar disorder	41	(12.2)
Anxiety disorder	34	(10.1)
Major depressive disorder	35	(10.4)
Acute conditions	32	(9.5)
Suicide attempt	30	(8.9)
Personality disorder	17	(5.1)
Delusional disorder	10	(3.0)
Dementia	8	(2.4)
Sleep disorder	3	(0.9)
Post-traumatic stress disorder	0	(0)
<i>Medication history</i>		
Antipsychotic	276	(82.1)
Stable antipsychotic (>60 days)	207	(61.6)
Hypnotic/anxiolytic	216	(64.3)
Antiemetic	163	(48.5)
Antidepressant	120	(35.7)
Antiepileptic	114	(33.9)
Dopaminergic drugs used in Parkinson's disease	20	(6.0)

57 Abbreviation: SD, standard deviation. Diagnoses and medications were assessed from the start of data
58 availability (1 January 2003) until day 121 before the index date.

59

60 **Supplementary Table 3. Characteristics of the 336 cases of Neuroleptic**
61 **Malignant Syndrome included in the Case-crossover Analysis as Assessed Before**
62 **the Reference Period**

Medication	No. of concordant patients	No. of discordant patients		
		Total No.	No. of exposures in reference period	No. of exposures in case period
Any antipsychotic	282	54	6	48
First generation antipsychotic	281	55	10	45
Haloperidol	272	64	10	54
Chlorpromazine	332	4	1	3
Sulpiride	316	20	8	12
Second generation antipsychotic	269	67	9	58
Quetiapine	290	46	7	39
Risperidone	294	42	12	30
Olanzapine	313	23	8	15
Clozapine	331	5	0	5
Amisulpride	326	10	4	6
Aripiprazole	330	6	2	4
Ziprasidone	332	4	1	3

Concordant patients have same exposure in both the reference and case period (either a prescription for the exposure in both periods or no prescription for the exposure in both periods).

Discordant patients crossover exposure between the reference and control period (either exposed in the reference period and not exposed in the case period or vice versa).

Supplementary Table 4. Summary of Concordant and Discordant Exposures for the 336 Cases in the Case-crossover Analysis

		OR (95% CI)		
<i>Select individual antipsychotic subgroup</i>		<i>Crude</i>	<i>Exposure-Time Trend Adjusted</i>	<i>Concurrent Medication and Exposure-Time Trend Adjusted*</i>
		(N=336)	(N=312)	(N=312)
	Haloperidol	5.40 (2.75, 10.60)	5.72 (2.61, 12.50)	4.40 (1.97, 9.81)
	Quetiapine	5.57 (2.49, 12.46)	4.74 (1.93, 11.61)	4.32 (1.70, 10.97)
	Risperidone	2.50 (1.28, 4.88)	2.19 (1.05, 4.58)	2.00 (0.93, 4.32)
	Olanzapine	1.88 (0.80, 4.42)	1.49 (0.60, 3.68)	1.23 (0.47, 3.18)
<i>Sensitivity analysis</i>				
<i>3-day lag time</i>	Haloperidol	5.22 (2.56, 10.66)	5.80 (2.52, 13.32)	4.46 (1.91, 10.42)
	Quetiapine	5.00 (2.22, 11.26)	4.34 (1.76, 10.70)	3.45 (1.35, 8.77)
	Risperidone	2.17 (1.09, 4.29)	1.85 (0.87, 3.94)	1.73 (0.78, 3.83)
	Olanzapine	1.17 (0.39, 3.47)	1.20 (0.44, 3.27)	0.91 (0.31, 2.64)
<i>7-day lag time</i>	Haloperidol	3.73 (1.92, 7.25)	4.54 (2.04, 10.09)	4.54 (2.03, 10.14)
	Quetiapine	4.43 (1.95, 10.06)	3.91 (1.57, 9.73)	3.64 (1.45, 9.15)
	Risperidone	1.92 (0.95, 3.85)	1.62 (0.75, 3.50)	1.47 (0.67, 3.20)
	Olanzapine	1.43 (0.54, 3.75)	1.06 (0.38, 2.95)	0.90 (0.32, 2.55)
<i>14-day lag time</i>	Haloperidol	3.67 (1.76, 7.66)	3.51 (1.56, 7.93)	4.55 (2.04, 10.17)
	Quetiapine	2.89 (1.35, 6.17)	2.56 (1.11, 5.88)	2.31 (0.99, 5.39)
	Risperidone	2.00 (0.97, 4.12)	1.88 (0.82, 4.29)	1.87 (0.81, 4.32)
	Olanzapine	1.17 (0.39, 3.47)	0.82 (0.26, 2.63)	0.64 (0.19, 2.14)
<i>20-day observation period</i>	Haloperidol	4.90 (2.48, 9.67)	4.88 (2.29, 10.37)	3.82 (1.75, 8.32)
	Quetiapine	3.18 (1.62, 6.27)	2.52 (1.19, 5.33)	2.26 (1.04, 4.94)
	Risperidone	2.00 (1.03, 3.89)	1.82 (0.88, 3.77)	1.73 (0.81, 3.70)
	Olanzapine	1.50 (0.67, 3.34)	1.22 (0.52, 2.87)	1.11 (0.46, 2.68)
<i>40-day observation period</i>	Haloperidol	7.50 (3.59, 15.68)	8.25 (3.44, 19.78)	7.74 (3.14, 19.05)
	Quetiapine	4.75 (2.22, 10.18)	3.93 (1.69, 9.15)	3.31 (1.38, 7.95)
	Risperidone	2.58 (1.33, 5.03)	2.45 (1.15, 5.23)	2.31 (1.05, 5.11)
	Olanzapine	2.29 (0.94, 5.56)	1.75 (0.69, 4.47)	1.52 (0.57, 4.02)
<i>Removal buffer period</i>	Haloperidol	3.54 (1.91, 6.55)	3.37 (1.70, 6.67)	2.78 (1.38, 5.60)
	Quetiapine	7.33 (2.20, 24.5)	8.72 (2.00, 38.02)	7.40 (1.66, 32.92)
	Risperidone	2.57 (1.07, 6.16)	2.71 (1.04, 7.05)	2.15 (0.80, 5.78)
	Olanzapine	2.17 (0.82, 5.70)	1.88 (0.68, 5.18)	1.50 (0.54, 4.22)
<i>365-day buffer period</i>	Haloperidol	9.71 (4.46, 21.15)	6.94 (3.06, 15.72)	5.13 (2.20, 11.96)
	Quetiapine	12.75 (4.61, 35.28)	8.94 (2.71, 29.47)	7.52 (2.17, 26.07)
	Risperidone	3.67 (1.94, 6.94)	2.06 (1.01, 4.19)	1.86 (0.88, 3.95)
	Olanzapine	3.43 (1.48, 7.96)	1.70 (0.69, 4.19)	1.60 (0.62, 4.18)
<i>Extended observation period</i>	Haloperidol	8.75 (4.21, 18.18)	9.03 (3.79, 21.52)	5.50 (2.17, 13.92)
	Quetiapine	6.63 (3.15, 13.93)	5.03 (2.19, 11.54)	3.92 (1.53, 10.04)
	Risperidone	3.08 (1.61, 5.91)	2.65 (1.29, 5.43)	2.53 (1.07, 6.00)
	Olanzapine	2.57 (1.07, 6.16)	2.07 (0.83, 5.20)	1.55 (0.48, 4.99)
<i>Monootherapy subgroup</i>	Haloperidol	4.00 (1.34, 11.97)	4.25 (1.19, 15.22)	3.36 (0.91, 12.45)
	Quetiapine	7.33 (2.20, 24.50)	8.15 (1.85, 35.93)	7.64 (1.67, 34.87)
	Risperidone	2.29 (0.94, 5.56)	1.82 (0.71, 4.66)	1.57 (0.59, 4.21)
	Olanzapine	0.33 (0.04, 3.21)	0.28 (0.03, 2.74)	0.23 (0.02, 2.56)

* Adjusted for concurrent use of hypnotic/anxiolytic, antiepileptic, PPI/H₂ blocker, antibacterial, antiviral, and antiemetic drugs, and diagnosis of acute medical conditions.

Abbreviations: CI, confidence interval; OR, odds ratio.

Supplementary Table 5. Odds Ratios of Neuroleptic Malignant Syndrome by Select Individual Antipsychotic

(A) Lag-time analyses: with lag-time period in length of 3, 7, or 14 days between index date and case period.

(B) 20-day reference/case period analysis: with reference and case period in length of 20 days.

(C) 40-day reference/case period analysis: with reference and case period in length of 40 days.

Supplementary Figure 1 (A, B, C). Graphical Presentation of the Study Design of Sensitivity Analyses

Supplementary Figure 1 (D, E, F). Graphical Presentation of the Study Design of Sensitivity Analyses