Anticholinergic Drug Exposure and the Risk of Dementia
A Nested Case-Control Study

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IMPORTANCE Anticholinergic medicines have short-term cognitive adverse effects, but it is uncertain whether long-term use of these drugs is associated with an increased risk of dementia.

OBJECTIVE To assess associations between anticholinergic drug treatments and risk of dementia in persons 55 years or older.

DESIGN, SETTING, AND PARTICIPANTS This nested case-control study took place in general practices in England that contributed to the QResearch primary care database. The study evaluated whether exposure to anticholinergic drugs was associated with dementia risk in 58,769 patients with a diagnosis of dementia and 225,574 controls 55 years or older matched by age, sex, general practice, and calendar time. Information on prescriptions for 56 drugs with strong anticholinergic properties was used to calculate measures of cumulative anticholinergic drug exposure. Data were analyzed from May 2016 to June 2018.

EXPOSURES The primary exposure was the total standardized daily doses (TSDDs) of anticholinergic drugs prescribed in the 1 to 11 years prior to the date of diagnosis of dementia or equivalent date in matched controls (index date).

MAIN OUTCOMES AND MEASURES Odds ratios (ORs) for dementia associated with cumulative exposure to anticholinergic drugs, adjusted for confounding variables.

RESULTS Of the entire study population (284,343 case patients and matched controls), 179,365 (63.1%) were women, and the mean (SD) age of the entire population was 82.2 (6.8) years. The adjusted OR for dementia increased from 1.06 (95% CI, 1.03-1.09) in the lowest overall anticholinergic exposure category (total exposure of 1-90 TSDDs) to 1.49 (95% CI, 1.44-1.54) in the highest category (>1095 TSDDs), compared with no anticholinergic drug prescriptions in the 1 to 11 years before the index date. There were significant increases in dementia risk for the anticholinergic antidepressants (adjusted OR [AOR], 1.29; 95% CI, 1.24-1.34), antiparkinson drugs (AOR, 1.52; 95% CI, 1.16-2.00), antipsychotics (AOR, 1.70; 95% CI, 1.53-1.90), bladder antimuscarinic drugs (AOR, 1.65; 95% CI, 1.56-1.75), and antiepileptic drugs (AOR, 1.39; 95% CI, 1.22-1.57) all for more than 1095 TSDDs. Results were similar when exposures were restricted to exposure windows of 3 to 13 years (AOR, 1.46; 95% CI, 1.41-1.52) and 5 to 20 years (AOR, 1.44; 95% CI, 1.32-1.57) before the index date for more than 1095 TSDDs. Associations were stronger in cases diagnosed before the age of 80 years. The population-attributable fraction associated with total anticholinergic drug exposure during the 1 to 11 years before diagnosis was 10.3%.

CONCLUSIONS AND RELEVANCE Exposure to several types of strong anticholinergic drugs is associated with an increased risk of dementia. These findings highlight the importance of reducing exposure to anticholinergic drugs in middle-aged and older people.

JAMA Intern Med. doi:10.1001/jamainternmed.2019.0677
Published online June 24, 2019.
A n estimated 47 million people worldwide were living with dementia in 2015,1 while in the United States around 5.7 million people have Alzheimer dementia.2 Modifiable risk factors, including hypertension, hearing loss, depression, diabetes, and smoking, account for around 35% of dementia cases.3 Anticholinergic drugs are another potentially modifiable risk factor. This broad group of drugs acts by blocking the neurotransmitter acetylcholine in the central and peripheral nervous system and includes some antihistamines, antidepressants, and medications for gastrointestinal and bladder disorders. These medicines can have short-term adverse effects, including confusion and memory loss in older people,3 4 but it is less certain whether long-term use increases the risk of dementia.

Observational studies of anticholinergic drugs and dementia risk7-10 have generally been relatively small, only assessed short-term exposure, or were subject to recall bias. These studies were also susceptible to protopathic bias because they did not account for anticholinergic drugs being prescribed to treat early symptoms of dementia before diagnosis. A cohort study11 that reduced protopathic bias by excluding prescriptions in the final year of follow-up found that higher cumulative anticholinergic drug use was associated with a significantly increased risk of dementia but had limited power for analysis of separate types of anticholinergic drug. A recent larger study12 found varying risks associated with different types of anticholinergic drugs and concluded that further research should examine individual anticholinergic drug classes.

This study was designed to assess the association between cumulative anticholinergic drug use and risk of dementia in a large, representative British population. The study objectives were to estimate dementia risks associated with different types of anticholinergic medication including analyses of prescriptions up to 20 years before diagnosis.

Methods

Study Design

This was a nested case-control study within a cohort of patients registered with practices in England contributing to the QResearch database (version 41). QResearch is an anonymized research database of more than 30 million individuals in over 1500 general practices that includes data recorded prospectively from routine health care. The data include demographic information, medical diagnoses, prescriptions, referrals, laboratory results, and clinical values.

The study was approved in accordance with the agreed procedure with the East Midlands Derby Research Ethics Committee, waiving written informed consent for deidentified patient data.

Selection of Cases and Controls

The base cohort included patients 55 years and older registered during the study period (January 1, 2004, to January 31, 2016) without a diagnosis of dementia at study entry, defined as the latest of the study start date (January 1, 2004), the patient’s 55th birthday, date of registration with the practice plus 1 year, or date when the practice computer system was installed plus 1 year. The cohort were followed up until the earliest date of death, transfer to another practice, or the study end date (January 31, 2016).

Case patients were those diagnosed with dementia during follow-up, identified using clinical codes recorded in the practice records or linked Office of National Statistics death records. Patients with prescriptions for acetylcholinesterase-inhibiting drugs (donepezil, galantamine, memantine, and rivastigmine) but without a recorded diagnosis of dementia were also included because these drugs are licensed only for patients with dementia. Case patients with diagnostic codes for specific subtypes of dementia associated with Huntington disease, Parkinson disease, Creutzfeldt-Jakob disease, or human immunodeficiency virus (HIV) were excluded, as were patients diagnosed with Parkinson disease, Huntington disease, or multiple sclerosis to reduce indication bias.

Each case patient was matched to 5 controls by age (within 1 year), sex, general practice, and calendar time using incidence density sampling.13 The index date for controls was the date of diagnosis for their matched case patient. Controls were excluded if they had a diagnosis of Parkinson disease, Huntington disease, or multiple sclerosis.

For the primary analyses, case patients and controls were only included if they had at least 11 years of recorded data prior to the index date, so that anticholinergic drug exposure could be assessed over a complete period of 10 years (excluding the 1-year period prior to the index date).

Exposures

There is incomplete consensus on which drugs are considered as having anticholinergic properties. We used the approach of Gray et al,13 which included drugs identified as having strong anticholinergic properties by the American Geriatrics Society 2012 Beers Criteria Update Expert Panel.14 We also included additional drugs in the Beers 2015 updated list of strong anticholinergic drugs,15 drugs listed as having a high anticholinergic burden in the Anticholinergic Cognitive Burden scale,16 or identified as high-potency anticholinergics in a systematic review,17 and some further drugs identified as having substantial anticholinergic properties in the British National Formulary; these may have been omitted in previous studies owing...
to their unavailability in the country where the study originated. eTable 1 in the Supplement shows the 56 anticholinergic drugs included in the study with details of their basis for inclusion.

We extracted details of prescriptions for the included anticholinergic drugs. To reduce protopathic biases, we did not include prescriptions issued in the year before the index date. In 2 additional analyses, we only included prescriptions issued up to 3 and up to 5 years before diagnosis.

The primary exposure variable was total cumulative anticholinergic drug exposure, which combined the different types of anticholinergic medications based on the method used by Gray et al.24 This involved calculating the total dose of each prescription by multiplying the number of tablets prescribed by the dose per tablet (or equivalent for solutions, inhalers, injections, or patches). These values were then divided by minimum effective daily dose values recommended for use in older adults to give a number of standardized daily doses for each prescription. We used minimum effective dose values from the Geriatric Dosage Handbook18 where available, and for the additional drugs we used the lowest recommended dose values (in older people if stated) in the British National Formulary (see ddd_index/) to standardize the prescribed doses.

The base cohort comprised 3,638,582 individuals aged 55 to 100 years. During a total of 20,005,739 person-years of follow-up, 128,517 people were diagnosed with dementia. After applying exclusion criteria, 58,769 case patients and 225,574 matched controls were eligible for inclusion (eFigure 1 in the Supplement). Case patients had a mean (SD) age of 82.4 (7.0) years at diagnosis, and 63.1% (37,105) were women (Table 1); eTable 2 in the Supplement details that in the 36,666 cases where dementia type was recorded, 22,034 (60.1%) patients had a diagnosis of Alzheimer disease (including mixed), 13,313 (36.3%) had a diagnosis of vascular dementia, and 1319 (3.6%) had other types of dementia.

### Results

The base cohort comprised 3,638,582 individuals aged 55 to 100 years. During a total of 20,005,739 person-years of follow-up, 128,517 people were diagnosed with dementia. After applying exclusion criteria, 58,769 case patients and 225,574 matched controls were eligible for inclusion (eFigure 1 in the Supplement). Case patients had a mean (SD) age of 82.4 (7.0) years at diagnosis, and 63.1% (37,105) were women (Table 1); eTable 2 in the Supplement details that in the 36,666 cases where dementia type was recorded, 22,034 (60.1%) patients had a diagnosis of Alzheimer disease (including mixed), 13,313 (36.3%) had a diagnosis of vascular dementia, and 1319 (3.6%) had other types of dementia.

### Statistical Analysis

We used conditional logistic regression to estimate odds ratios (ORs) adjusted for the confounding variables. The exposure window in the main analyses comprised the 1 to 11 years before the index date. We categorized the anticholinergic exposure variable into 5 categories (0, 1-90, 91-365, 366-1095, and >1095 TSDDs). Similar we assessed associations for the 11 separate types of anticholinergic drug. Data were analyzed from May 2016 to June 2018.

We carried out subgroup analyses and interaction tests by age at index date (younger than 80 years and 80 years and older), by sex, and separately in case patients diagnosed with Alzheimer disease (including mixed), vascular dementia, and other or unspecified types of dementia with their respective matched controls.

We carried out the following sensitivity analyses:

1. we assessed anticholinergic exposure over a time window of 3 to 13 years before the index date by excluding prescriptions in the 3 years before the index date;
2. we assessed anticholinergic exposure over a time window of 5 to 20 years before the index date to further reduce potential protopathic biases and to assess associations for longer term exposure;
3. we removed those anticholinergic drugs not included by Gray et al18 so we could directly compare associations;
4. we used multiple imputation by chained equations to replace missing values for body mass index, smoking status, and alcohol consumption. We created 10 multiply imputed data sets and combined results using Rubin rules29; and
5. we repeated the analyses using the cumulative exposure variable standardized by WHO DDD values.

We calculated population-attributable fractions by combining adjusted odds ratios (AORs) with the proportions of cases in the different categories of anticholinergic drug exposure.30,31 We used $P < .01$ (2-tailed) to determine statistical significance. We used Stata (version 15.1) for all analyses.

### Anticholinergic Drug Exposure

In the 1 to 11 years before the index date, 56.6% of case patients (33,253) and 51.0% of controls (115,096) were prescribed at least 1 anticholinergic drug, with a median of 6 pre-
The most frequently prescribed types of anticholinergic drugs were antidepressants (27.1% of case patients, 23.3% of controls), antivertigo/antiemetic drugs (23.8% of case patients, 21.7% of controls), and bladder antimuscarinic drugs (11.7% of case patients, 8.3% of controls) (see eFigure 2 in the Supplement). eTable 3 in the Supplement provides descriptive information for the 56 different anticholinergic drugs included in the study. eTables 4 and 5 in the Supplement present descriptive information on anticholinergic drugs prescribed in the 3 to 13 years and 5 to 20 years before the index date, respectively.

**Associations With Dementia**

The AOR associated with total cumulative anticholinergic exposure in the 1 to 11 years before the index date increased from 1.06 (95% CI, 1.03-1.09) for 1 to 90 TSDDs to 1.49 (95% CI, 1.44-1.54) for more than 1095 TSDDs, compared with non-use (Table 4). Results were similar but with slightly lower ORs when restricted to the 3 to 13 and 5 to 20 years before the index date; for example, for the 5 to 20 years before the

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**Table 1. Demographic Characteristics of Case Patients and Matched Controls**

| Characteristic                          | Study Participants, No. (%) |
|-----------------------------------------|-----------------------------|
|                                         | Case Patients (n = 58,769)   | Controls (n = 225,574)   |
| Age at diagnosis of dementia/index date, mean (SD), y | 82.4 (7.0)                  | 82.1 (6.8)               |
| Age at diagnosis/index date, y          |                             |                            |
| 55-64                                   | 685 (1.2)                   | 2577 (1.1)                |
| 65-74                                   | 6983 (11.9)                 | 26,952 (12.0)             |
| 75-84                                   | 26,610 (45.3)               | 106,705 (47.3)            |
| 85-94                                   | 23,075 (39.3)               | 86,148 (38.2)             |
| ≥95                                     | 1416 (2.4)                  | 3192 (1.4)                |
| Men                                     | 21,664 (36.9)               | 83,314 (36.9)             |
| Women                                   | 37,105 (63.1)               | 142,260 (63.1)            |
| Ethnicity recorded                      | 45,008 (76.6)               | 174,660 (77.4)            |
| White/not recorded                      | 57,004 (97.0)               | 220,081 (97.6)            |
| Indian                                  | 341 (0.6)                   | 1302 (0.6)                |
| Pakistani                                | 138 (0.2)                   | 431 (0.2)                 |
| Bangladeshi                              | 107 (0.2)                   | 271 (0.1)                 |
| Other Asian                             | 110 (0.2)                   | 444 (0.2)                 |
| Caribbean                                | 629 (1.1)                   | 1726 (0.8)                |
| Black African                           | 99 (0.2)                    | 292 (0.1)                 |
| Chinese                                  | 43 (0.1)                    | 217 (0.1)                 |
| Other                                    | 298 (0.5)                   | 810 (0.4)                 |
| Townsend deprivation score, fifths*     | 15,802 (26.9)               | 65,507 (29.0)             |
| 2                                        | 14,628 (24.9)               | 57,835 (25.6)             |
| 3                                        | 13,003 (22.1)               | 48,432 (21.5)             |
| 4                                        | 9558 (16.3)                 | 34,310 (15.2)             |
| 5 (most deprived)                       | 5701 (9.7)                  | 19,244 (8.5)              |
| BMI recorded                             | 53,518 (91.1)               | 204,764 (90.8)            |
| BMI, mean (SD)                           | 26.5 (4.4)                  | 26.8 (4.4)                |
| Smoking status                           |                             |                            |
| Nonsmoker                                | 33,936 (57.7)               | 132,732 (58.8)            |
| Ex-smoker                                | 16,285 (27.7)               | 61,168 (27.1)             |
| Light smoker (1-9 cigarettes/d)          | 4455 (7.6)                  | 15,795 (7.0)              |
| Moderate smoker (10-19 cigarettes/d)     | 1795 (3.1)                  | 6443 (2.9)                |
| Heavy smoker (≥20 cigarettes/d)          | 1069 (1.8)                  | 3714 (1.7)                |
| Not recorded                             | 1229 (2.1)                  | 5722 (2.5)                |
| Alcohol intake                           |                             |                            |
| Nondrinker                               | 20,191 (34.4)               | 73,287 (32.5)             |
| Trivial (<1 U/d)                         | 19,253 (32.8)               | 75,330 (33.4)             |
| Light (1-2 U/d)                          | 6928 (11.8)                 | 27,494 (12.2)             |
| Moderate (3-6 U/d)                       | 6117 (10.4)                 | 24,443 (10.8)             |
| Heavy (7-9 U/d)                          | 468 (0.8)                   | 1510 (0.7)                |
| Very heavy (>9 U/d)                      | 124 (0.2)                   | 356 (0.2)                 |
| Not recorded                             | 5686 (9.7)                  | 23,154 (10.3)             |
| Missing values for BMI, smoking status, or alcohol intake | 7770 (13.2) | 30,758 (13.6) |

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; U/d, units of alcohol per day.

* Deprivation fifths using quintiles for the entire QResearch database across all ages.

**Table 2. Prevalence of Comorbidities and Prescribed Medications in Case Patients and Matched Controls**

| Characteristic                          | Study Participants, No. (%) |
|-----------------------------------------|-----------------------------|
|                                         | Case Patients (n = 58,769)   | Controls (n = 225,574)   |
| Comorbidity*                            |                             |                            |
| Hypertension                            | 19,907 (33.9)               | 73,267 (32.5)             |
| Stroke                                  | 1483 (2.5)                  | 3936 (1.7)                |
| Transient ischemic attack               | 1717 (2.9)                  | 5110 (2.3)                |
| Subarachnoid hemorrhage                 | 177 (0.3)                   | 453 (0.2)                 |
| Coronary heart disease                  | 7778 (13.2)                 | 25,872 (11.5)             |
| Heart failure                           | 990 (1.7)                   | 3149 (1.4)                |
| Atrial fibrillation                     | 1774 (3.0)                  | 5900 (2.6)                |
| Hyperlipidemia                          | 4123 (7.0)                  | 13,986 (6.2)              |
| Diabetes                                | 4612 (7.9)                  | 12,929 (5.7)              |
| Anxiety                                 | 3693 (6.3)                  | 12,348 (5.5)              |
| Depression                              | 8106 (13.8)                 | 26,086 (11.6)             |
| Bipolar disorder                        | 152 (0.3)                   | 262 (0.1)                 |
| Schizophrenia                           | 265 (0.5)                   | 559 (0.3)                 |
| Severe head injury                      | 211 (0.4)                   | 689 (0.3)                 |
| Severe learning difficulties            | 6 (0.0)                     | 5 (0.0)                   |
| Down syndrome                           | 54 (0.1)                    | 2 (0.0)                   |
| Cognitive decline                       | 184 (0.3)                   | 364 (0.2)                 |
| Asthma                                  | 4482 (7.6)                  | 16,243 (7.2)              |
| Chronic obstructive pulmonary disease   | 1558 (2.7)                  | 5228 (2.3)                |
| Renal disease                           | 176 (0.3)                   | 594 (0.3)                 |
| Medications*                            |                             |                            |
| Aspirin                                 | 12,162 (20.7)               | 40,329 (17.9)             |
| Nonsteroidal antiinflammatory drugs     | 21,222 (36.1)               | 79,412 (35.2)             |
| Antihypertensives                       | 25,377 (43.2)               | 92,708 (41.1)             |
| Statins                                 | 7804 (13.3)                 | 25,218 (11.2)             |
| Anxiolytic                              | 2756 (4.7)                  | 8822 (3.9)                |
| Hypnotic                                | 4749 (8.1)                  | 15,855 (7.0)              |

* Comorbidities and medications assessed at index date minus 11 years.
index date the AOR was 1.44 (95% CI, 1.32-1.57) for more than 1095 TSDDs (Table 4).

Among specific types of anticholinergic drugs there were significant increases in risk associated with use of antidepressants, antiparkinson drugs, antipsychotics, bladder antimuscarinics, and antiepileptic drugs (Table 5). Adjusted odds ratios in the highest exposure category (>1095 TSDDs) were 1.29 (95% CI, 1.24-1.34) for antidepressants, 1.52 (95% CI, 1.16-2.00) for antiparkinson drugs, 1.70 (95% CI, 1.53-1.90) for antipsychotics, 1.65 (95% CI, 1.56-1.75) for bladder antimuscarinics, and 1.39 (95% CI, 1.22-1.57) for antiepileptic drugs, all compared with nonuse. For antivertigo/antiemetic drugs, as detailed in Table 5, there was a significantly increased risk compared with nonuse. For antivertigo/antiemetic drugs, as detailed in Table 5, there was a significantly increased risk compared with nonuse. For antiparkinson drugs, there was a significantly increased risk associated with antihistamines, skeletal muscle relaxants, gastrointestinal antispasmodics, antiarrhythmics, or antimuscarinic bronchodilators, although the numbers of patients exposed were small for skeletal muscle relaxants and antiarrhythmics. Patterns of risk were similar in the 3- to 13- and 5- to 20-year exposure windows (eTable 6 in the Supplement), except for antipsychotic drug exposure in the 5- to 20-year window, where there were no statistically significant increases in risk; the AOR for more than 1095 TSDDs was 1.23 (95% CI, 0.93-1.62). For some drug types, numbers were too small to allow analysis for the 5 to 20 years before the index date (eTable 7 in the Supplement).

The population-attributable fraction associated with total anticholinergic drug exposure during the 1 to 11 years before diagnosis was 10.3%. For the 3 to 13 years before diagnosis, it was 9.0%, and it was 9.7% for the 5 to 20 years before diagnosis.

### Additional Analyses

There were stronger associations in case patients diagnosed before age 80 years than at 80 years or older, both for total drug exposure and for antidepressants, antipsychotics, and bladder antimuscarinics (eTable 8 in the Supplement). For total cumulative exposure, the AOR for more than 1095 TSDDs was 1.81 (95% CI, 1.71-1.91) in cases diagnosed before age 80 years, whereas it was 1.35 (95% CI, 1.30-1.40) in cases diagnosed at 80 years or older. Associations were similar in men and women (eTable 9 in the Supplement).

Adjusted odds ratios were generally higher for vascular dementia than Alzheimer disease (eTable 10 in the Supplement); for example, in the 1- to 11-year exposure window, the AOR for more than 1095 TSDDs was 1.68 (95% CI, 1.57-1.79) for vascular dementia, and 1.37 (95% CI, 1.30-1.44) for Alzheimer disease.

Results were similar when DDD values were used to calculate cumulative exposure (eTable 12 in the Supplement). Sensitivity analyses using multiply imputed data (eTable 13 in the Supplement) or restricted to anticholinergic drugs included in the study by Gray et al13 (eTable 14 in the Supplement) did not change study findings.
Discussion

This large, nested case-control study found an increased risk of dementia associated with anticholinergic medication use. Associations were strongest for the anticholinergic antidepressants, bladder antimuscarinics, antipsychotics, and antiepileptic drugs. Associations were also stronger in cases diagnosed before the age of 80 years and in cases diagnosed with vascular dementia rather than with Alzheimer disease. There were no significantly increased risks for antihistamines, gastrointestinal antispasmodics, antimuscarinic bronchodilators, antiarrhythmics, or skeletal muscle relaxants, although the numbers of patients prescribed skeletal muscle relaxants and antiarrhythmic drugs were small, giving imprecise estimates.

There was nearly a 50% increased odds of dementia associated with total anticholinergic exposure of more than 1095 TSDDs within a 10-year period, which is equivalent to 3 years’ daily use of a single strong anticholinergic medication at the minimum effective dose recommended for older people. This observational study has shown associations, but is not able to evaluate causality. However, if this association is causal, the population-attributable fractions indicate that around 10% of dementia diagnoses are attributable to anticholinergic drug exposure, which would equate, for example, to around 20 000 of the 209 600 new cases of dementia per year in the United Kingdom.22 This proportion is sizeable and is comparable with estimates for other modifiable risk factors for dementia, such as 5% for midlife hypertension, 3% for diabetes, 14% for later-life smoking, and 6.5% for physical inactivity.1

The finding of more pronounced associations for vascular dementia than for other types is novel. It raises questions about the mechanisms by which anticholinergic drugs may increase the risk of subsequent dementia. These may include vascular and inflammatory changes,33,34 as well as the more obvious mechanism of chronic cholinergic depletion. Perhaps the mechanism underlying the potential effects of anticholinergic drugs is not solely through blocking acetylcholine and causing an excess of Alzheimer disease, so future research should give consideration to possible mechanisms.

We included a large representative sample of people diagnosed with dementia and matched controls. All eligible case patients and controls were included, so there is no selection

| Exposure Category | Study Participants, No (%) | OR (95% CI) |
|-------------------|---------------------------|------------|
|                   | Case Patients | Controls | Unadjusted | Adjusted a |
| Exposure in the 1 to 11 Years Before Index Date | |
| Patients, No. | 58 769 | 225 574 | NA | NA |
| Cumulative use (TSDDs) | | | | |
| Nonuse | 25 516 (43.4) | 110 478 (49.0) | 1 [Reference] | 1 [Reference] |
| 1-90 | 12 546 (21.4) | 50 220 (22.3) | 1.09 (1.06-1.11) | 1.06 (1.03-1.09) |
| 91-365 | 6370 (10.8) | 23 302 (10.3) | 1.20 (1.16-1.24) | 1.17 (1.13-1.21) |
| 366-1095 | 4537 (7.7) | 14 138 (6.3) | 1.40 (1.35-1.46) | 1.36 (1.30-1.41) |
| >1095 | 9800 (16.7) | 27 436 (12.2) | 1.58 (1.53-1.62) | 1.49 (1.44-1.54) |
| Exposure in the 3 to 13 Years Before Index Date | |
| Patients, No. | 45 621 | 169 020 | NA | NA |
| Cumulative use (TSDDs) | | | | |
| Nonuse | 20 545 (45.0) | 84 676 (50.1) | 1 [Reference] | 1 [Reference] |
| 1-90 | 9749 (21.4) | 37 553 (22.2) | 1.07 (1.05-1.10) | 1.05 (1.02-1.08) |
| 91-365 | 5079 (11.1) | 17 470 (10.3) | 1.22 (1.17-1.26) | 1.18 (1.13-1.23) |
| 366-1095 | 3286 (7.2) | 10 423 (6.2) | 1.32 (1.27-1.38) | 1.25 (1.19-1.31) |
| >1095 | 6962 (15.3) | 18 898 (11.2) | 1.55 (1.50-1.60) | 1.46 (1.41-1.52) |
| Exposure in the 5 to 20 Years Before Index Date | |
| Patients, No. | 8283 | 27 200 | NA | NA |
| Cumulative use (TSDDs) | | | | |
| Nonuse | 3335 (40.3) | 12 281 (45.2) | 1 [Reference] | 1 [Reference] |
| 1-90 | 1924 (23.2) | 6531 (24.0) | 1.09 (1.02-1.16) | 1.07 (1.00-1.15) |
| 91-365 | 1003 (12.1) | 3278 (12.1) | 1.15 (1.06-1.25) | 1.11 (1.01-1.21) |
| 366-1095 | 699 (8.4) | 1811 (6.7) | 1.44 (1.31-1.59) | 1.33 (1.20-1.48) |
| >1095 | 1322 (16.0) | 3299 (12.1) | 1.52 (1.40-1.64) | 1.44 (1.32-1.57) |

Abbreviations: OR, odds ratio; NA, not applicable; TSDD, total standardized daily dose.

a Adjusted for body mass index, calculated as weight in kilograms divided by height in meters squared, smoking status, alcohol consumption, Townsend deprivation score, ethnic group, coronary heart disease, atrial fibrillation, heart failure, hypertension, hyperlipidemia, diabetes (type 1 and type 2), stroke, transient ischemic attack, subarachnoid hemorrhage, renal disease, asthma, chronic obstructive pulmonary disease, anxiety, depression, bipolar disorder, schizophrenia, severe head injury, cognitive decline/memory loss, antihypertensive drugs, aspirin, hypnotics, anxiolytic drugs, nonsteroidal antiinflammatory drugs, statins, and with matching by age, sex, general practice, and calendar time.
Table 5. ORs for Total Cumulative Use of Different Types of Anticholinergic Drugs in the 1 to 11 Years Before the Index Date

| Drug Type                  | Study Participants, No. (%) | Odds Ratio (95%CI) | Unadjusted | Adjusted for the Other Drug Types | Fully Adjusted |
|---------------------------|-----------------------------|-------------------|------------|----------------------------------|----------------|
|                           | Case Patients (n = 58,769)  |                   |            |                                  |                |
|                           | Controls (n = 225,574)      |                   |            |                                  |                |
| **Antihistamines, TSDDs** | Nonuse                      | 52,312 (89.0)     | 1 [Reference] | 1 [Reference] | 1 [Reference] |
|                           | 1-90                         | 4,987 (8.5)       | 1.05 (1.02-1.09) | 1.02 (0.98-1.05) | 1.03 (0.99-1.07) |
|                           | 91-365                       | 923 (1.6)         | 1.14 (1.06-1.23) | 1.06 (0.99-1.15) | 1.03 (0.95-1.12) |
|                           | 366-1095                     | 280 (0.5)         | 1.06 (0.93-1.22) | 0.98 (0.85-1.12) | 1.02 (0.88-1.18) |
|                           | >1095                        | 267 (0.5)         | 1.22 (1.06-1.41) | 1.14 (0.99-1.31) | 1.14 (0.98-1.34) |
| **Antidepressants, TSDDs**| Nonuse                      | 42,831 (72.9)     | 1 [Reference] | 1 [Reference] | 1 [Reference] |
|                           | 1-90                         | 5,098 (8.7)       | 1.08 (1.04-1.11) | 1.04 (1.01-1.08) | 1.02 (0.98-1.06) |
|                           | 91-365                       | 3,463 (5.9)       | 1.20 (1.15-1.24) | 1.14 (1.10-1.19) | 1.12 (1.07-1.17) |
|                           | 366-1095                     | 2,227 (3.8)       | 1.35 (1.29-1.42) | 1.27 (1.20-1.33) | 1.25 (1.18-1.32) |
|                           | >1095                        | 5,150 (8.8)       | 1.47 (1.42-1.52) | 1.34 (1.29-1.39) | 1.29 (1.24-1.34) |
| **Antivertigo/Antiemetics, TSDDs**| Nonuse                      | 44,800 (76.2)     | 1 [Reference] | 1 [Reference] | 1 [Reference] |
|                           | 1-90                         | 11,427 (19.4)     | 1.10 (1.07-1.12) | 1.10 (1.03-1.08) | 1.05 (1.02-1.08) |
|                           | 91-365                       | 1,574 (2.7)       | 1.23 (1.16-1.31) | 1.14 (1.10-1.19) | 1.12 (1.07-1.17) |
|                           | 366-1095                     | 611 (1.1)         | 1.47 (1.34-1.61) | 1.33 (1.21-1.47) | 1.41 (1.27-1.56) |
|                           | >1095                        | 351 (0.6)         | 1.20 (1.06-1.35) | 1.06 (0.94-1.20) | 1.08 (0.94-1.24) |
| **Antiparkinson Agents, TSDDs**| Nonuse                      | 58,477 (99.5)     | 1 [Reference] | 1 [Reference] | 1 [Reference] |
|                           | 1-90                         | 68 (0.1)          | 1.43 (1.08-1.90) | 1.04 (0.78-1.38) | 1.01 (0.73-1.39) |
|                           | 91-365                       | 50 (0.1)          | 3.29 (2.25-4.81) | 2.07 (1.40-3.05) | 1.68 (1.09-2.58) |
|                           | 366-1095                     | 39 (0.1)          | 2.08 (1.40-3.09) | 1.29 (0.86-1.94) | 1.03 (0.66-1.61) |
|                           | >1095                        | 135 (0.2)         | 2.39 (1.93-2.97) | 1.61 (1.29-2.03) | 1.52 (1.16-2.00) |
| **Antipsychotics, TSDDs**  | Nonuse                      | 56,957 (96.9)     | 1 [Reference] | 1 [Reference] | 1 [Reference] |
|                           | 1-90                         | 388 (0.7)         | 1.71 (1.51-1.93) | 1.56 (1.38-1.76) | 1.44 (1.25-1.66) |
|                           | 91-365                       | 332 (0.6)         | 1.90 (1.66-2.17) | 1.67 (1.46-1.91) | 1.41 (1.21-1.65) |
|                           | 366-1095                     | 304 (0.5)         | 2.45 (2.12-2.83) | 2.15 (1.85-2.49) | 2.09 (1.76-2.47) |
|                           | >1095                        | 788 (1.3)         | 2.29 (2.09-2.50) | 1.89 (1.72-2.07) | 1.70 (1.53-1.90) |
| **Bladder Antimuscarinics, TSDDs**| Nonuse                      | 51,905 (88.3)     | 1 [Reference] | 1 [Reference] | 1 [Reference] |
|                           | 1-90                         | 2,139 (3.6)       | 1.21 (1.15-1.27) | 1.18 (1.12-1.24) | 1.19 (1.13-1.26) |
|                           | 91-365                       | 1,417 (2.4)       | 1.38 (1.30-1.47) | 1.33 (1.25-1.41) | 1.35 (1.27-1.45) |
|                           | 366-1095                     | 1,244 (2.1)       | 1.71 (1.59-1.83) | 1.63 (1.52-1.74) | 1.65 (1.53-1.78) |
|                           | >1095                        | 2,064 (3.5)       | 1.73 (1.64-1.82) | 1.65 (1.57-1.74) | 1.65 (1.56-1.75) |
| **Skeletal Muscle Relaxants, TSDDs**| Nonuse                      | 58,340 (99.3)     | 1 [Reference] | 1 [Reference] | 1 [Reference] |
|                           | 1-90                         | 372 (0.6)         | 1.08 (0.96-1.22) | 1.01 (0.89-1.14) | 0.98 (0.86-1.11) |
|                           | 91-365                       | 39 (0.1)          | 1.38 (0.95-1.99) | 1.17 (0.81-1.70) | 1.12 (0.77-1.65) |
|                           | 366-1095                     | 9 (0)             | 0.90 (0.44-1.88) | 0.84 (0.40-1.75) | 0.99 (0.46-2.10) |
|                           | >1095                        | 9 (0)             | 1.09 (0.52-2.29) | 0.90 (0.42-1.91) | 1.10 (0.47-2.55) |
| **Gastrointestinal Antispasmodics, TSDDs**| Nonuse                      | 54,733 (93.1)     | 1 [Reference] | 1 [Reference] | 1 [Reference] |
|                           | 1-90                         | 2,765 (4.7)       | 0.97 (0.93-1.01) | 0.90 (0.86-0.94) | 0.90 (0.85-0.94) |
|                           | 91-365                       | 722 (1.2)         | 1.05 (0.96-1.14) | 0.94 (0.86-1.02) | 0.93 (0.85-1.02) |
|                           | 366-1095                     | 267 (0.5)         | 1.11 (0.97-1.27) | 0.98 (0.85-1.12) | 0.93 (0.80-1.09) |
|                           | >1095                        | 282 (0.5)         | 1.19 (1.04-1.36) | 1.03 (0.90-1.18) | 1.04 (0.90-1.20) |

(continued)
bias due to nonresponse, and data were recorded prospectively, so results are not susceptible to recall bias. Comprehensive data on prescriptions meant that we could derive a measure of total anticholinergic drug exposure, which accounted for the quantity and dose prescribed.

Our findings are consistent with other studies, including a US cohort study of 3434 participants,39 which reported a hazard ratio of 1.54 (95% CI, 1.21-1.96) for the highest exposure category (>1095 TSDDs), similar to our AOR of 1.49 (95% CI, 1.44-1.54). With our larger sample size we could also examine specific types of anticholinergic drugs and account for a broader range of confounders. A study by Richardson et al,12 using another United Kingdom primary care database (CPRD), reported findings similar to ours, despite some differences in the drugs included, exposure measures used, exposure windows, and the confounding variables accounted for. For example, we included drugs based on the American Geriatrics Society 2012 Beers Criteria Update Expert Panel,14 whereas Richardson et al12 used drugs included in the 2012 update of the Anticholinergic Cognitive Burden scale.33 While both CPRD and QResearch are large United Kingdom databases, QResearch is the most nationally representative, while CPRD is more geographically restricted.36 Despite these differences, Richardson et al12 also found increases in dementia risk for the groups with acetylcholinesterase-inhibiting drugs rather than anticholinergic drugs, which was not significant when prescriptions in vivo were used. They also found that the association may be due to protopathic bias. Some bias due to prescriptions for prodromal symptoms occurring more than 5 years before diagnosis may remain because, while there is an average of 1 to 5 years between onset of symptoms and dementia diagnosis,39,40 some early symptoms such as cognitive decline and depression can start to emerge up to 10 years before diagnosis.39,40 There is ongoing debate, however, as to whether depression is a risk factor for dementia rather than a prodromal symptom.1,41
Conclusions

The present study adds further evidence of potential risks associated with strong anticholinergic drugs, particularly those that are antidepressants, bladder antimuscarinic drugs, antiparkinson drugs, and epilepsy drugs. Adverse effects should be considered alongside benefits when these drugs are prescribed, and alternative treatments should be considered where possible, such as other types of antidepressant or nonpharmacological treatments for depression, alternative antiparkinsonian drugs, and bladder training or mirabegron for overactive bladders. We found greater increases in risk associated with people diagnosed with dementia before the age of 80, which indicates that anticholinergic drugs should be prescribed with caution in middle-aged and older people.

ARTICLE INFORMATION

Accepted for Publication: February 19, 2019
Published Online: June 24, 2019.
doi:10.1001/jamainternmed.2019.0677

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Author Contributions: Dr Coupland had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Obtained funding: Coupland, Morriss, Hippsley-Cox.

Administrative, technical, or material support: Dening, Morriss, Moore, Hippsley-Cox.

Study supervision: Coupland.

Conflict of Interest Disclosures: Dr Coupland reported personal fees from ClinRisk Ltd outside the submitted work. Julia Hippsley-Cox reported personal fees from ClinRisk Ltd outside the submitted work. No other disclosures were reported.

Funding/Support: The project was funded by the National Institute for Health Research (NIHR) School for Primary Care Research (project number 265). Additional funding was provided by the Faculty of Medicine and Health Sciences Research Board, University of Nottingham. QResearch receives support from the NIHR Nottingham Biomedical Research Centre. Dr Morriss’s contribution to the study has been funded through the NIHR Collaboration for Leadership in Applied Health Research and Care East 15 Midlands (CLAHRC EM), NIHR MindTech, MedTech, and In Vitro Cooperative. Drs Hippsley-Cox, Coupland, and Morriss acknowledge funding from the NIHR Nottingham Biomedical Research Centre.

Role of the Funder/Sponsor: The NIHR approved the study design, but did not play a role in the conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: This article presents independent research funded by the NIHR School for Primary Care Research. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. The Office for National Statistics bears no responsibility for the analysis or interpretation of the data.

Additional Contributions: We acknowledge the contribution of practices who contribute to the QResearch database and to Egton Medical Information Systems (EMIS) and the University of Nottingham for expertise in establishing, developing, and supporting the database. We thank the Office for National Statistics for providing the mortality data. This work uses data provided by patients and collected by the NHS as part of their care and support. None of the additional contributors who assisted with the study received compensation.

Data Sharing Statement: The patient level data from the QResearch database are specifically licensed according to its governance framework. See http://www.qresearch.org for further details.

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