Title page

Study title:

Mortality risk associated with haloperidol use compared with other antipsychotics: an 11-year population-based propensity-score-matched cohort study

Running heading:

Risk of mortality associated with haloperidol compared with other antipsychotics

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Abstract

Background: Haloperidol remains a frequently prescribed first-generation antipsychotic. However, the mortality risk by all-cause, cardiovascular disease (CVD), and pneumonia associated with haloperidol compared with other antipsychotics is unknown.

Objective: This study investigated the mortality risk associated with long-term haloperidol treatment compared with other antipsychotics.

Methods: We identified incident antipsychotic users from 2004 to 2014 in the Clinical Data Analysis and Reporting System (CDARS), a population-based clinical database managed by the Hong Kong Hospital Authority. Haloperidol users and other antipsychotic users (risperidone, quetiapine, olanzapine, chlorpromazine, aripiprazole, sulpiride, amisulpride or trifluoperazine) were matched on the propensity score. Hazard ratios (HR) for all-cause mortality and death due to CVD and pneumonia were estimated with 95% confidence intervals (95% CI) using a Cox proportional hazards model.

Results: 136 593 antipsychotic users were included. During a mean follow-up of 3.2 years, the incidence of all-cause mortality ranged from 186.8/1000 person-years for haloperidol, to 10.4/1000 person-years for trifluoperazine. Compared with haloperidol, a lower risk of all-cause mortality was associated with non-haloperidol antipsychotics, with HRs ranging from 0.68 (95% CI 0.64 to 0.72 [chlorpromazine]) to 0.43 (95% CI 0.36 to 0.53 [trifluoperazine]). Risperidone,

quetiapine, sulpiride, chlorpromazine, aripiprazole, and trifluoperazine were associated with a significantly lower risk of pneumonia-related mortality. A significantly lower risk of CVD mortality was observed for risperidone, sulpiride, chlorpromazine and quetiapine.

Conclusion: Haloperidol was associated with increased overall mortality when compared with other antipsychotics in long-term follow-up. Treatment with haloperidol should be carefully considered, especially in older patients, and patients at risk of CVD or pneumonia, since non-haloperidol agents appear to be associated with lower risk of death.

Key points:

In this population-based cohort study, the use of haloperidol was associated with an increased risk of death compared with several other commonly prescribed antipsychotics.

The use of haloperidol was associated with an increased risk of death due to cardiovascular disease or pneumonia when compared with risperidone, quetiapine, sulpiride, and chlorpromazine. While haloperidol remains commonly used in different clinical contexts, our findings broaden our understanding of the potential risks involved when compared to other antipsychotics and can guide antipsychotic prescribing decisions.

Main text

1. Introduction

Haloperidol, initially approved by the United States Food and Drug Administration in 1967, is the most commonly used first-generation antipsychotic in Asia , Europe [1] and America [2]. Studies suggest that haloperidol is associated with an increased risk of mortality compared with other first-generation antipsychotics [3, 4]. The Finnish 11-year follow-up study of patients with schizophrenia (FIN11 study) reported that haloperidol was associated with a 37% increase in all-cause mortality risk compared with perphenazine [3]. A more recent cohort study using Taiwan's National Health Insurance Research Database reported a 118% increased mortality risk in haloperidol users versus chlorpromazine users, regardless of indication [4].

Second-generation antipsychotics represent 40%-80% of all antipsychotic prescriptions in North America and Hong Kong [1, 5, 6] and were prescribed to over 70% of patients receiving antipsychotics in the United Kingdom [7]. Although several studies were conducted to compare the risk of mortality among haloperidol users with other antipsychotic users, these studies were limited by potential confounding [3, 4, 8]. Notably, the health characteristics of patients on haloperidol might be systematically different from patients on other antipsychotics. In the Taiwanese cohort study, haloperidol users were older, had more severe mental illness and were frailer with regard to somatic comorbidities, compared to chlorpromazine users [4]. Particularly, a potentially important confounder, the status of terminal illness was not accounted for in most of the previous studies [3, 4, 9-11], potentially leading to biased estimates.

Besides all-cause mortality, characterization of the specific cause of death can inform clinical practice. A substantial proportion of deaths in those taking antipsychotics could be attributed to

acute cardiovascular disease (including stroke, ventricular arrhythmia and myocardial infarction) and infection (mainly pneumonia) [12, 13]. Evidence on quantifying the mortality risk of these specific causes associated with haloperidol and other antipsychotics is currently lacking.

In this population-based study, we restricted our cohort to patients without terminal diseases and used propensity score matching to compare mortality risk between antipsychotic users who had comparable baseline characteristics to control for confounding. We further investigated the risk of specific cause of death (death from cardiovascular disease, and death from pneumonia) associated with haloperidol compared with other antipsychotics.

2. Methods

2.1.Data sources

Data were retrieved from the Clinical Data Analysis and Reporting System (CDARS), a clinical database managed by the Hong Kong Hospital Authority which provides primary, secondary and tertiary healthcare to 7.5 million Hong Kong residents (representing 5.5-6.2 million adults between 2004-2014) through 41 public hospitals and institutions, 47 specialist outpatient clinics and 73 general outpatient clinics. Patient demographic information and clinical data (records of diagnosis, prescriptions, pharmacy dispensing, admission/discharge information, emergency attendance, laboratory test results) from all in-patient, out-patient and emergency settings since 1995 are available in CDARS for audit and research proposes [14, 15]. In CDARS, the British National Formulary (BNF) is used to categorize medication details, including prescription period, dosage and dosage form. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) is used to record diagnosis. The death records and cause of death were obtained from regional death registries of the Hong Kong Immigration Department. Data of cause of death is classified using the International Classification of Diseases, 10th

Revision, Clinical Modification (ICD-10-CM). Anonymous patient identifiers are generated to protect confidentiality. CDARS has been used in several epidemiological studies [16-20] to investigate the safety of medications.

2.2.Cohort study design

To investigate a delayed and rare outcome such as mortality in long-term treatment, a cohort study design is preferred due to its long follow-up period and large sample size [15]. We identified all patients aged 18 or above who were prescribed an antipsychotic drug (BNF 4.2.1 and 4.2.2, **eTable 1**) from 1 January 2004 to 31 December 2014. We included incident antipsychotic users, defined as individuals who did not receive an antipsychotic prescription at least 180 days prior to the index date (start date of the incident prescription). We excluded patients with terminal illnesses including malignant neoplasm, patients with a recent diagnosis of delirium (180 days before index date), or patients receiving palliative care (**eTable 2**) as the inclusion of these patients may introduce confounding [8]. We excluded patients whose first antipsychotic prescription was a short-acting injection (i.e. non-depot formulation) as this is typically prescribed for acute symptoms. Antipsychotics used for acute behavioral disturbance in emergency settings (mainly single doses or short-acting injections for acute disorder or undifferentiated agitation) were not included. A similar exclusion criterion was applied in previous studies investigating mortality risk of older patients on antipsychotics.

The follow-up started from the incident antipsychotic prescription start date (day 1) and ended at the earliest occurrence of any of the following: death, end of study (31 December 2016), switching to another antipsychotic or starting concurrent prescription of another antipsychotic. We censored the follow-up at drug switching/concurrent prescription to prevent the potential effect of drug-drug interactions. The exposure of interest was any incident prescription of

antipsychotic with haloperidol as the reference group. The primary outcome was all-cause mortality. Secondary outcomes were cardiovascular-related death and pneumonia-related death (**eTable 3**). In the original study protocol, we also explored suicidal death and rheumatoid arthritis, as secondary outcome and negative control outcome, respectively. However, due to low incidence of events, both outcomes were not included due to lack of power.

To study the duration of effect, follow-up was sub-divided into short-term (day 1-30), mid-term (day 31-180) and long-term (day 181 to the end of follow-up). To study the dosage effect, we conducted a subgroup analysis on relative levels of cumulative dosage, which was derived using the defined daily dose (DDD) as low dose (<0.5 DDD/day), moderate dose (0.5 to < 1.5 DDD/day), high dose (≥1.5 DDD/day) or missing dosage. A similar categorization was applied in a study investigating mortality risk in patients on psychotropic drugs, including antipsychotics.

2.3.Propensity score matching

Propensity score is the conditional probability of receiving treatment [21]. By matching patients in different treatment groups on the estimated propensity score, confounding due to non-random treatment allocation can be controlled [21]. In this study, the propensity score estimated patients' probability of receiving haloperidol over other antipsychotics, derived from a logistic regression model. In this model, the dependent variable was the prescription of antipsychotics (haloperidol or other) and covariates were sex, age, comorbidities (diagnostic record before day 1 of the following: schizophrenia, bipolar disorder, other psychoses, major depressive disorder, dementia, anxiety disorder, delusional disorder, personality disorder, post-traumatic stress disorder, sleep disorder, behavioral problem, myocardial infarction, arrhythmia, other ischemic heart disease, congestive heart disease, hypertension, cerebrovascular disease, diabetes, chronic kidney disease, hypothyroidism, Parkinson's disease, hepatic disease and chronic obstructive pulmonary

disease), recent medication (antidepressant, hypnotic, anxiolytic, antiepileptic, antidiabetic, drugs used in hypertension and heart failure, antiplatelet, calcium channel blocker, diuretic, beta blocker, antiarrhythmic, digoxin, nitrate, anticoagulant, peripheral vasodilator, lipid-regulating drug, antimanic, oral corticosteroid, non-steroidal anti-inflammatory drug [NSAID], proton pump inhibitor [PPI], histamine-2 receptor blocker [H_2 blocker], antibacterial, antifungal and antiviral prescribed in the 365 days before day 1, and the total number of prescriptions in the 365 days before day 1), and recent healthcare service usage (number of inpatient admissions, outpatient clinic appointments and emergency attendances in the 365 days before day 1) (**eTable 1** and **eTable 2**). After trimming 5% of patients with extreme propensity scores, patient(s) prescribed with haloperidol were matched to each patient on non-haloperidol antipsychotics on the propensity score within a stratum of sex and 5-year age band using a parallel, variable-matching-ratio (up to 2:1) nearest neighbor algorithm. This matching method has been demonstrated to improve matching precision, and allow a similar distribution of observed baseline characteristics among matched subjects [22]. The propensity score calculation, trimming and matching were conducted for each non-haloperidol antipsychotics. To examine the matching performance, we calculated weighted standardized differences of each covariate between haloperidol and other antipsychotic groups before and after matching (**eTable 4, 5, 6 and 7**). Those with a value less than 0.1 after matching were considered to have negligible imbalance in the covariates.

2.4.Statistical and sensitivity analyses

The hazard ratio (HR) of each outcome with 95% confidence intervals (95% CI) was estimated using the Cox proportional hazards model in the matched cohorts for each antipsychotic drug versus haloperidol. HRs for each outcome were estimated for the short-term, mid-term and long-

term, also in the low-dose, moderate-dose and high-dose subgroups. More commonly prescribed first-generation antipsychotics (haloperidol, chlorpromazine, sulpiride, and trifluoperazine) and second-generation antipsychotics (risperidone, quetiapine, clozapine, olanzapine, amisulpride, and aripiprazole) in Hong Kong [5] were reported in this study. Since mental illness requiring antipsychotic treatment is usually a chronic condition, we assumed that antipsychotic treatment was continuous once the incident prescription started. To verify this assumption, we conducted a sensitivity analysis which censored the follow-up at the cessation of antipsychotic prescription. Two prescriptions with a gap of no more than 28 days apart were considered continuous. Analyses were independently conducted by KSJL and AYSW and results were crosschecked using R (version 3.33; R core team) and SAS (version 9.3; SAS Institute, Inc) for quality assurance. A two-sided p-value of 0.05 was considered statistically significant. We also reported the survival curves by all-cause mortality for each propensity-score-matched cohort.

Ethical approval was obtained from the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference Number: UW 15-619).

3. Results

3.1.Baseline characteristics

A total of 136 593 new antipsychotic users were identified during the study period after application of the exclusion criteria (**Figure 1**). Summary statistics of demographics and the number of included patients by subgroup are shown in **Table 1**. Haloperidol was the most commonly prescribed antipsychotic, followed by quetiapine, risperidone and sulpiride (**Table 1**). The total follow-up was 438 333 person-years (mean 3.2 person-years). Successfully matched subjects showed similar baseline characteristics with a weighted standardized difference less than 0.1 (**eFigure 1**), except for hypertension, ischemic heart diseases, cerebrovascular diseases,

antiplatelet, calcium channel blocker, beta-blocker, nitrate, lipid-regulating drug, NSAID, PPI/H_2 blocker and antibacterial drugs in aripiprazole-haloperidol matches, and PPI/H_2 blockers in olanzapine-haloperidol matches (**eTable 6**).

3.2.Risk of mortality

During the follow-up, there were 44 400 deaths, of which 6 841 were cardiovascular-related, and 16 141 were pneumonia-related. Patients aged over 65 had the highest mortality rate (205.0 per 1000 person-years) among all subgroups. Patients on haloperidol presented with the highest mortality rate (186.8 per 1000 person-years) among all antipsychotics (**Table 1**). Survival curves by all-cause mortality for each propensity-score-matched cohort were reported (**eFigure 2-9**).

The results of primary analysis showed that non-haloperidol antipsychotics were associated with a statistically significantly lower risk of mortality versus haloperidol, with HRs ranging from 0.43 for trifluoperazine (95% CI 0.36-0.53) to 0.68 for chlorpromazine (95% CI 0.64-0.72) (**Table 2**). Cardiovascular-related mortality was significantly lower for risperidone (HR 0.79 [95% CI 0.66-0.93]), sulpiride (HR 0.78 [95% CI 0.64-0.96]), chlorpromazine (HR 0.76 [95% CI 0.65-0.90]) and quetiapine (HR 0.67 [95% CI 0.57-78]) compared with haloperidol. Significantly lower pneumonia-related mortality risk was observed for all non-haloperidol antipsychotics, except amisulpride and olanzapine, with HRs varying from 0.38 (95% CI 0.24-0.61) for trifluoperazine to 0.76 (95% CI 0.68-0.85) for risperidone.

For duration of effect (**eTable 8**), a lower risk of all-cause mortality was observed for non-haloperidol antipsychotics. This association occurred consistently throughout the follow-up except for the short-term prescription of aripiprazole. For cardiovascular-related mortality, lower HRs were observed for quetiapine for all time periods, risperidone for short-term period and

chlorpromazine for long-term period. For pneumonia-related mortality, a lower risk was observed in all time periods for chlorpromazine, quetiapine and risperidone, the short-term period for sulpiride, the mid-term period for trifluoperazine, and the long-term period for aripiprazole, sulpiride and trifluoperazine.

Dosage level analysis suggested a lower risk of all-cause mortality in the low-dose and moderate-dose groups for chlorpromazine, risperidone, quetiapine, olanzapine and aripiprazole, which was similar to the primary analysis (**eTable 9**). A lower risk of mortality from cardiovascular diseases and pneumonia was observed associated with low-dose prescriptions of risperidone, quetiapine, and chlorpromazine. Moderate-dose prescriptions of quetiapine and chlorpromazine were associated with a significantly lower risk of pneumonia-related death. However, estimates in most of the high-dose groups were imprecise due to the small sample size.

In the sensitivity analysis, with the follow-up censored at cessation of the prescription, similar HRs for all-cause mortality were observed for quetiapine, risperidone, aripiprazole, amisulpride, sulpiride and trifluoperazine (**eTable 10**). A HR less than 1 was observed in chlorpromazine and olanzapine for all-cause mortality but this did not reach statistical significance. Similarly, a lower risk of cardiovascular- and pneumonia-related mortality was observed for quetiapine and risperidone. Consistent with the primary analysis, sulpiride was associated a significantly lower risk of pneumonia-related mortality.

4. Discussion

4.1.Risk of mortality

Based on our results, all-cause mortality was higher for haloperidol compared with other antipsychotics. The increased risk of mortality associated with haloperidol was in line with previous studies, which compared haloperidol to chlorpromazine, olanzapine and risperidone,

regardless of age (adult or older patients treated with antipsychotic). The increased risk of mortality with haloperidol was consistent throughout time (short-term, mid-term or long-term). Compared with haloperidol, aripiprazole and trifluoperazine were associated with approximately 50% lower mortality risk in the all-time follow-up, suggesting that aripiprazole and trifluoperazine could be preferred choices for long-term treatment, especially aripiprazole, which was associated with a 58% lower all-cause mortality risk in long-term follow-up. The mortality risks associated with chlorpromazine and olanzapine are yet to be confirmed since consistent results were not detected in the sensitivity analysis.

In the current literature, a systematic review and meta-analysis published in 2015 pooled results of 17 randomized controlled trials and found no statistically significant increase in mortality risk associated with first-generation antipsychotics versus placebo [23]. Other two randomized controlled trials concluded that there was no statistically significant difference in effectiveness outcome in managing delirium and coma in critically ill patients when comparing haloperidol to placebo [24], or ziprasidone [25]. However, due to the different clinical setting, patient group, or outcome measurement, direct comparison cannot be made with our study results.

For cardiovascular-related mortality, quetiapine was associated with a lower risk throughout the follow-up. For other antipsychotics, a lower risk of cardiovascular-related death compared to haloperidol was only observed in the long-term prescription of chlorpromazine and the short-term prescription of risperidone. The arrhythmogenic effect of haloperidol might explain the higher risk of cardiovascular-related mortality [26]. A 45% cardiovascular-related lower death risk was observed with the long-term prescription of aripiprazole compared to haloperidol, however, this difference was not statistically significant. The favorable safety profile of aripiprazole in terms of QTc prolongation and metabolic syndrome may explain the reduced

cardiovascular-related mortality [27-29]. In older adults on antipsychotic treatment, mortality risk contributed by stroke has been reported as minimal [30]. However, these studies were based on clinical settings in western countries [26-30], in which the epidemiology of cardiovascular disease differs from China [31]. Future studies with larger sample size or longer follow-up are needed to validate results of cardiovascular mortality in Chinese population with more certainty. For pneumonia-related deaths, antipsychotics have been associated with an increased risk compared with non-antipsychotic medication [32]. However, whether the risk differs between antipsychotic drugs has rarely been investigated. In this study, haloperidol was associated with an increased risk of pneumonia-related mortality compared to other antipsychotics. It has been suggested that haloperidol might have immunosuppressive activity by suppressing thymidine incorporation and cytokine secretion [33]. We are not aware of reports of other antipsychotics included in our study exhibiting a similar immunosuppressive effect. A high risk of pneumonia might also be explained by the tendency of haloperidol to cause extrapyramidal-symptom-related dysphagia , which has been suggested as a risk factor of community-acquired pneumonia in older patients [34]. Consistent with a previous study in the United States investigating the risk of pneumonia with second-generation antipsychotic drugs, the risk of pneumonia-related deaths with risperidone, olanzapine, quetiapine and aripiprazole was lower than haloperidol in our study.

After patient exclusion and matching, the baseline characteristics among all matched cohorts were generally well balanced, except the number of drugs used for the treatment of cardiovascular disease, gastrointestinal disease, inflammation and infection. These medications were more frequently prescribed with aripiprazole and olanzapine than with haloperidol. The weighted standardized difference of these medications was above 0.1 but below 0.2. This result

indicates that patients prescribed aripiprazole and olanzapine had more comorbidities than matched patients prescribed haloperidol. However, since the results suggest a generally lower risk of all-cause, cardiovascular-related and pneumonia-related mortality associated with non-haloperidol antipsychotics, the imbalance of baseline characteristics would only underestimate the magnitude of the decreased risk of aripiprazole and olanzapine and, consequently, is unlikely to change our conclusion. Another important risk factor for mortality is age. As older patients are at increased risk of mortality (regardless of antipsychotic treatment), the imbalance in age between the comparison groups at cohort entry could bias the estimation of relative risk. For example, in the Taiwanese study, when compared to patients aged less than 18, the risk of death for patients aged 18 to 65-years-old was 12-fold higher, and for patients over 65, as high as 30-fold [4]. Although age was adjusted in the statistical analysis, confounding by age may not be entirely eliminated [4]. Similarly, in the FIN11 study, a higher mortality risk was observed in older patients. However, the age distribution among antipsychotic patients was not reported in FIN11 [3]. In our study, the potential effect of age was eliminated by matching. Age differences between patients prescribed haloperidol and other antipsychotics were negligible in the matched cohorts.

Future research should evaluate other potential mechanisms that may contribute to excess mortality with haloperidol, such as neurotoxicity [35]. Furthermore, the assessment of effect modification by genetic factors is also warranted.

4.2.Clinical implications

As the higher risk of cardiovascular and pneumonia-related mortality was associated with haloperidol compared with quetiapine and risperidone, clinicians should assess a patient's risk of pneumonia and cardiovascular events, before prescribing haloperidol over quetiapine or

risperidone. For long-term management, second-generation antipsychotics that were associated with a lower mortality risk should be considered the preferred option, especially in geographical regions with a high prescribing prevalence of haloperidol, and for patients with risk factors for cardiovascular disease or pneumonia.

Although current evidence suggests that haloperidol has a less than ideal safety profile, it remains one of the most prescribed antipsychotics in geriatric patients in Australasia, the United States and parts of Europe [2, 36]. In light of our findings, extensive prescribing of haloperidol should be viewed as a global public health concern, especially for older patients.

The high prescribing prevalence of haloperidol might be due to its lower cost. However, pharmacoeconomic studies based on Asian and European healthcare settings demonstrate that the use of haloperidol was associated with a higher subsequent and overall downstream cost in the long-term, despite a lower direct medication cost compared with olanzapine and quetiapine [37, 38]. The decision to prescribe haloperidol should be critically evaluated by clinical practitioners and policy makers.

4.3.Strengths and limitations

To our knowledge, this is the first population-based, propensity-score-matched cohort study investigating the mortality risk associated with haloperidol versus other individual antipsychotics. We report the mortality rates to describe the overall public health burden at the population level. The long follow-up period and the large sample size, required for an investigation into the long-term safety profiles, would be difficult to achieve with a clinical trial design. Direct drug-drug comparisons were applied to inform practice in antipsychotic selection. Furthermore, we excluded patients with terminal illness to reduce confounding by indication, and used a rigorous propensity score matching method to allow comparisons between patients with

similar baseline characteristics. This between-person confounding was not well addressed in previous studies.

There are some limitations in this study. First, no private healthcare data were included in this study. However, since antipsychotic treatment is usually chronic and the costs are fully covered in the public sector, our data likely captures the majority of long-term prescriptions for antipsychotics. Second, for recently marketed antipsychotics (such as aripiprazole), sample sizes and length of follow-up on these analyses might be insufficient to detect significant effects. This may also apply to subgroup analyses. However, we still detected significantly decreased risks of all-cause mortality for these antipsychotics. Additionally, our analysis may be limited by the misclassification of certain diagnoses particularly for acute medical conditions such as delirium. Further validation study on delirium diagnosis is required. Despite propensity score matching and restricting the cohort by excluding patients with acute medication conditions and terminal illnesses, the possibility of residual confounding due to prescription indication and disease severity remains. Finally, an inherent limitation of pharmacoepidemiological studies is that patients' adherence to prescribed medications is unknown, which may introduce misclassification bias. To reduce the effect of such bias, prescriptions with a gap period of no more than 28 days apart were assumed continuous. Results of this study should be interpreted cautiously under consideration of these limitations.

5. Conclusion

To conclude, haloperidol was associated with an increased risk of mortality, due to any cause, cardiovascular disease and pneumonia, as compared with non-haloperidol antipsychotics. Clinicians and policymakers should critically evaluate the use of antipsychotics, especially the

use of haloperidol, in older patients and those at profound risk of cardiovascular disease or pneumonia.

Table 1. Summary Statistics of Demographic Information, Number of Included Patients by Subgroup, and Mortality Rate by Subgroup

Table 2. Mortality Rate and Relative Risk of Mortality in Propensity Score Matched Cohorts

Figure 1. Selection of Patients for Analysis of Mortality Risk Associated with Antipsychotics

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Compliance with Ethical Standards

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Conflict of interest

All authors declare that no other support has been received from any organization for the submitted work; no other financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted study. KSJL was formerly employed by the University of Hong Kong where the majority of the work was completed, and is currently employed by MRL, MSD China at submission. Outside the summited work, EWC received research funding from Wellcome Trust, United Kingdom; National Natural Science Fund of

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Data Sharing:

No additional data available.

Supplementary material:

435 eFigure 2-9. Kaplan-Meier Curve of All-cause Mortality among Patients Prescribed

436 Antipsychotic Drugs versus Haloperidol Matching by Propensity Score

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