

Antipsychotic prescribing and mortality in people with dementia before and during the COVID-19 pandemic: a retrospective cohort study

VERSIONS

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0.1	17/6/2021	Tim Wilkinson	Project outline
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OBJECTIVES

- Describe the extent to which antipsychotic prescribing for people with dementia has changed during the COVID-19 pandemic.
 - Describe the demographics of people with dementia who were and were not prescribed an antipsychotic between 2016-2021.
 - Conduct a time series analysis to look at the pattern of antipsychotic prescribing in people with dementia from 2016-2021.
 - Compare trends of antipsychotic prescribing to benzodiazepine prescribing in people with dementia between 2016-2021.
 - Describe the range and distribution of durations of risperidone treatment (the only antipsychotic medication licensed for use in Alzheimer's disease).
- Describe the mortality rates, all causes of death and rates of cerebrovascular and cardiovascular disease in people with dementia, before and during the COVID-19 pandemic (2016-2021).
 - Conduct a time series analysis of all-cause, cardiovascular and cerebrovascular mortality in people with dementia between 2016-2021.
 - Describe the leading causes of death in people with dementia, from January 2020 until the end of follow up.

BACKGROUND

The COVID-19 pandemic has disproportionately affected people with dementia in terms of mortality and quality of life (1–4). A recent UK survey revealed that people with dementia have experienced increased rates of agitation, restlessness, stress, anxiety and depression during the pandemic(5).

Antipsychotic medications can be used to treat symptoms of agitation, aggression, distress and psychosis in people with dementia when alternative approaches have failed (6,7). However, antipsychotic use has been associated with an increased risk of adverse outcomes, including stroke (8,9), myocardial infarction (10,11) and death (12).

NHS England produces monthly reports on the proportion of people with dementia who are prescribed an antipsychotic drug. This proportion remained constant throughout 2018-2019 but appeared to increase in March 2020, around the time when social restrictions were introduced in England to reduce the spread of COVID-19 (7). Rates of antipsychotic prescribing appeared to remain high throughout 2020, presumably due to increased agitation due to COVID-19 restrictions. However, the insights that can be gained from these publicly available data are limited, as they do not account for seasonal changes in prescribing trends and cannot provide further information on the demographics of people prescribed antipsychotic medications compared to those not prescribed these drugs.

This study will create a cohort from Welsh routinely-collected health data to explore trends in antipsychotic prescribing in people with dementia before and during the COVID-19 pandemic. We will also describe trends in cerebrovascular, cardiovascular and all-cause mortality in people with dementia before and during the pandemic, to assess whether any change in prescribing patterns is associated with a change in these outcomes.

PROTOCOL

Data sources

The CVD-COVID-UK initiative is a UK-wide initiative established to accelerate research on COVID-19 and cardiovascular disease, by facilitating access to linked routinely-collected electronic health record (EHR) data from England, Scotland and Wales (13). This study will use the CVD-COVID-UK initiative to access Welsh routinely-collected EHR data from the Secure Anonymised Information Linkage (SAIL) Databank (<https://saildatabank.com>). SAIL contains anonymised, individual-level, population-scale linked routinely-collected EHR and social care data sources for the population of Wales (14–16). Primary care data are available in SAIL for approximately 84% of the Welsh population. Data are accessed via a remotely-accessible, privacy-protecting trusted research environment (TRE).

This study will use a population-based cohort of people with dementia, composed of linked, anonymised, primary care (Welsh Longitudinal General Practice [WLGP]), hospital admissions (Patient Episode Database for Wales [PEDW]), mortality (Annual District Death Extract [ADDE], Annual District Death Daily [ADDD] and Consolidated Death Data Source [CDDS]), deprivation (Welsh Demographic Service Dataset [WDSD]), pharmacy drug dispensing data (Wales Dispensing Dataset [WDDS]) and care home (CARE) data.

Identifying people with dementia

We will use a validated list of codes in primary care (Read version 2) or hospital admissions (International Classification of Diseases version 10 [ICD-10]) data to identify people with dementia (all-cause dementia) (Appendix 1)(17). We will define dementia as the presence of ≥ 1 dementia codes in either data source, using the date of the first dementia code as the date of diagnosis. We will not use prescription of a dementia medication (donepezil, rivastigmine, galantamine, memantine) to identify dementia cases but, for people with a prescription for a dementia medication prior to the date of the first dementia diagnostic code, we will use the date of the first prescription as the date of dementia diagnosis. For sensitivity analyses, we will also identify people with Alzheimer's disease and vascular dementia subtypes (Appendix 1).

Study period

The study period will begin on 1st January 2016 and will run until 1st August 2021. Follow-up for each participant will start at the date of dementia diagnosis or, if a participant received a dementia diagnosis prior to the study start date, follow-up will start on 1st January 2016. Study follow-up for each participant will end at the earliest of the date of death, or 1st August 2021.

Eligibility criteria

We will include all participants who were alive and registered with a SAIL general practitioner (GP) on 1st January 2016 and who received a dementia diagnosis prior to or during the study period. We will exclude people with a dementia diagnosis <60 years, due to the low rates of dementia and mortality in these ages and the reduced accuracy of dementia diagnostic coding in younger ages (18).

Exposure

We will define exposure to antipsychotic medications using the prescription data, which are part of the Read-coded primary care data (Appendix 2). As a comparison, we will also identify exposure to benzodiazepines, an alternative class of drugs that can treat agitation or distress in people with dementia.

We conducted exploratory comparisons of the total numbers of drug prescriptions available in the primary care prescribing data (WLGP) and in the community pharmacy dispensing (WDDS) data. This demonstrated lower numbers of dispensed drugs compared to prescriptions early in the study period

(2016-2017), presumably relating to missing dispensing data. Therefore, we will use the primary care prescribing (WLGP) data for most of the analyses in this study, as it appears to be more complete. However, unlike primary care data, WDDS contains drug dose and pack size information. Therefore, we will only use the WDDS to calculate the average duration of risperidone treatment.

Outcomes

We will use mortality data to describe trends in all-cause mortality, mortality due to myocardial infarction and mortality due to stroke over the study period. We will study fatal stroke and myocardial infarction, to avoid the uncertainty of whether repeated non-fatal stroke or myocardial infarction codes (such as those identified in hospital admissions data) represent recurrent events or the same event coded multiple times. We will use the code lists for stroke and myocardial infarction that were developed during the creation of the SAIL Dementia electronic Cohort(16).

Statistical analysis

Demographics

We will describe the demographics of the study cohort and the subgroup of participants prescribed an antipsychotic drug at any point during follow-up (Table 1). We will estimate frailty in all participants with a minimum of five years of available primary care prior to the study start date, using the electronic Frailty Index (eFI) (19). The eFI algorithm uses primary care data to estimate an individual participant's frailty, defined as 'fit', 'mild', 'moderate' and 'severe'. We will use the preceding five years of primary care data to calculate the frailty score.

Objective 1: Antipsychotic prescribing trends

We will describe the demographics of people prescribed antipsychotic drugs compared to the entire study population. We will describe the age-standardised monthly rate of antipsychotic and benzodiazepine prescribing between 2016-2021 in people with dementia using a time series analysis. We will standardise ages based on the age distribution in the study cohort in January 2020 (the month in which the first COVID-19 case was identified in the UK). In addition to describing prescribing rates in the whole cohort population, we will stratify by sex, age (5-year bands), dementia subtype and care home versus community residence. We will describe the prescribing patterns for all antipsychotic drugs combined, as well as the top three most commonly prescribed antipsychotic drugs.

Risperidone is the only antipsychotic medication currently licensed for use in Alzheimer's disease in the UK. Its license covers use for six weeks only, to treat persistent aggression in patients with moderate to severe Alzheimer's disease (20). Using an estimated daily dose of 2mg (the maximum dose for this indication is 1mg twice daily), we will use the drug dose and pack size fields in the WDDS data to estimate the duration of risperidone treatment in study participants exposed to this drug. We will consider <7 days between risperidone treatment courses in an individual as a single treatment period. If there are periods of ≥7 days between treatment courses, we will count these as separate treatment periods.

Objective 2: Mortality, cerebrovascular and cardiovascular disease

We will conduct an age-standardised time series analysis to investigate changes in all-cause mortality, stroke mortality and myocardial infarction mortality between 2016 to 2021. We will compare mortality rates in which stroke or myocardial infarction are listed as the underlying cause of death (primary position), to rates of these diagnoses being listed anywhere on the death certificate (any position). As with antipsychotic prescribing trends, we will stratify by sex, age (5-year bands), dementia subtype and care home residency. We will also describe the leading causes of death in people with dementia from January 2020 (when the first COVID-19 case was recorded in the UK) until the end of follow-up. To determine causes of death, we will group ICD-10 codes using the same method as that employed by the Office for National Statistics (ONS) when collating UK mortality

figures (Appendix 3) (21). We will report the number of participants who died with COVID-19 during follow-up.

We will use SQL for data management and R (<https://www.r-project.org/>) for statistical analysis. We will make code publicly available via Github.

EXAMPLE RESULTS SECTION

1. Participant demographics

Figure 1: Participant flow diagram.

Description of included participants:

- Number of people in the study, person-years of follow up (median).
- Age at dementia diagnosis (median, IQR).
- Age at death (median, IQR).

	Number (%)	
	Whole cohort	Prescribed antipsychotic drug
Sex		
Female		
Male		
Deprivation (quintiles)*		
1 (most deprived)		
2		
3		
4		
5 (least deprived)		
Resident in care home*		
Dementia subtype†		
Alzheimer's disease		
Vascular dementia		
Frontotemporal dementia		
Dementia with Lewy Bodies		
Unspecified		
Date of dementia diagnosis		
Before 1/1/2016		
On or after 1/1/2016		
Frailty (eFI)*		
Fit		
Mild		
Moderate		
Severe		
Missing ‡		
Previous stroke*		
Previous myocardial infarction*		

Table 1. Participant characteristics

Demographics of whole cohort and subgroup who were prescribed an antipsychotic drug at any point during follow-up.

eFI – electronic Frailty Index.

*Prior to or at study start date (1/1/2016).

†Categories not mutually exclusive, apart from 'unspecified' category, which reflects the number of participants with no subtype code.

‡eFI will not be calculated for participants who did not have five years of available primary care data prior to 1/1/2016.

2. Antipsychotic prescribing

- Proportion of participants prescribed an antipsychotic at any point during follow up.
- Demographics of people prescribed an antipsychotic at any point compared to the total population (Table 1).
- Figure 2: Graph showing prescribing of all antipsychotic drugs over time during the study period, as well as top 3 antipsychotic drugs prescribed during the study period. Include benzodiazepine prescribing as a comparison.
- Figure 3: Time series graph showing antipsychotic drug prescribing during the study period, accounting for seasonality (graphs with individual antipsychotic drugs in supplement).
- Narrative description of antipsychotic prescribing trends over time.
- Figure 4: Risperidone prescriptions frequency histogram, displaying the distribution of treatment durations once risperidone is prescribed (dispensing data).

3. Mortality, cardiovascular and cerebrovascular disease

- Number (proportion) of deaths (all-cause) during follow up.
- Number (proportion) of deaths from COVID-19 from 01/01/20 until end of follow-up, from subpopulation of people who were alive on 01/01/20.
- Age at death (all-cause) and age at death from COVID-19 (median, IQR).
- Figure 5: Age-standardised mortality during the study period – all-cause, stroke and myocardial infarction.
- Figure 6: Age-standardised time series showing all-cause, myocardial infarction and stroke mortality during the study period, accounting for seasonality.
- Figure 7: Age-stratified all-cause, cardiovascular and cerebrovascular disease mortality during the study period.
- Narrative description of mortality from any cause and due to stroke and myocardial infarction over time.
- Figure 8: Treemap showing 10 leading causes of death from 01/01/20 until end of follow-up.

SUPPLEMENTARY MATERIAL

Appendix 1: Disease code lists (ICD-10 and Read V2)

Appendix 2: Drug codes (Read V2)

Appendix 3: Code groupings for causes of death (ICD-10)

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