**Multiple adverse outcomes associated with antipsychotic use in people with dementia: a population-based cohort study**

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**What is already known on this topic**

* Despite safety concerns, antipsychotics continue to be frequently prescribed for the management of behavioural and psychological symptoms of dementia (BPSD).
* Current regulatory warnings for antipsychotic treatment for BPSD are based on evidence of increased risks for stroke and death.
* Evidence of other adverse outcomes is less conclusive or is more limited amongst people with dementia. Comparisons of risks for multiple adverse events are also difficult due to different study designs and populations.

**What this study adds**

* Antipsychotic use in patients with dementia was associated with elevated risks of stroke, venous thromboembolism (VTE), myocardial infarction, heart failure, fracture, pneumonia, and acute kidney injury (AKI), compared with non-use, but no increased risk for ventricular arrhythmia was observed.
* Relative hazards were highest for pneumonia, AKI, stroke, and VTE. Absolute risk, and risk difference between antipsychotic users and their matched comparators, was also largest for pneumonia.
* Risks for these wide-ranging adverse outcomes need to be considered before prescribing antipsychotic drug treatment to people with dementia.

**ABSTRACT**

**Objectives**

To investigate risks of multiple adverse outcomes associated with antipsychotics use in people with dementia.

**Design**

Population-based matched cohort study using inverse probability treatment weights by propensity score.

**Setting**

Linked primary care, hospital and mortality data from Clinical Practice Research Datalink (CPRD) in England.

**Participants**

People diagnosed with dementia between 1st January 1998 and 31st May 2018 (n=173,910), with each new antipsychotic user (n=35,339) matched with up to 15 comparators without antipsychotic exposure using incidence density sampling.

**Main outcome measures**

Hazard ratios (HR) for stroke, venous thromboembolism (VTE), myocardial infarction (MI), heart failure, ventricular arrhythmia, fracture, pneumonia, and acute kidney injury (AKI), stratified by periods of antipsychotics exposure, with absolute risks calculated using cumulative incidence in antipsychotic users versus matched comparators.

**Results**

Compared to non-exposure, antipsychotic exposure was associated with elevated risks for all outcomes, except ventricular arrhythmia. In the 90 days following a prescription, HRs were 2.19 (95% CI 2.10 to 2.28) for pneumonia, 1.72 (95% CI 1.61 to 1.84) for AKI, 1.62 (95% CI 1.46 to 1.80) for VTE, 1.61 (95% CI 1.52 to 1.71) for stroke, 1.43 (95% CI 1.35 to 1.52) for fracture, 1.28 (95% CI 1.15 to 1.42) for MI, and 1.27 (95% CI 1.18 to 1.37) for heart failure. On the contrary, no elevated risks were observed for the negative control outcome (appendicitis and cholecystitis). At 90 days following a first prescription, absolute risk differences for antipsychotic users versus their matched comparators ranged from 2.99% (95% CI 2.77 to 3.22) for pneumonia, to 0.13% (95% CI 0.06 to 0.21) for MI and VTE.

**Conclusions**

A wider range of adverse outcomes associated with antipsychotics use in people with dementia was identified than previously highlighted in regulatory alerts, with the highest risks soon after treatment initiation.

**List of abbreviations**

ARB - Angiotensin-II receptor blockers

ACE - Angiotensin converting enzyme inhibitors

AKI - Acute kidney injury

BPSD - Behavioural and psychological symptoms of dementia

COPD - Chronic obstructive pulmonary disease

CPRD - Clinical Practice Research Datalink

ESKD - End stage kidney disease

FDA - US Food and Drug Administration

HES - Hospital Episode Statistics

HR - Hazard ratio

HRT - Hormone replacement therapy

ICD-10 - International Classification of Diseases (ICD-10)

IMD - Index of Multiple Deprivation

IPTW - Inverse probability of treatment weights

MI - Myocardial infarction

NICE - National Institute for Health and Care Excellence

NIHR - National Institute of Health and Care Research

NNH - Number needed to harm

NHS – National Health Service

NSAID - Nonsteroidal anti-inflammatory drugs

ONS - Office for National Statistics

SHR – Subhazard ratio

UK - United Kingdom

VTE - Venous thromboembolism

**INTRODUCTION**

Dementia is a clinical syndrome characterised by progressive cognitive decline and functional disability, with estimates suggesting that by 2050, around 152.8 million people globally will be affected.1 Behavioural and psychological symptoms of dementia (BPSD) are a common feature of the disease, and include symptoms such as apathy, depression, aggression, anxiety, irritability, delirium, and psychosis. BPSD can negatively impact the quality of life of patients and their carers, and is associated with early institutionalisation.2,3 Antipsychotics are commonly prescribed for the management of BPSD, despite longstanding concerns about their safety.4-6 During the COVID-19 pandemic, the proportion of people with dementia prescribed antipsychotics increased, possibly due to worsened BPSD symptoms linked to lockdown measures and/or reduced availability of non-pharmaceutical treatment options.7 According to the UK’s National Institute for Health and Care Excellence (NICE) guidelines, antipsychotics should only be prescribed for the treatment of BPSD if non-pharmacological interventions have been ineffective, if patients are at risk of harming themselves or others, or are experiencing agitation, hallucinations or delusions that are causing them severe distress.8 They should only be prescribed at the lowest effective dose and for the shortest possible time. Only two antipsychotics, risperidone (an atypical, or second generation, antipsychotic) and haloperidol (a typical, or first generation, antipsychotic), are licensed in the UK for the treatment of BPSD,9 although others have been commonly prescribed off-label.5,10

Based on evidence from clinical trials of risperidone, the US Food and Drug Administration (FDA) first issued a warning in 2003 of the increased risks of cerebrovascular adverse events (e.g. stroke, transient ischemic attack) associated with atypical antipsychotics use in older adults with dementia.11 A meta-analysis of 17 trials among such patients subsequently found a 1.6-1.7 times elevated mortality risk with atypical antipsychotics compared with placebo, which led the FDA to issue a ‘black box’ warning in 2005 for all atypical antipsychotics.11 This warning was extended to typical antipsychotics in 2008, after two observational studies reported that the risk of death associated with their use amongst older people might be even greater than for atypical antipsychotics.12-14 The increased risks for stroke and mortality have been consistently reported by many observational studies and meta-analyses since,11,15-21 and have led to regulatory safety warnings and national interventions in the UK, US, and Europe, aiming to reduce inappropriate prescribing of these drugs for the treatment of BPSD.8,11,22-26 Other adverse outcomes have also been investigated in observational studies,27-29 but with the exception of pneumonia,14,30-32 the evidence is less conclusive or is more limited amongst people with dementia. For example, there has been inconsistent or limited evidence on risks for myocardial infarction (MI),33,34 ventricular arrhythmia,35,36 venous thromboembolism (VTE),37-40 fractures,41-43 and acute kidney injury (AKI).44-46 Most studies also reported only one outcome or type of outcomes. Examining multiple adverse events in a single cohort is needed to give a more comprehensive estimate of the total potential harm associated with these drugs in people with dementia.

Using linked primary and secondary care data in England, the aim of this study was to investigate the risks of a range of adverse outcomes potentially associated with antipsychotic use in a large cohort of people with dementia, namely: stroke, VTE, MI, heart failure, ventricular arrhythmia, fractures, pneumonia, and AKI. We report both relative and absolute risks.

**METHODS**

**Data sources**

The study used anonymised electronic health records from the Clinical Practice Research Datalink (CPRD). In the United Kingdom (UK), residents are required to be registered with a primary care general practice in order to receive care from the National Health Service (NHS). The NHS is a publicly funded healthcare service, free at the point of use. Over 98% of the UK population are registered with a general practice and their electronic health records are transferred when they change practice.47,48 Community prescribing is most often done by the general practitioner, including antipsychotic treatment recommended by specialists. CPRD data are sourced from over 2,000 general practices covering around 20% of the UK population. It contains information on diagnoses, primary health care contacts, prescribed medication, laboratory test results, and referrals to secondary healthcare services.47,48 There are two databases within CPRD: Aurum and GOLD. CPRD Aurum includes data from contributing general practices in England that use the EMIS Web® patient management software, and CPRD GOLD consists of patient data from practices across all four UK nations which use the Vision® system. Both datasets are broadly representative of the UK population.47-49 Primary care data from general practices in England can be linked to other datasets including hospital admissions (in Hospital Episode Statistics [HES]), and mortality and Index of Multiple Deprivation (IMD) data from the Office for National Statistics (ONS). Individual patients can opt-out of sharing their records with the CPRD, and individual patient consent was not required as all data were de-identified. The study was approved by the CPRD Independent Scientific Advisory Committee (protocol 18\_168). CPRD also has ethics approval from the Health Research Authority to support research using anonymised patient data (Research Ethics Committee reference 21/EM/0265).50

**Study population**

We delineated two cohorts, one each from Aurum and GOLD. For the latter, we included patients from English practices only since linkage to hospital admission and mortality data were required in our analyses. To ensure that the study dataset would not contain any duplicate patient records, we used the ‘bridging file’ provided by CPRD to identify English practices that have migrated from the GOLD to the Aurum dataset and removed such practices from the GOLD dataset. For both cohorts, we included patients who had a first dementia diagnosis code between 1st January 1998 and 31st May 2018. Dementia was identified from Read, SNOMED, or EMIS codes used in the databases (see Appendix). We defined the date of first dementia diagnosis as the date of first dementia code. Patients needed to be aged 50 years or over at the time of dementia diagnosis, have been registered with the CPRD practice for at least a year, not prescribed an antipsychotic in the 365 days before their first dementia code, and that their records were eligible for linkage to the HES, mortality and IMD data. In addition, since anticholinesterases (such as donepezil, rivastigmine and galantamine) may sometimes be prescribed to patients showing signs of dementia before their first dementia code, patients with an anticholinesterase prescription before their first dementia code were excluded. Supplementary Figures S1 and S2 show how the two cohorts for Aurum and GOLD, respectively, were delineated.

**Study design**

We implemented a matched cohort design. A graphical depiction of the study design is shown in Supplementary Figure S3.51 For the Aurum and GOLD cohorts separately, patients exposed to antipsychotics were defined as patients in each cohort issued with an antipsychotic prescription following (or on the same day as) the date of their first dementia diagnosis, with the date of first antipsychotic prescription being the ‘index date’ after which outcomes were measured. For each outcome, follow-up began from the date of the first antipsychotic prescription (the ‘index date’) and ended on the earliest of: date of first diagnosis of outcome (i.e. the earliest recording of the outcome whether it was from the patient’s primary or secondary care or mortality records – see ‘Outcomes’ section below), death, transfer out of general practice, last data collection date of the general practice, two years from the date of antipsychotics initiation, or 31st May 2018. Since patients who have experienced an outcome were potentially at higher risk of subsequently experiencing the same event, which could confound any risks associated with antipsychotic use, patients with a history of the specific outcome under investigation before the index date were excluded from the analysis of that outcome. For example, patients with a record of stroke before the index date were excluded from the analysis of stroke but would still be eligible for the study of other outcomes. For the analysis of AKI, patients diagnosed with end stage kidney disease (ESKD) before the index date were also excluded, and a diagnosis of ESKD after the index date was an additional condition for follow-up end.44

‘Matched comparators’ were defined as follows. Each patient exposed to antipsychotics on or after their date of first dementia diagnosis (as defined above) was matched using incidence density sampling with up to 15 randomly selected patients who had the same date of first dementia diagnosis (or up to 56 days after) and who had not been prescribed an antipsychotic before their first dementia diagnosis. Incidence density sampling involves matching with respect to sampling time, with each ‘case’ (i.e. antipsychotic user in our study) being matched to one or more comparators who are eligible to, but have not become a ‘case’ at the time of matching.52 The selection of comparators was done with replacement, i.e. an individual could be used as a comparator in multiple matched sets. In our study, this means that patients were eligible to be a ‘non-user’ matched comparator up to the date of their first antipsychotic prescription. Matched comparators with a history of the specific outcome under investigation before the index date were excluded from the analysis of that event. For each outcome, follow-up of matched comparators began on the same day as the patient they were matched to (the index date), and ended on the earliest of: date of their first antipsychotic prescription (if any), or date of one of the end of follow-up events described earlier for the antipsychotic users.

**Exposure**

We included both typical and atypical antipsychotics, identified by product codes in Aurum and GOLD - see the Appendix for lists of drugs included. Code lists were reviewed by senior author DMA (pharmacist). Since previous studies have shown a temporal relationship between antipsychotic exposure and development of adverse outcomes,30,31,53 exposure to antipsychotics was treated as a time-varying variable, classified as current, recent and past use. Current use was defined as the first 90 days from the date of an antipsychotic prescription, recent use as up to 180 days after current use ended, and past use as the time after the recent use period had ended. If a patient was issued another prescription during the 90 days following their last prescription, their current use period would be extended by 90 days from the date of their latest prescription. For example, if a patient had two prescriptions and the second was issued 60 days after the first, their current use period would be a total of 150 days: 60 days following the first prescription plus 90 days following the second. At the end of the 150 days current use period, the next 180 days would be the recent use period, and the time after this recent use period would be past use. Since patients could have multiple prescriptions over time, they could move between the three exposure categories during follow-up, and could therefore be defined as current/recent/past users more than once. See the Appendix for further information of how this definition is applied.

As post-hoc analyses, we also investigated typical versus atypical antipsychotics, and specific drug substances: haloperidol, risperidone, quetiapine, and other antipsychotics (as a combined category).

**Outcomes**

Outcomes were stroke, VTE (including deep venous thrombosis and pulmonary embolism), MI, heart failure, ventricular arrhythmia, fractures, pneumonia, and AKI. With the exceptions of pneumonia and AKI, outcomes were identified by Read, SNOMED, or EMIS codes in the primary care records, and by International Classification of Diseases (ICD-10) codes from linked secondary care data from HES and cause of death data from the ONS mortality records. For pneumonia and AKI, we only included cases that were diagnosed in hospitals or as a cause of death, ascertained from HES and ONS data.

We also investigated appendicitis and cholecystitis (combined) as an unrelated (negative control) outcome to detect potential unmeasured confounding.54 These outcomes were chosen as there was no evidence from the literature that antipsychotic use was associated with the risk of developing these conditions. These cases were identified by Read, SNOMED, EMIS, and ICD-10 codes. All code lists were checked by the clinicians (BG, AJA, DRM) and are available in the Appendix.

**Covariates**

We used propensity score methods to control for imbalances in measurable patient characteristics between exposed and their matched unexposed patients, with patient demographics, lifestyle, comorbidities, and prescribed medications included in the propensity score models. We applied a counterfactual framework for causal inference to estimate the average treatment effect adjusting for inverse probability of treatment weights (IPTW) generated from the propensity score models (see ‘Statistical analysis’ subsection).55,56 Selection of covariates was informed by the literature, based on their potential associations with antipsychotic initiation and study outcomes.31,34,44,57,58 All variables were assessed before the index date (Supplementary Figure S3). Demographics variables included: sex, age at dementia diagnosis, age at start of follow-up, ethnicity, and IMD quintiles of the location of the general practice. Comorbidities were derived as dichotomous variables and included a history of: hypertension, types 1 and 2 diabetes mellitus, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, moderate or severe renal disease, moderate or severe liver disease, atrial fibrillation, cancer, and serious mental illness (bipolar disorders, schizophrenia, schizoaffective disorders, and other psychotic disorders). Lifestyle factors included smoking status and alcohol use. Medication covariates were represented as dichotomous indicators, defined by at least two prescriptions for each of the following drugs in the 12 months before the index date: antiplatelets, oral anticoagulants, angiotensin converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARB), alpha blockers, beta blockers, calcium channel blockers, diuretics, lipid lowering drugs, insulin and antidiabetic drugs, nonsteroidal anti-inflammatory drugs (NSAID), antidepressants, benzodiazepines, and lithium. We also additionally included the following potential confounders for the investigations of VTE and fractures: prescriptions for hormone replacement therapy (HRT) and selective oestrogen receptor modulators (for VTE);59,60 a history of inflammatory bowel disease (for pneumonia and fractures);61,62 prescriptions for immunosuppressants, oral corticosteroids, and inhaled corticosteroids (for pneumonia).63,64

**Statistical analysis**

For each patient included in the study, we derived a propensity score representing their probability of receiving antipsychotic treatment. Propensity scores were estimated using multivariable logistic regression with exposure to antipsychotic treatment as the dependent variable and the covariates listed earlier as predictors. Patients with missing information on ethnicity, IMD, smoking, or alcohol use, were grouped into an ‘unknown’ category for each of these variables and included into the propensity score models. The Hosmer-Lemeshow test and likelihood ratio test were used to test the fit of the models and interaction terms were included to improve the model fit.65 The derived scores were used as IPTW to reweigh the data, balancing the distribution of baseline covariates between antipsychotic users and non-users (matched comparators), i.e. standardised differences <0.1 after weighting.66 Propensity scores models were run for each outcome, and for the Aurum and GOLD cohorts separately. For further information, see ‘Propensity score methods to control for potential confounding’ section in the Appendix.

Analyses estimating harms were then conducted after combining (appending) the Aurum and GOLD datasets. We used Cox regression survival analyses to estimate the risks of each outcome associated with antipsychotic use relative to the comparator cohort, and reported the results as hazard ratios (HRs). Exposure to antipsychotic was treated as a time-varying variable. To account for the matched design, we fitted stratified models according to the matched sets and used robust variance estimation. In all models, we also included a covariate indicating whether the patient was from the Aurum or GOLD cohort, and calculated HRs with IPTW adjustments. Cox regression assumes proportional hazards, i.e. relative hazard of the outcome remains constant during the follow-up period.67 We assessed this assumption using the Grambsch-Therneau test based on the Schoenfeld residuals.68 Because this assumption did not hold for all outcomes examined, in addition to reporting the HRs pertaining to the whole follow-up period, we estimated HRs separately for the following time windows: the first 7 days, 8 to 30 days, 31 to 180 days, 181 to 365 days, and 366 days to two years (see the Appendix for an illustration of stratification of follow-up time). For each outcome, we calculated the incidence rate and the number needed to harm (NNH) over the first 180 days as well as two years after start of follow-up. The NNH represents the number of patients needed to be treated with antipsychotic for one additional patient to experience the outcome compared with no treatment. We also calculated cumulative incidence percentages (absolute risks) for each outcome accounting for competing mortality risks based on the recommendations made by Gooley et al.69 These were calculated at 90 days, 180 days, 365 days, and two years after start of follow-up, for antipsychotic users and their matched comparators separately. We also reported the difference in cumulative incidence between antipsychotic users and their matched comparators at these time points. Analyses were conducted using Stata/MP v16.1.

**Sensitivity analyses**

We investigated two other definitions of antipsychotic use as sensitivity analyses: the first 60 days as current use followed by 120 days of recent use; and a current use period of 30 days followed by a recent use period of 60 days. We also conducted the following post-hoc sensitivity analyses. Firstly, since levomepromazine is often prescribed in palliative care to treat distressing symptoms in the last days of life,70 we censored the patients at the time of their first levomepromazine prescription. Secondly, we used Fine-Gray subdistribution hazard regression models to estimate the hazard of each adverse outcomes taking into account the competing risks of death.71 These results were reported as subhazard ratios (SHRs). Thirdly, we compared the incidence rates and hazards of adverse outcomes for males versus females. For these sex-specific analyses, we modified the existing matched cohort by excluding the comparators who were of a different sex from the antipsychotic user to whom they were matched. We then derived a new propensity score for each patient by excluding sex as a covariate in the propensity score models. Male versus female incidence rate ratios (IRR) and their 95% CI were calculated using the ‘iri’ command in Stata. To investigate whether hazards of each adverse outcome associated with antipsychotic use differed by sex, we fitted Cox regression models with sex, antipsychotic exposure, and their interaction as covariates. Sex-specific HRs and ratios of male-to-female HRs were reported.

**Patient and public involvement**

This study is part of a National Institute of Health and Care Research (NIHR) funded programme (RP-PG-1214-20012): “Avoiding patient harm through the application of prescribing safety indicators in English general practices” (acronym: PRoTeCT). Two patient and public involvement members in the project team contributed to the study design and protocol of this study. However, our study was not co-produced with patients with dementia or with their carers.

**RESULTS**

**Characteristics of study population**

A total of 173,910 patients with dementia were eligible for inclusion in the study: 139,772 patients (62.9% women) in the Aurum dataset, and 34,138 patients (63.4% women) in GOLD. The mean age at dementia diagnosis for patients in both cohorts was 82.1 (SD 7.9) years, and the median age was 83 years (IQR 10 in Aurum, and 9 in GOLD). A total of 35,339 patients (28,187 in Aurum, 7152 in Gold) were prescribed an antipsychotic during the study period and a matched set was generated for each of these patients. The mean number of days between first dementia diagnosis and date of first antipsychotics prescription was 693.8 (SD 771.1, median 443) in Aurum, and 576.6 (SD 670.0, median 342) in GOLD. A total of 544,203 antipsychotic prescriptions (433,694 in Aurum, 110,509 in GOLD) were issued, of which 25.3% were for a typical and 74.7% for an atypical antipsychotic. The most commonly prescribed antipsychotics were risperidone (29.8% of all prescriptions), quetiapine (28.7%), haloperidol (10.5%), and olanzapine (8.8%), which together accounted for almost 80% of all prescriptions (Supplementary Table S1).

Since we excluded patients who had a history of the event before the start of follow-up, the number of patients and matched sets included in analysis varies by outcome. Table 1 shows the number and baseline characteristics of patients for the analysis of stroke, before and after IPT weighting. Antipsychotic users were more likely than their matched comparators to have a history of serious mental illness and to be prescribed antidepressants or benzodiazepines in the 12 months before start of follow-up. After IPT weighting, standardised differences were <0.1 for all covariates. Baseline characteristics of patients included in the analyses of other outcomes were similar to those reported for stroke (Supplementary Tables S2-S9).

**Incidence rates and** **relative hazards of adverse outcomes**

***All antipsychotics***

In the two years following antipsychotics initiation, the highest incidence rates of adverse outcomes were for pneumonia, fractures, and stroke, whilst ventricular arrhythmias were rare (Table 2). Figure 1 shows the HRs of adverse outcomes associated with current, recent, past and any exposure to antipsychotics, versus non-exposure (i.e. matched-comparators). With the exceptions of ventricular arrhythmia, any exposure to antipsychotics was associated with elevated risks for all adverse outcomes, ranging from HR=2.03 (95% CI 1.96 to 2.10) for pneumonia to HR=1.16 (95% CI 1.09 to 1.24) for heart failure. Current use (i.e. prescribed in the previous 90 days) was associated with particularly high risks for pneumonia HR=2.19 (95% CI 2.10 to 2.28), AKI HR=1.72 (95% CI 1.61 to 1.84), VTE HR=1.62 (95% CI 1.46 to 1.80), and stroke HR=1.61 (95% CI 1.52 to 1.71). Recent antipsychotic use (i.e. in the 180 days after current use ended) was also associated with increased risk for these outcomes, as well as for fractures, but past exposure to antipsychotics (i.e. after recent use ended) was not associated with increased risks of the adverse outcomes examined, except for pneumonia. For the unrelated outcome (appendicitis and cholecystitis), there were no significant associations with current, recent or any antipsychotic exposure, but a statistically significant association observed with past use (HR 1.90, 95% CI 1.01 to 3.56).

Table 2 shows that the NNH ranged from 9 (95% CI 9 to 10) for pneumonia to 167 (95% CI 116 to 301) for MI during the first 180 days following antipsychotics initiation, and from 15 (95% CI 14 to 16) for pneumonia to 254 (95% CI 183 to 413) for MI after two years. These figures suggest that over the 180 days following drug initiation, antipsychotics use might be associated with one additional case of pneumonia for every 9 patients treated, and one additional case of MI for every 167 patients treated. At two years, there might be one additional case of pneumonia for every 15 patients treated, and one additional case of MI for every 254 patients treated.

Table 3 shows HRs stratified by follow-up time (except for ventricular arrhythmia and the unrelated outcome where number of cases was very low). For almost all outcomes, relative hazards were highest in the first seven days after initiation of antipsychotic treatment. Risks for pneumonia were particularly elevated in the first seven days (HR 9.99, 95% CI 8.78 to 11.4), and remained substantial afterwards (HR 3.39, 95% CI 3.04 to 3.77, between 8-30 days). No elevated risks for heart failure was found for current users after 180 days since treatment started, nor for MI one year after drug initiation. However, risks for stroke, VTE, fracture, pneumonia, and AKI remained elevated amongst continuous antipsychotic users up to two years after initiation of treatment.

***Types of antipsychotics***

During the current use period of 90 days following a prescription, both typical and atypical antipsychotics were associated with elevated risks of all adverse outcomes, except for ventricular arrhythmia and the unrelated outcome, compared with non-exposure (Supplementary Table S10). Hazards were higher when current exposure to typical antipsychotics were directly compared to atypical antipsychotics for stroke (HR 1.23, 95% CI 1.09 to 1.40), heart failure (HR 1.18, 95% CI 1.01 to 1.39), fractures (HR 1.22, 95% CI 1.08 to 1.38), pneumonia (HR 1.92, 95% CI 1.77 to 2.08), and AKI (HR 1.22, 95% CI 1.05 to 1.42), but no significant differences between the two types of drug were found for the risks of VTE or MI.

Supplementary Table S11 shows the risks of adverse outcomes associated with haloperidol (the most commonly prescribed typical antipsychotic), and with risperidone and quetiapine (the two most commonly prescribed atypical antipsychotics). During the current use period of 90 days following a prescription, both risperidone and haloperidol were associated with elevated risks of all adverse outcomes except for ventricular arrhythmia and the unrelated outcome, compared with non-exposure. Current use of quetiapine was also associated with elevated risks for fracture, pneumonia, and AKI, compared with non-exposure. Amongst current users of haloperidol or risperidone, risks for fracture, pneumonia, and AKI were higher for haloperidol versus risperidone, but risks for stroke, VTE, MI, and heart failure were similar for the two drugs. With the exceptions of MI, ventricular arrhythmia, and the unrelated outcome, risks of all adverse outcomes were higher for haloperidol versus quetiapine, especially for pneumonia (HR 2.53, 95% CI 2.21 to 2.89) and VTE (HR 1.99, 95% CI 1.33 to 2.97). Amongst current users of quetiapine compared against risperidone, there were no significant differences in their risks for MI, heart failure, or fracture. However, risks for stroke (HR 0.64, 95% CI 0.53 to 0.78), VTE (HR 0.49, 95% CI 0.36 to 0.68), pneumonia (HR 0.72, 95% CI 0.63 to 0.81), and AKI (HR 0.81, 95% CI 0.67 to 0.96), were lower for quetiapine than risperidone.

**Absolute risks of adverse outcomes**

Cumulative incidence for all outcomes examined was higher for antipsychotic users versus matched-comparators, with the exception of ventricular arrhythmia and the unrelated outcome (Table 4). Absolute risk, as well as the risk difference, was particularly large for pneumonia. In the 90 days after initiation of antipsychotic treatment, cumulative incidence of pneumonia amongst antipsychotic users was 4.48% (95% CI 4.26 to 4.71) vs 1.49% (95% CI 1.45 to 1.53) in the matched cohort of non-exposed (difference 2.99%, 95% CI 2.77 to 3.22). At one year, this rose to 10.41% (95% CI 10.05 to 10.78) for antipsychotic users compared with 5.63% (95% CI 5.55 to 5.70) for non-exposure (difference 4.78%, 95% CI 4.41 to 5.16).

**Sensitivity analyses**

Sensitivity analysis with two other definitions of antipsychotic exposure found similar results (Supplementary Figures S4 and S5). Of the 544,203 antipsychotic prescriptions issued, 1.3% was for levomepromazine (Supplementary Table 1). Results remained virtually the same when patients were censored at the time of their first levomepromazine prescription (Supplementary Figure S6). Results of the Fine-Gray models taking into account the competing risks of death also showed broadly similar patterns of hazards to those from the Cox models (Supplementary Table S12 and Figure S7). Sex-specific analyses showed that males have higher incidence rates of all adverse outcomes than for females, except for fractures and VTE where incidence was higher for females than for males (Supplementary Table S13). Compared with female antipsychotic users, male users have elevated hazards for pneumonia and AKI (male-to-female HR 1.16, 95% 1.08 to 1.25 for pneumonia; 1.22, 95% CI 1.08 to 1.37 for AKI), but lower hazard for stroke (male-to-female HR 0.81, 95% CI 0.73 to 0.91). There were no significant differences by sex in the hazards for VTE, MI, heart failure, ventricular arrhythmia, or fractures (Supplementary Table S14).

**DISCUSSION**

**Principal findings**

In this population-based cohort study of people with dementia, exposure to antipsychotics was associated with elevated risks for stroke, VTE, MI, heart failure, fracture, pneumonia, and AKI, versus non-exposure. Elevated risks were observed amongst current and recent users and were highest in the first week following initiation of treatment. In the 90 days following a prescription, relative hazards were highest for pneumonia, AKI, stroke, and VTE, with the increased risks ranging from 1.5-fold (for VTE) to two-fold (for pneumonia) versus non-exposure. No increased risk was found for ventricular arrhythmia or the unrelated outcome. Difference in absolute risks cumulative incidence between antipsychotic users and their matched comparators were substantial for most adverse events, and largest for pneumonia. In the 90 days following a prescription, risks of stroke, heart failure, fractures, pneumonia, and AKI were higher for typical versus atypical antipsychotics, while no significant differences between the two classes of drug were found for the risks of VTE or MI. Haloperidol was associated with higher risks than risperidone for fractures, pneumonia, and AKI, but no significant differences between the two drugs were found for the other outcomes. Risks of almost all adverse outcomes were higher for haloperidol versus quetiapine. There were no significant differences between risperidone and quetiapine for the risks for MI, heart failure, or fracture, but risks for stroke, VTE, pneumonia, and AKI were lower for quetiapine versus risperidone.

**Comparison with previous findings**

In a population-based study in Wales, Dennis et al (2017) reported no increased risks for non-fatal acute cardiac events associated with antipsychotic use for patients with all-cause dementia, although elevated risks were found for those with Alzheimer’s disease.37 Systematic reviews and meta-analyses of studies not limited to patients with dementia have also reported inconsistent evidence for MI, or lack of robustness of these data.33,34,72 Our findings for MI were similar to those reported by Pariente et al (2012), who first documented a modest and time-limited increase in risk of this outcome associated with antipsychotic use amongst patients with dementia.57 In a study of nursing home residents in the US, users of typical antipsychotics, but not atypical antipsychotics, were more likely than non-users to be hospitalised for ventricular arrhythmia or cardiac arrest,35 and in a study not limited to older people, Wu et al reported elevated risks for ventricular arrhythmia and/or sudden cardiac death associated with both typical and atypical antipsychotics.36 We did not find any association with ventricular arrhythmia but the number of events was low, and we did not examine cardiac arrest/sudden death.

Increased risks of VTE associated with antipsychotic use has been reported in the general population,38 but meta-analyses found risks of VTE were only elevated amongst younger users.39,40 Our findings are consistent with Dennis (2017), who reported elevated risks of VTE in the 12 months following drug initiation (prior event rate ratio 1.95, 95% CI 1.83 to 2.0).37 However, in absolute terms, these risks were relatively low compared with other outcomes examined in this study.

We found both relative and absolute risks for pneumonia were the highest amongst all outcomes examined. Current users of antipsychotics had a two-fold elevated risk compared with non-users (Figure 1), and although this magnitude of increased risk was comparable to those reported previously,14,31,32 we additionally observed that risks were greater in the first week following drug initiation. Knol et al (2008) also reported particularly high risk for hospital-diagnosed pneumonia in the first week, but the magnitude of elevation (OR=4.5, 95% CI 2.8 to 7.3) was much lower than that we observed.30 The mechanisms linking antipsychotics exposure and development of pneumonia is not well-understood, and there is significant pharmacological heterogeneity among individual drugs, but antipsychotics-induced extrapyramidal symptoms, sedation, xerostomia (dry mouth) and dyskinesia/impaired swallowing, are commonly considered as potential risk factors.73 In addition, since elderly people with pneumonia may be less likely than younger patients to present with respiratory symptoms but more likely to show signs of delirium,74 it is possible that reverse causality might have contributed to the high risks observed in the early days following drug initiation, as delirium due to the onset of pneumonia might have been treated with antipsychotics before the diagnosis of pneumonia was made.30 However, although causality cannot be inferred, the particularly high elevated risks observed for a range of outcomes and not only for pneumonia in the early days following drug initiation are consistent with other studies.28 This could be partly explained by only patients who tolerated the first days of drug exposure being given further prescriptions.

The use of atypical antipsychotics in older adults has been shown to be associated with elevated risk of AKI.44-46 Hwang et al (2014) and Ryan et al (2017) both reported significant increased risks compared with non-users in the 90 days following atypical antipsychotic initiation.44,45 In contrast, Sharon et al (2022) observed no elevated risks for the broad category of atypical antipsychotics although significant increased risk was found for olanzapine.46 Increased risks for AKI were found for both typical and atypical antipsychotics in our study, with the risks being higher for haloperidol than for risperidone and quetiapine.

In a meta-analysis of observational studies, antipsychotic use was found to be associated with elevated risks of hip fracture amongst people with dementia.41 In their self-controlled case series study of elderly patients, Wang et al (2021) also reported increased risks of falls and fractures following antipsychotic initiation, but incidence was found to be even higher in the 14 days before treatment started.43 Similar findings were also reported by Brännström et al (2020), suggesting that the risks observed during the treatment periods might not be attributable to antipsychotics alone.42 While we cannot eliminate confounding in our study, we had minimised this risk by adjusting for a large number of both clinical and non-clinical characteristics which might have influenced treatment assignment. We also found no elevated risks associated with current or recent antipsychotic use for the negative control outcomes (appendicitis and cholecystitis).

Our study found that the risks of stroke and heart failure were higher for typical than for atypical antipsychotics, but risks of VTE and MI were similar between the two classes of drug. We also found no significant differences between haloperidol and risperidone in the risks of these four outcomes, but significantly increased risks for stroke, VTE, and heart failure for haloperidol versus quetiapine. Previous studies of elderly patients have reported that the risks associated with typical and atypical antipsychotics for cardiovascular or cerebrovascular events were similar for the two classes of drugs,17,75-77 but risks of these outcomes and of all-cause mortality were elevated for haloperidol versus risperidone.21,77 For fractures and pneumonia, our study found that their risks were higher for typical than atypical antipsychotics and for haloperidol versus risperidone or quetiapine. Findings from previous studies comparing these risks by antipsychotics types have not been consistent.30-32,75,76

**Strengths and limitations**

A key strength of this study was the investigation of a wide range of adverse events in a large population-based cohort, and the reporting of both relative and absolute risks differences over multiple time periods. Previous studies have commonly focused on a single outcome or type of outcome such as cerebrovascular events, and on the reporting of relative risks. By examining the same cohort at risk, we were able to directly compare the hazards of multiple outcomes without differential inter-cohort biases. In addition, only patients with a clinician-recorded diagnosis of dementia were included, and we have adjusted for many variables that might have influenced probability of antipsychotic initiation, seeking to minimise confounding by indication. CPRD is one of the largest primary care databases in the world, and is broadly representative of the UK population.47-49 It includes all prescriptions issued in participating primary care practices in the UK and is recognised as a high-quality resource to support international pharmacovigilance.78 Its longitudinal nature with linked data from secondary care and mortality records enabled us to capture the study outcomes from multiple sources, as well as information on prescribing and co-morbidities.79,80 Our findings were also robust to different classifications of exposure periods and no associations were found between current and recent antipsychotic use with the development of the negative control outcome. However, a significant association with past use was observed which we are unable to explain.

As with all observational studies, residual confounding cannot be excluded. For example, polypharmacy is common amongst the elderly population, which could lead to drug-drug interactions and potentially confound our findings.81,82 We also do not have information on the indication for the antipsychotics treatment. We have minimised the risk of confounding through the use of propensity score methods to control for imbalances in measurable patient characteristics between antipsychotic users and their matched comparators. However, unlike in randomised control trials which, if properly conducted, could account for both observed and unobserved differences between the treated and untreated groups, propensity scores method can only adjust for the observed differences between the two groups. Additionally, our choice of covariates was based on the literature and discussions with clinical experts, and was not formally structured by the use of, for example, a directed acyclic graph. However, although the strong associations with pneumonia in the first seven days of antipsychotic initiation may partially be attributed to reverse causality, that is less likely to explain associations over longer time periods. We also found no elevated risk for appendicitis and cholecystitis during current and recent use, our negative control outcome which was included to detect potential unmeasured confounding.54 Another limitation of our study is that although prescriptions issued in primary care are very reliable in CPRD, information on dosage are not well-recorded, nor is there information on medication adherence or prescriptions issued while a patient is in hospital.48 Misclassification of exposure is therefore a potential issue. Like other routinely collected electronic health data that are collected for administrative rather than research purposes, there are also potential issues with coding errors, missing or incomplete information, and variations in data quality between practices and healthcare settings. Although data have undergone quality checks before being released and our use of linked data would have helped to address such issues, we are restricted to data that is coded in patients’ electronic health records. In addition, despite the representativeness of the CPRD data, care should be taken in making inferences beyond the population studied. Our sex-specific investigations were also conducted as post-hoc analyses. By using existing matched sets but restricting the comparators to those of the same sex as the antipsychotic user they were matched to, the number of comparators was greatly reduced. Although we found some evidence of differences in hazards for stroke, pneumonia, and AKI between male and female users of antipsychotics, further research is needed to validate these findings.

**Implications for practice and policy**

The mechanisms underlying the links between antipsychotics and these outcomes are not fully understood. In the UK, US, and Europe, current regulatory warnings of antipsychotics for the treatment of BPSD were mostly based on evidence of increased risks for stroke and mortality.8,11,22-26 This study finds a considerably wider range of harms associated with antipsychotics use in people with dementia, and the risks of harm are highest soon after initiation. Our findings have to be seen in the context of trial evidence of at-best modest benefit on BPSD. The efficacy of antipsychotics in the management of BPSD remains inconclusive.83-86 Atypical antipsychotics, including risperidone which is one of two antipsychotics licensed in the UK for the treatment of BPSD, have the strongest evidence base but the benefits are only modest.83,86

Any potential benefits of antipsychotic treatment therefore need to be weighed against their risk of serious harm across multiple outcomes. Although there may be times when an antipsychotic prescription is the least-bad option, clinicians should actively consider the considerable risks, taking into account the patients’ pre-existing co-morbidities and living support available. The NNH reported in this study can help to inform clinical judgements on the appropriateness of treatments taking account of the modest potential benefits reported in clinical trials. Where prescriptions of such drugs are needed, treatment plans should be reviewed regularly with the patients and their carers to reassess the need for continuing treatment.9 In addition,given the higher risks of adverse events in the early days following drug initiation, clinical examinations should be taken before and clinical reviews conducted shortly after the start of treatment. Our study has also reaffirmed that these drugs should only be prescribed for the shortest period possible.9 Although regulators have made efforts to limit the use of these drugs to the most severe cases of BPSD,8,83,87 antipsychotic prescribing in dementia remains common and has even increased in recent years.4,5,88,89 If such trends continue, further communication on the associated risks could be considered by guideline developers or regulators after a review of the totality of evidence. Greater accountability and monitoring in the use of these drugs may be called for, and additional legal reforms may be required to regulate compliance.90 There is evidence in recent years of other psychotropic drugs such as antidepressants, benzodiazepines, mood stabilisers and anticonvulsants being prescribed in lieu of antipsychotics for the treatment of BPSD.28,91,92 These drugs, however, also pose their own risks. Further research is needed into safer pharmaceutical treatment of BPSD and more efficacious, easy to deliver, initial non-pharmacologic treatments.

**Conclusions**

Antipsychotic use is associated with a wide range of serious adverse outcomes in people with dementia, with relatively large absolute risks of harm for some outcomes. These risks should be considered in future regulatory decisions, alongside cerebrovascular events and mortality. Any potential benefits of antipsychotic treatment need to be weighed against risk of serious harm and treatment plans should be reviewed regularly. Antipsychotic impact on BPSD is modest at best but the proportion of patients with dementia prescribed antipsychotics has increased in recent years. Our findings that antipsychotics are associated with a wider range of risks than previously known are therefore of direct relevance to guideline developers, regulators and clinicians considering the appropriateness of antipsychotic prescribing in BPSD.

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**COMPETING INTERESTS**

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PLHM has full access to all data and all authors have full access to the statistical reports and tables in the study. PLHM can take responsibility for the integrity of the data and the accuracy of the data analysis.

**AUTHOR CONTRIBUTIONS**

All authors contributed to the study concept and design, and the acquisition, analysis, or interpretation of data. Clinical codes were reviewed by BG, DM, TvS, AJA and DMA. PLHM conducted the statistical analyses and wrote the first draft of the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version. AJA, DMA, RAE, BG, DRM, AS, and TvS obtained the funding. The corresponding author (PLHM) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

The lead author (PLHM: manuscript guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted.

**DATA SHARING**

Electronic health records are, by definition, considered sensitive data in the UK by the Data Protection Act and cannot be shared via public deposition because of information governance restriction in place to protect patient confidentiality. Access to CPRD data is subject to protocol approval via CPRD’s Research Data Governance Process. For more information, see <https://cprd.com/data-access>. Linked HES, ONS mortality, and IMD data can also be requested from CPRD.

**DISSEMINATION TO PARTICIPANTS AND RELATED PATIENT AND PUBLIC COMMUNITIES**

This study used anonymised electronic health records from the CPRD and it is therefore not possible to disseminate our findings directly to the patients whose data we used. Our study is part of a NIHR funded programme (RP-PG-1214-20012): “Avoiding patient harm through the application of prescribing safety indicators in English general practices” (acronym: PRoTeCT). We have experienced patient and public involvement members aligned to the programme who we will consult in the results dissemination. In addition, senior author DA is Director of NIHR Greater Manchester Patient Safety Research Collaboration (GMPSRC) and co-authors MJC and AJA are affiliated with it. The PSRC has a community of public contributors including patients, carers, and people accessing health and social care services. We will work with this network to disseminate our findings.

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Figure 1. Hazard ratios (adjusted for IPT weights) of adverse outcomes associated with current, recent, and past antipsychotic use; with current use being defined as the first 90 days from the date of an antipsychotic prescription, recent use as up to 180 days after current use ended, and past use as after recent use.

**Table 1. Baseline characteristics of antipsychotic users and matched comparators included in the analysis of stroke (CPRD Aurum and GOLD combined data). (See Supplementary Tables S2 to S9 for baseline characteristics for other outcomes)**

|  | Before IPT weighting | After IPT weighting |
| --- | --- | --- |
| Antipsychotics users (n=24,696)  | Matched comparators (n=344,232) | Standardised difference | Antipsychotics users, % | Matched comparators, % | Standardised difference  |
| ***Demographics*** |  |  |  |  |  |  |
| *Sex (%)* |  |  |  |  |  |  |
| Male  | 35.6 | 34.1 | 0.032 | 34.1 | 34.2 | -0.002 |
| Female  | 64.4 | 65.9 | -0.032 | 65.9 | 65.8 | 0.002 |
|  |  |  |  |  |  |  |
| *Age* |  |  |  |  |  |  |
| Mean (SD) age at dementia diagnosis | 81.1 (8.2) | 80.5 (8.0) | 0.079 | 80.5 (8.0) | 80.5 (8.0) | 0.003 |
| Mean (SD) age at start of follow up | 82.7 (8.1) | 81.8 (8.0) | 0.118 | 81.8 (8.0) | 81.9 (8.0) | -0.003 |
|  |  |  |  |  |  |  |
| *Ethnicity (%)* |  |  |  |  |  |  |
| White  | 73.1 | 75.6 | -0.057 | 74.4 | 75.4 | -0.022 |
| Non-White  | 2.0 | 2.5 | -0.037 | 2.5 | 2.5 | 0.005 |
| Unknown  | 24.9 | 21.9 | 0.071 | 23.0 | 22.1 | 0.021 |
|  |  |  |  |  |  |  |
| *IMD quintile (%)* |  |  |  |  |  |  |
| 1 (least deprived) | 21.8 | 23.0 | -0.029 | 22.7 | 22.9 | -0.007 |
| 2 | 22.3 | 22.8 | -0.013 | 22.7 | 22.8 | -0.003 |
| 3 | 21.3 | 20.3 | 0.025 | 20.2 | 20.4 | -0.005 |
| 4 | 18.4 | 18.3 | 0.003 | 18.5 | 18.3 | 0.004 |
| 5 (most deprived) | 16.1 | 15.4 | 0.017 | 15.9 | 15.5 | 0.012 |
| Unknown | 0.1 | 0.1 | 0.001 | 0.1 | 0.1 | -0.001 |
|  |  |  |  |  |  |  |
| ***Lifestyle*** |  |  |  |  |  |  |
| Smoking (%) |  |  |  |  |  |  |
| Current smoker | 16.7 | 17.0 | -0.006 | 17.1 | 16.9 | 0.003 |
| Ex-smoker | 43.2 | 43.4 | -0.005 | 42.8 | 43.4 | -0.011 |
| Never smoker | 33.8 | 34.0 | -0.004 | 34.1 | 34.0 | 0.004 |
| Unknown | 6.3 | 5.7 | 0.027 | 6.0 | 5.7 | 0.011 |
|  |  |  |  |  |  |  |
| Alcohol use (%) |  |  |  |  |  |  |
| Non-drinker | 15.9 | 15.1 | 0.022 | 15.5 | 15.2 | 0.010 |
| Light drinker | 11.4 | 11.7 | -0.009 | 11.6 | 11.7 | -0.003 |
| Former drinker | 4.1 | 3.6 | 0.027 | 3.6 | 3.6 | 0.000 |
| Moderate drinker | 37.2 | 38.9 | -0.035 | 38.1 | 38.8 | -0.014 |
| Heavy drinker | 4.2 | 4.5 | -0.014 | 4.6 | 4.5 | 0.002 |
| Unknown | 27.2 | 26.2 | 0.022 | 26.7 | 26.3 | 0.009 |
|  |  |  |  |  |  |  |
| ***Comorbidities (%)* a** |  |  |  |  |  |  |
| Hypertension | 37.6 | 39.1 | -0.029 | 38.6 | 39.0 | -0.007 |
| Diabetes | 13.5 | 13.9 | -0.011 | 13.8 | 13.9 | -0.002 |
| COPD | 17.9 | 16.8 |  0.029 | 17.1 | 16.9 | 0.007 |
| Rheumatoid arthritis | 2.0 | 2.0 |  0.005 | 2.0 | 2.0 | 0.004 |
| Moderate/severe renal disease | 21.3 | 19.6 |  0.042 | 19.4 | 19.7 | -0.009 |
| Moderate/severe liver disease | 0.7 | 0.7 | -0.004 | 0.7 | 0.7 | 0.001 |
| Atrial fibrillation | 12.4 | 11.4 |  0.030 | 11.4 | 11.5 | -0.001 |
| Cancer | 16.2 | 13.3 |  0.083 | 13.4 | 13.5 | -0.001 |
| Serious mental illness | 2.3 | 1.0 |  0.105 | 1.2 | 1.1 | 0.011 |
|  |  |  |  |  |  |  |
| ***Prescribed medications (%)*** |  |  |  |  |  |  |
| Antiplatelets | 33.6 | 33.2 |  0.007 | 33.4 | 33.3 | 0.003 |
| Oral anticoagulants | 6.0 | 5.8 |  0.011 | 5.8 | 5.8 | -0.002 |
| ACE inhibitors or ARB | 23.5 | 26.3 | -0.064 | 25.8 | 26.1 | -0.006 |
| Alpha blockers | 6.3 | 6.5 | -0.011 | 6.4 | 6.5 | -0.005 |
| Beta blockers | 18.2 | 18.0 |  0.006 | 17.9 | 18.0 | -0.002 |
| Calcium channel blockers | 17.6 | 19.7 | -0.052 | 19.5 | 19.5 | -0.001 |
| Diuretics | 28.1 | 27.8 |  0.007 | 27.9 | 27.8 | 0.001 |
| Lipid lowering drugs | 26.8 | 29.2 | -0.053 | 28.7 | 29.0 | -0.007 |
| Insulin and antidiabetic drugs | 9.0 | 9.6 | -0.019 | 9.5 | 9.6 | -0.001 |
| NSAID | 12.0 | 11.8 |  0.007 | 11.9 | 11.8 | 0.002 |
| Antidepressants | 34.8 | 26.2 |  0.188 | 27.0 | 26.7 | 0.006 |
| Benzodiazepines | 14.9 | 6.4 |  0.278 | 7.2 | 7.0 | 0.005 |
| Lithium | 0.3 | 0.2 |  0.011 | 0.3 | 0.2 | 0.012 |

a History of the condition

**Table 2. Incidence rates (per 10,000 person years) and number needed to harm of adverse outcomes associated with antipsychotic use during the first 180 days and 2 years of follow-up period**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | 180 days after start of follow-up | Two years after start of follow-up |
|  |  | Number of outcomes  | Person-years | Incidence rates (95% CI)(per 10,000 person-years) | Number needed to harm (95% CI) | Number of outcomes  | Person-years | Incidence rates (95% CI)(per 10,000 person-years) | Number needed to harm (95% CI) |
| Stroke | Antipsychotics user | 673 | 9075 | 741.6 (687.6, 799.8) | 29 (25, 35) | 1493 | 24,555 | 608.0 (578.0, 639.7) | 41 (36, 47) |
| Matched comparators  | 6046 | 151,712 | 398.5 (388.6, 408.7) |  | 16,694 | 460,387 | 362.6 (357.1, 368.2) |  |
| VTE a  | Antipsychotics user | 218 | 11,181 | 195.0 (170.7, 222.7) | 107 (83, 149) | 494 | 30,315 | 163.0 (149.2, 178.0) | 167 (134, 221) |
| Matched comparators  | 1950 | 192,168 | 101.5 (97.1, 106.1) |  | 6035 | 585,379 | 103.1 (100.5, 105.7) |  |
| Myocardial infarction | Antipsychotics user | 206 | 10,817 | 190.4 (166.1, 218.3) | 167 (116, 301) | 502 | 29,518 | 170.1 (155.8, 185.6) | 254 (183, 413) |
| Matched comparators  | 2420 | 185,230 | 130.6 (125.5, 136.0) |  | 7380 | 564,626 | 130.7 (127.8, 133.7) |  |
| Heart failure | Antipsychotics user | 476 | 10,466 | 454.8 (415.7, 497.6) | 63 (50, 86) | 978 | 28,603 | 341.9 (321.2, 364.0) | 166 (122, 260) |
| Matched comparators  | 5275 | 177,578 | 297.1 (289.1, 305.2) |  | 15,278 | 542,612 | 281.6 (277.1, 286.1) |  |
| Ventricular arrhythmia  | Antipsychotics user | 16 | 11,807 | 13.6 (8.3, 22.1) | N/A d | 40 | 32,143 | 12.4 (9.1, 17.0) | N/A d |
| Matched comparators  | 321 | 204,697 | 15.7 (14.1, 17.5) |  | 886 | 623,749 | 14.2 (13.3, 15.2) |  |
| Fractures | Antipsychotics user | 626 | 7587 | 825.1 (762.9, 892.3) | 40 (32, 54) | 1574 | 20,255 | 777.1 (739.6, 816.4) | 45 (38, 55) |
| Matched comparators  | 7088 | 123,179 | 575.4 (562.2, 589.0) |  | 20,764 | 373,288 | 556.2 (548.7, 563.9) |  |
| Pneumonia | Antipsychotics user | 1849 | 10,909 | 1694.9 (1619.4, 1774.0) | 9 (9, 10) | 3807 | 29,659 | 1283.6 (1243.5, 1325.0) | 15 (14, 16) |
| Matched comparators  | 11,160 | 185,609 | 601.3 (590.2, 612.5) |  | 34,209 | 566,545 | 603.8 (597.5, 610.3) |  |
| AKI b | Antipsychotics user | 657 | 11,213 | 585.9 (542.8, 632.5) | 35 (30, 42) | 1300 | 30,583 | 425.1 (402.6, 448.8) | 84 (70, 105) |
| Matched comparators  | 5706 | 190,438 | 299.6 (292.0, 307.5) |  | 17,848 | 582,080 | 306.6 (302.2, 311.2) |  |
| Unrelated outcome c | Antipsychotics user | 19 | 11,090 | 17.1 (10.9, 26.9) | N/A d | 53 | 30,192 | 17.6 (13.4, 23.0) | N/A d |
| Matched comparators  | 344 | 191,110 | 18.0 (16.2, 20.0) |  | 1026 | 582,200 | 17.6 (16.6, 18.7) |  |

a VTE - Venous thromboembolism

b AKI - Acute kidney injury

c Unrelated outcome - Appendicitis and cholecystitis

d N/A because there was no significant difference between the incidence rate for antipsychotic users and the incidence rate for matched comparators.

**Table 3. Hazard ratios (adjusted for IPT weights) of adverse outcomes associated with current, recent, and past antipsychotic use stratified by follow-up period; with current use being defined as the first 90 days from the date of an antipsychotic prescription, recent use as up to 180 days after current use ended, and past use as after recent use. a**

| Hazard ratio (95% confidence interval) | Antipsychotic use | Follow-up period |
| --- | --- | --- |
| 0-7 days | 8-30 days | 31-180 days | 181-365 days | 366 days-2 years |
| Stroke | Current | 3.75 (3.00, 4.69) | 1.57 (1.28, 1.92) | 1.54 (1.39, 1.70) | 1.52 (1.34, 1.73) | 1.55 (1.38, 1.74) |
|  | Recent | - | - | 1.72 (1.35, 2.20) | 1.47 (1.19, 1.82) | 1.32 (0.98, 1.79) |
|  | Past | - | - | - | 1.66 (1.15, 2.39) | 1.04 (0.85, 1.28) |
| VTE b | Current | 2.05 (1.19, 3.56) | 1.92 (1.36, 2.70) | 1.67 (1.41, 1.99) | 1.39 (1.10, 1.75) | 1.61 (1.33, 1.96) |
|  | Recent | - | - | 2.14 (1.46, 3.15) | 1.27 (0.86, 1.89) | 1.58 (1.01, 2.48) |
|  | Past | - | - | - | 0.62 (0.23, 1.65) | 0.95 (0.67, 1.35) |
| Myocardial infarction | Current | 2.33 (1.41, 3.83) | 1.61 (1.15, 2.26) | 1.27 (1.06, 1.52) | 1.39 (1.13, 1.70) | 1.02 (0.83, 1.27) |
|  | Recent | - | - | 0.89 (0.52, 1.52) | 1.34 (0.96, 1.88) | 1.28 (0.80, 2.03) |
|  | Past | - | - | - | 1.25 (0.70, 2.23) | 0.91 (0.66, 1.25) |
| Heart failure  | Current | 2.85 (2.15, 3.78) | 1.95 (1.59, 2.40) | 1.32 (1.17, 1.49) | 1.12 (0.95, 1.31) | 0.97 (0.82, 1.14) |
|  | Recent | - | - | 0.99 (0.72, 1.37) | 0.80 (0.59, 1.09) | 0.80 (0.54, 1.20) |
|  | Past | - | - | - | 1.11 (0.74, 1.67) | 0.81 (0.63, 1.04) |
| Fracture | Current | 2.22 (1.66, 2.98) | 1.49 (1.22, 1.83) | 1.37 (1.24, 1.52) | 1.29 (1.14, 1.46) | 1.53 (1.38, 1.71) |
|  | Recent | - | - | 1.07 (0.82, 1.41) | 1.28 (1.04, 1.58) | 1.61 (1.25, 2.07) |
|  | Past | - | - | - | 1.02 (0.69, 1.50) | 1.07 (0.89, 1.28) |
| Pneumonia  | Current | 9.99 (8.78, 11.4) | 3.39 (3.04, 3.77) | 2.03 (1.89, 2.17) | 1.79 (1.64, 1.95) | 1.71 (1.58, 1.85) |
|  | Recent | - | - | 1.93 (1.63, 2.29) | 1.77 (1.53, 2.05) | 1.40 (1.14, 1.72) |
|  | Past | - | - | - | 1.38 (1.07, 1.79) | 1.48 (1.32, 1.67) |
| AKI c | Current | 3.79 (2.96, 4.87) | 2.61 (2.17, 3.13) | 2.03 (1.84, 2.25) | 1.27 (1.09, 1.48) | 1.26 (1.10, 1.44) |
|  | Recent | - | - | 1.36 (1.03, 1.81) | 1.05 (0.80, 1.38) | 1.23 (0.85, 1.79) |
|  | Past | - | - | - | 1.47 (1.03, 2.09) | 1.08 (0.88, 1.32) |

a Not reported for ventricular arrhythmia and unrelated outcome (appendicitis and cholecystitis) because of small number of cases.

b VTE - Venous thromboembolism

c AKI - Acute kidney injury

**Table 4. Cumulative incidence of adverse outcomes associated with antipsychotic use at 90 days, 180 days, 365 days (one year), and two years after start of follow-up**

|  | 90 days | 180 days | 365 days (1 year) | 2 years |
| --- | --- | --- | --- | --- |
| n  | Cumulative incidence, % (95% CI) | n  | Cumulative incidence, % (95% CI) | n  | Cumulative incidence, % (95% CI) | n  | Cumulative incidence, % (95% CI) |
| Stroke | Antipsychotics user | 412 | 1.74 (1.59, 1.91) | 673 | 2.96 (2.75, 3.19) | 1041 | 4.89 (4.61, 5.19) | 1493 | 7.75 (7.38, 8.14) |
| Matched comparators | 3419 | 1.04 (1.01, 1.08) | 6046 | 1.91 (1.86, 1.96) | 10,420 | 3.50 (3.43, 3.56) | 16,694 | 6.28 (6.19, 6.37) |
| Difference |  | 0.70 (0.54, 0.87) |  | 1.06 (0.84, 1.28) |  | 1.39 (1.10, 1.70) |  | 1.47 (1.08, 1.87) |
| VTE a | Antipsychotics user | 114 | 0.39 (0.32, 0.46) | 218 | 0.79 (0.69, 0.90) | 329 | 1.25 (1.12, 1.39) | 494 | 2.09 (1.91, 2.28) |
| Matched comparators  | 1052 | 0.26 (0.24, 0.27) | 1950 | 0.49 (0.47, 0.51) | 3607 | 0.97 (0.94, 1.00) | 6035 | 1.83 (1.78, 1.88) |
| Difference |  | 0.13 (0.06, 0.21) |  | 0.30 (0.20, 0.41) |  | 0.29 (0.15, 0.43) |  | 0.26 (0.08, 0.46) |
| Myocardial infarction | Antipsychotics user | 130 | 0.46 (0.39, 0.54) | 206 | 0.75 (0.65, 0.86) | 350 | 1.39 (1.25, 1.54) | 502 | 2.19 (2.00, 2.39) |
| Matched comparators  | 1319 | 0.33 (0.31, 0.35) | 2420 | 0.63 (0.61, 0.66) | 4429 | 1.23 (1.20, 1.27) | 7380 | 2.31 (2.26, 2.37) |
| Difference |  | 0.13 (0.06, 0.21) |  | 0.12 (0.02, 0.23) |  | 0.16 (0.01, 0.31) |  | -0.13 (-0.32, 0.08) |
| Heart failure | Antipsychotics user | 311 | 1.15 (1.03, 1.27) | 476 | 1.81 (1.66, 1.97) | 712 | 2.89 (2.69, 3.11) | 978 | 4.37 (4.10, 4.64) |
| Matched comparators  | 2824 | 0.74 (0.72, 0.77) | 5275 | 1.43 (1.39, 1.47) | 9462 | 2.73 (2.68, 2.79) | 15,278 | 4.95 (4.87, 5.02) |
| Difference |  | 0.40 (0.28, 0.53) |  | 0.38 (0.22, 0.55) |  | 0.16 (-0.05, 0.38) |  | -0.58 (-0.86, -0.29) |
| Ventricular arrhythmia b | Antipsychotics user | 10 | - | 16 | - | 30 | 0.11 (0.08, 0.15) | 40 | 0.16 (0.11, 0.21) |
| Matched comparators  | 181 | - | 321 | - | 549 | 0.14 (0.13, 0.15) | 886 | 0.25 (0.23, 0.26) |
| Difference |  | - |  | - |  | -0.03 (-0.06, 0.02) |  | -0.09 (-0.14, -0.03) |
| Fractures | Antipsychotics user | 367 | 1.88 (1.70, 2.07) | 626 | 3.34 (3.09, 3.60) | 1016 | 5.80 (5.46, 6.15) | 1574 | 9.99 (9.52, 10.47) |
| Matched comparators  | 3777 | 1.42 (1.37, 1.46) | 7088 | 2.75 (2.69, 2.81) | 12,694 | 5.22 (5.13, 5.31) | 20,764 | 9.50 (9.37, 9.62) |
| Difference |  | 0.46 (0.28, 0.66) |  | 0.59 (0.33, 0.86) |  | 0.58 (0.23, 0.94) |  | 0.49 (0.01, 0.99) |
| Pneumonia | Antipsychotics user | 1283 | 4.48 (4.26, 4.71) | 1849 | 6.72 (6.44, 7.01) | 2695 | 10.41 (10.05, 10.78) | 3807 | 16.23 (15.76, 16.71) |
| Matched comparators  | 5945 | 1.49 (1.45, 1.53) | 11,160 | 2.89 (2.84, 2.94) | 20,395 | 5.63 (5.55, 5.70) | 34,209 | 10.59 (10.49, 10.70) |
| Difference |  | 2.99 (2.77, 3.22) |  | 3.83 (3.54, 4.12) |  | 4.78 (4.41, 5.16) |  | 5.64 (5.15, 6.13) |
| AKI c | Antipsychotics user | 420 | 1.46 (1.33, 1.60) | 657 | 2.34 (2.17, 2.52) | 933 | 3.52 (3.31, 3.75) | 1300 | 5.38 (5.10, 5.67) |
| Matched comparators  | 3020 | 0.74 (0.71, 0.76) | 5706 | 1.44 (1.41, 1.48) | 10,505 | 2.83 (2.78, 2.88) | 17,848 | 5.40 (5.32, 5.48) |
| Difference |  | 0.73 (0.60, 0.87) |  | 0.90 (0.73, 1.08) |  | 0.70 (0.47, 0.93) |  | -0.02 (-0.31, 0.28) |
| Unrelated outcome b, d | Antipsychotics user | 14 | - | 19 | - | 34 | 0.13 (0.10, 0.19) | 53 | 0.23 (0.17, 0.30) |
| Matched comparators  | 184 | - | 344 | - | 615 | 0.17 (0.15, 0.18) | 1026 | 0.31 (0.29, 0.33) |
| Difference |  | - |  | - |  | -0.03 (-0.07, 0.02) |  | -0.08 (-0.14, -0.01) |

a VTE - Venous thromboembolism

b Not estimated for 90 days or 180 days due to small number of cases

c AKI - Acute kidney injury

d Unrelated outcome - Appendicitis and cholecystitis



**Figure 1. Hazard ratios (adjusted for IPT weights) of adverse outcomes associated with current, recent, and past antipsychotic use; with current use being defined as the first 90 days from the date of an antipsychotic prescription, recent use as up to 180 days after current use ended, and past use as after recent use.**