Anticholinergic drugs and risk of dementia: case-control study

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ABSTRACT

OBJECTIVES

To estimate the association between the duration and level of exposure to different classes of anticholinergic drugs and subsequent incident dementia.

DESIGN

Case-control study.

SETTING

General practices in the UK contributing to the Clinical Practice Research Datalink.

PARTICIPANTS

40 770 patients aged 65-99 with a diagnosis of dementia between April 2006 and July 2015, and 283 933 controls without dementia.

INTERVENTIONS

Daily defined doses of anticholinergic drugs coded using the Anticholinergic Cognitive Burden (ACB) scale, in total and grouped by subclass, prescribed 4-20 years before a diagnosis of dementia.

MAIN OUTCOME MEASURES

Odds ratios for incident dementia, adjusted for a range of demographic and health related covariates.

RESULTS

14 453 (35%) cases and 86 403 (30%) controls were prescribed at least one anticholinergic drug with an ACB score of 3 (definite anticholinergic activity) during the exposure period. The adjusted odds ratio for any anticholinergic drug with an ACB score of 3 was 1.11 (95% confidence interval 1.08 to 1.14). Dementia was associated with an increasing average ACB score. When considered by drug class, gastrointestinal drugs with an ACB score of 3 were not distinctively linked to dementia. The risk of dementia increased with greater exposure for antidepressant, urological, and antiparkinson drugs with an ACB score of 3. This result was also observed for exposure 15-20 years before a diagnosis.

CONCLUSIONS

A robust association between some classes of anticholinergic drugs and future dementia incidence was observed. This could be caused by a class specific effect, or by drugs being used for very early symptoms of dementia. Future research should examine anticholinergic drug classes as opposed to anticholinergic effects intrinsically or summing scales for anticholinergic exposure.

TRIAL REGISTRATION

Registered to the European Union electronic Register of Post-Authorisation Studies EUPAS8705.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Use of drugs with anticholinergic activity is associated with impaired cognition in the short term

It is not known if the reported associations between the use of anticholinergic drugs and future cognitive decline and dementia incidence can be attributed to anticholinergic activity

WHAT THIS STUDY ADDS

Antidepressant, urological, and antiparkinson drugs with definite anticholinergic activity are linked to future dementia incidence, with associations persisting up to 20 years after exposure

Gastrointestinal and cardiovascular anticholinergic drugs are not positively associated with later dementia incidence

There is no evidence for a cumulative harm of drugs considered possibly anticholinergic

Introduction

Dementia is a leading cause of disability and death,[1] and its prevention is a global public health priority. Dementia is caused by a number of different neurodegenerative processes that contribute to irreversible cognitive decline and associated symptoms, such as the progressive loss of independence and daily functioning. Mixed dementias are more prevalent than is often recognised, with symptoms often more closely linked to overall pathological burden as opposed to any specific disease process.[2 3] No disease modifying treatments for dementia exist, however, age specific dementia incidence across populations is declining, suggesting that changing lifestyles or environment may lead to a meaningful change in the prevalence of dementia.[4] Hence identifying and reducing the exposure to risk factors that can affect any aspect of long term brain health is important for dementia prevention and cognitive health in the population.[5]

Middle aged and older populations are increasingly taking multiple drugs,[6 7] but the potential adverse events of long term use are not well understood. Anticholinergic drugs block the neurotransmitter acetylcholine in the central or peripheral nervous system, and have diverse actions depending on the site. Anticholinergic drugs are indicated for depression, gastrointestinal disorders, Parkinson's disease, urinary incontinence, epilepsy, and to manage allergies. It is well known that anticholinergics affect cognition,[8] and guidelines suggest they are to be avoided among frail older people.[9] Use of anticholinergic drugs among people with dementia is recognised as inappropriate by both the Beers and the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) criteria.[10 11] Over the past decade, prolonged exposure to anticholinergic drugs has been linked to long term cognitive decline or dementia incidence among community living cohorts and nursing home residents.[12-17] However, these studies have been limited in their ability to determine if the increased risk is specific to the anticholinergic action itself, and

whether or not the association is owing to the drugs or the underlying conditions for which they were prescribed. In particular, late life depression is thought to be an early symptom of dementia,[18 19] whereas studies of whether midlife depression is a risk factor for later life dementia have had mixed findings.[20 21]

We present a nested case-control study using the UK's Clinical Practice Research Datalink (CPRD), in which we select patients with a new diagnosis of dementia, and compare their prescriptions of anticholinergic drugs 4-20 years before a diagnosis of dementia with that of a matched group of control patients without dementia. We had three objectives. Firstly, to estimate the association between chronic anticholinergic drug use and future dementia incidence while controlling for potential confounders. Secondly, to explore whether any observed effect was specific to a particular drug class. Thirdly, to test how the association varied with the time to dementia incidence and amount of exposure within each class.

Methods

Study design

We performed a nested case-control study using data from the Clinical Practice Research Datalink (CPRD), which includes anonymised diagnosis, referral, and prescribing records for more than 11.3 million patients from 674 primary care practices in the UK. CPRD data are broadly representative of the UK population in terms of sex, age, and ethnicity.[22] All coded information in the primary care record for each selected patient is available to researchers. This includes demographic detail, lifestyle information, any diagnoses and symptoms recorded by the general practitioner, referrals to other healthcare services and subsequent findings, and treatments initiated or continued in primary care. In the UK, a patient's registered primary care practice is the coordinator of most of their healthcare, and acts as the main gateway for access to secondary care. Hence most of a patient's healthcare information is held in their primary care record. Secondary care episodes or privately obtained healthcare may not always be communicated to the patient's registered primary care practice. An up to standard (UTS) date is assigned to a CPRD practice when the data recorded by the practice are of an acceptable research standard. Records of therapies and diagnoses made before the UTS date are available, but may be incomplete.

Selection of cases and controls

Patients aged 65-99 with a recorded diagnosis of dementia made between April 2006 and July 2015 were eligible to be selected as cases. We also required at least six years of UTS data before a diagnosis to allow for a four year delay before a diagnosis of dementia, at least a one year drug exposure period (DEP), and to ascertain covariates, we required data for one year before the DEP. A diagnosis of dementia was defined as the presence in the patient's record of any Read codes for dementia as a diagnosis, symptom, or referral, or prescription for a cognitive enhancer (memantine, donepezil, rivastigmine, galantamine, or tacrine) if a code for a diagnosis of dementia was recorded within 12 months. Dementia codes were derived by comparing a previous published list with the Department of Health's Quality and Outcomes Framework list of business codes for dementia.[23 24] These two code lists overlapped almost completely. The combined list was reviewed by our clinical team, and all codes were included in our final definition—except those that related explicitly to alcohol related dementia (see supplementary materials, appendix 1 for a full list). Cases were excluded if they had been diagnosed with motor neurone disease, HIV or AIDS, multiple sclerosis, Down's syndrome, or alcohol abuse before diagnosis of dementia.

Using the diagnosis of dementia date as the index date, each case was matched to a maximum of seven controls not having been diagnosed with dementia before the index date. Cases and controls were matched on sex, year of birth (within three years), years of UTS data history, and area level deprivation measured by the index of multiple deprivation quintile of each practice based on its postcode.[25] We used incidence density sampling to select controls, hence cases were eligible to be selected as controls for other cases with earlier index dates.[26] Seven controls were used to maximise the power to detect associations with potentially rare exposures or covariates, and to adhere to the limits of the data provider regarding the maximum sample size for a single study.

Patients were excluded if their date of diagnosis of dementia was ambiguous. That is, if dementia annual review, history of dementia, assessment of psychotic and behavioural symptoms of dementia, or antipsychotic drug therapy for dementia was recorded before the index date.

Anticholinergic drugs exposure

A DEP was defined for each case-control group, starting at least one year after the UTS date and ending four years before the index date. The start and end dates of the DEP were identical within sets of cases and controls. We excluded exposures in the four years before the index date to avoid protopathic bias, whereby the drug is given for a sign or symptom of dementia before a diagnosis of dementia.[27]

Estimating the anticholinergic effect of individual drugs on the human brain is difficult. Serum anticholinergic activity measured by a receptor bioassay does not correlate well with effects on cognition,[16 28] and so the anticholinergic effects of drugs are usually classified using scales developed by expert consensus aided by a literature review.[29] In this study, all drugs prescribed to each patient during the DEP were classified according to the 2012 update of the Anticholinergic Cognitive Burden (ACB) scale.[30] Drugs with serum anticholinergic activity or in vitro affinity to muscarinic receptors, but with no known clinically relevant negative cognitive effects are assigned a score of 1 (possibly anticholinergic). Drugs with established

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and clinically relevant anticholinergic effects are assigned a score of 2 based on blood-brain penetration (definitely anticholinergic). Drugs with a score of 2 that also have reported associations with delirium are assigned a score of 3 (definitely anticholinergic). All other drugs are assigned a score of 0. For the drugs available in the UK in the last 30 years without an ACB score, we made the following assumptions: thiazide diuretics, loop diuretics, and antihistamines have an ACB score of 1; tricyclic antidepressants have an ACB score of 3; and creams, eye drops, and ear drops have an ACB score of 0.

Our primary exposures were the number of defined daily doses (DDDs) prescribed for drugs within a drug class for each ACB score during the DEP. The DDD is defined as the assumed average maintenance daily dose for a drug based on its main indication in adults, using the DDD values assigned by the World Health Organisation's (WHO) Collaborating Centre for Drug Statistics Methodology. For prescriptions of different drugs with the same ACB score, DDDs were summed. We then categorised exposure during the DEP as 0, 1-13, 14-89, 90-364, 365-1459, or more than 1460 DDDs.

We further categorised the drugs with anticholinergic properties as either analgesic (WHO Anatomical Therapeutic Chemical code N02), antidepressant (N06A), antipsychotic (N05A), cardiovascular (C), gastrointestinal (A), antiparkinson (N04), respiratory (R), urological (G04), or other. These categories separate the main indications for anticholinergic drugs and correlate closely with their pharmacological action. Drugs in these classes have similar receptor bindings.

Finally, an average ACB score was calculated as the average across the DEP of the sum of the ACB score for each drug being used at any given time. This was then categorised into groups reflecting approximate quintiles of the sample, but with two additional groups representing those with particularly high (3-5 and 5 or more) average ACB scores.

Covariates

We considered potential confounders to be any variable suspected to be linked to dementia incidence or an indication for any of the drugs examined. A full list of covariates and their definitions are available (see supplementary materials, appendix 2). In summary, we included diagnoses of cardiovascular disease, other dementia risk factors and correlates, other indications for anticholinergics, other drug use, sociodemographic variables, and records of health related lifestyle information where available.

Exposures could occur at any time during an individual's DEP and so, as with many case-control studies,[31] it is not clear at what point we should determine the presence or absence of confounding factors. Our primary analysis measured confounders recorded up to the end of the DEP to best capture the indications of the drugs. We also coded the status of each patient with respect to each covariate up to the start of the DEP, as some variables could be consequences of drug exposure.

Statistical analysis

Patterns of exposures and covariates were described for case and control groups separately.

Primary analysis compared the number of DDDs of drugs with an ACB score of 1, 2, or 3 prescribed to cases and controls during the DEP, controlling for covariates recorded at the end of each DEP. We used multiple conditional logistic regression to estimate the independent association between classes of anticholinergic prescriptions and a diagnosis of dementia, adjusting for all other anticholinergic classes and covariates described previously. Adjusted odds ratios are reported with 95% confidence intervals, however, $P<0.01$ was prespecified as a threshold for statistical significance owing to the large number of subgroups being examined. All analysis was conducted with Stata version 14 (StataCorp, College Station, TX).

Secondary prespecified analyses included: disaggregation of exposure by drug class; testing the effect of exposure 4-10, 10-15, and 15-20 years before the index date in those with 6 or more, 11 or more, and 16 or more years of UTS data history respectively; and testing the effect of the average ACB score over the DEP.

Sensitivity analyses included repeating our primary analysis three times. Firstly, to adjust for covariates measured up to the start rather than the end of the DEP, and the following post hoc analyses. Secondly, to emulate a new user design by excluding patients prescribed medications with an ACB score of 2 or 3 in the 12 months before the DEP.[32] Thirdly, to recode binary exposure variables to correspond to 90 or more DDDs prescribed instead of any prescription during the DEP, to represent longer term rather than one-off exposure.

To test the likely impact of missing lifestyle covariate data, we compared findings with and without adjustment for these lifestyle variables in complete data and in the full dataset using a missing category for each variable. As with other analyses of routine data, diagnosed health conditions or other drugs are assumed absent if there is no mention in the primary care record. Deprivation is based on practice location and so is known for all patients.

For a final prespecified sensitivity analysis, we recoded drugs by using the Anticholinergic Drug Scale (ADS) instead of the ACB scale. ADS classifies the degree of anticholinergic activity of each drugs on a scale from 0 (no anticholinergic effect) to 3 (marked anticholinergic effect) in accordance with a literature review and expert consensus.[33] Sample size was determined by the maximum available data within CPRD.

Patient involvement

Four Alzheimer's Society Research Network Volunteers acted as study monitors and service user representatives on our study steering committee. These individuals have all acted as carers of people with dementia. The

monitors contributed to our protocol development by sharing their experiences of psychoactive drug use and their view of the balance between the benefits of drug use and potential cognitive decline. Monitors met the study team to discuss study progress every six months. They are assisting us with the dissemination of our study, making sure that lay summaries of results are accessible and easily understood.

Results

The source population consisted of 66 136 patients with a diagnosis of dementia between April 2006 and July 2015. After applying the exclusion criteria, our analysis included 40 770 cases and 283 933 controls, with the majority of cases being matched to seven controls (see supplementary materials, figure 1). Most patients (n=254 083, 78%) were from general practices in England, with 30 817 (9%) from Scotland, 29 575 (9%) from Wales, and 10 228 (3%) from Northern Ireland. The median age of patients at index date was 83 (interquartile range 78-87) and 63% were female. The median drug exposure period (DEP) was 7.1 years (interquartile range 4.0-11.3, range 1-16). Table 1 shows that diagnoses of conditions related to dementia and indications for anticholinergics increased during the DEP. As an example, the proportion of dementia cases diagnosed with depression at the start of the DEP was 12% (n=5071), rising to 20% (n=8030) during the DEP. Information on smoking status, harmful alcohol use, and body mass index becomes more complete by the end of the DEP. As expected, the average body mass index decreases during the DEP for dementia cases, but increases for the control group.

Frequency of anticholinergic drugs use

During the DEP, 14 453 (35%) cases and 86 403 (30%) controls were prescribed at least one anticholinergic drug with an Anticholinergic Cognitive Burden (ACB) score of 3. A total of 1 793 505 prescriptions for drugs with an ACB score of 3 were written during the DEP. The five most common drugs were amitriptyline (29%), dosulepin (also known as dothiepin; 16%), paroxetine (8%), oxybutynin (7%), and tolterodine (7%). Only 1429 (3.5%) cases and 7909 (2.8%) controls were prescribed drugs with an ACB score of 2, with carbamazepine accounting for 87% of these prescriptions. Most patients (89% of cases and 87% of controls) received at least one prescription for a drug with an ACB score of 1 during the DEP, with cardiovascular drugs accounting for 63% of these prescriptions. The number of prescriptions for each ACB score is further described in supplementary materials, table 1.

Primary analysis

Table 2 shows that there was a positive and significant association between the prescription of any drug with an ACB score of 1, 2, or 3 and dementia with corresponding odds ratios of 1.10 (95% confidence interval 1.06 to 1.15), 1.10 (1.03 to 1.16), and 1.11 (1.08 to 1.14). These values were adjusted for covariates measured at the end of the DEP. A dose-response effect was evident for prescribed doses of drugs with an ACB score of 2 or 3. However, there was no dose-response effect for drugs with an ACB score of 1. Table 2 shows that an odds ratio of approximately 1.1 was seen for those prescribed drugs with an ACB score of 1, regardless of the number prescribed, including those with less than 14 DDD exposure. The associations are attenuated from the crude rates when adjusting for drug use at the start of the DEP, and are further reduced only slightly when adjusting for covariates at the end of the DEP.

There was a dose-response effect linking average anticholinergic load, measured by the average ACB score over the DEP, with dementia incidence, although this is only evident for those with an average score of 3 or more (table 2).

Exposure by drug class

Table 3 shows that, when analysed by class, there was a significant association between dementia incidence and any prescription of antidepressant, antiparkinson, or urological drugs with an ACB score of 3, but no association with antispasmodic, antipsychotic, antihistamine, or other drugs with an ACB score of 3. Prescriptions for drugs with an ACB score of 2 were relatively rare, and so results are imprecise in this group, but there is some evidence for an association between dementia incidence and prescription of antiparkinson drugs. We found positive associations for antidepressant drugs with an ACB score of 1 with an increased risk of dementia, but not with any other drugs with an ACB score of 1. Supplementary materials table 2 shows the associations between dementia incidence and the number of DDDs by drug class. These associations are consistent with the findings in table 3, except that a tentative effect of antihistamines with an ACB score of 3 is seen for patients with more than 365 DDDs prescribed during the DEP. Use of gastrointestinal drugs with an ACB score of 1 or 3, and cardiovascular drugs with an ACB score of 1 was associated with a minor reduction in the risk of dementia.

Exposure by time before a diagnosis of dementia

Table 4 shows the effect of exposure in three different periods (4-10, 10-15, and 15-20 years) before the index date. Associations with prescriptions for drugs with an ACB score of 3 were consistent across the DEP. Associations with prescriptions for drugs with an ACB score of 1 and 2 were more apparent closer to the index date. In particular, the prescription of any drug with an ACB score of 3 15-20 years before a diagnosis of dementia was significantly associated with greater dementia incidence with an odds ratio of 1.17 (95% confidence interval 1.10 to 1.24) adjusted for covariates at the start of the DEP. Prescriptions at 15-20 years before a diagnosis of dementia for antidepressant and urological drugs with an ACB score of 3 remained consistently significantly associated with dementia incidence with odds ratios of 1.19 (1.10 to

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Table 1 | Characteristics of 40 770 case patients with a diagnosis of dementia and 283 933 controls from the Clinical Practice Research Datalink at the start and end of the drug exposure period (DEP). Values are numbers (percentages) unless stated otherwise

Characteristic	Start		End	
	Cases	Controls	Cases	Controls
Lifestyle				
Current smoker*	5058 (12.4)	34 652 (12.2)	4516 (11.1)	30 976 (10.9)
Harmful alcohol use†	166 (0.4)	980 (0.3)	377 (0.9)	2316 (0.8)
Mean (SD) body mass index‡	26.4 (6.3)	26.5 (6.9)	26.1 (5.2)	26.8 (5.6)
Cardiovascular or cerebrovascular and related diagnoses				
Diabetes	2734 (6.7)	16 362 (5.8)	5392 (13.2)	34 015 (12.0)
Diabetes complications	418 (1.0)	2206 (0.8)	1378 (3.4)	7678 (2.7)
Hyperlipidemia	2740 (6.7)	16 369 (5.8)	6481 (15.9)	40 796 (14.4)
Hypertension	13 328 (32.7)	91 737 (32.3)	22 104 (54.2)	155 262 (54.7)
Stroke or transient ischaemic attack	1969 (4.8)	11 734 (4.1)	4747 (11.6)	25 856 (9.1)
Congestive heart disease	5279 (12.9)	33947 (12)	8388 (20.6)	54 615 (19.2)
Heart failure	819 (2.0)	5921 (2.1)	2140 (5.2)	15 961 (5.6)
Peripheral arterial disease	897 (2.2)	5953 (2.1)	2110 (5.2)	13 818 (4.9)
Atrial fibrillation	1303 (3.2)	8856 (3.1)	3744 (9.2)	24 591 (8.7)
Angina	3704 (9.1)	23 213 (8.2)	6006 (14.7)	38 602 (13.6)
Myocardial infarction	1820 (4.5)	12 051 (4.2)	2908 (7.1)	19 602 (6.9)
Coronary artery operations	831 (2.0)	5261 (1.9)	1711 (4.2)	11 002 (3.9)
Deep vein thrombosis	552 (1.4)	4172 (1.5)	1110 (2.7)	8101 (2.9)
Mental health diagnoses				
Depression	5071 (12.4)	29 676 (10.5)	8030 (19.7)	44 264 (15.6)
Severe depression	400 (1.0)	2175 (0.8)	804 (2.0)	4056 (1.4)
Depression symptoms	1393 (3.4)	7880 (2.8)	4577 (11.2)	24 220 (8.5)
Mean (SD) depression duration (years)§	13.8 (12.8)	14.2 (12.8)	14.3 (13.0)	15.2 (13.2)
Severe mental illness	294 (0.7)	1558 (0.5)	431 (1.1)	2078 (0.7)
Anxiety	3641 (8.9)	22 229 (7.8)	6190 (15.2)	35 598 (12.5)
Anxiety symptoms	1172 (2.9)	6457 (2.3)	3763 (9.2)	20 366 (7.2)
Other diagnoses				
Parkinson's disease	237 (0.6)	958 (0.3)	1448 (3.6)	4283 (1.5)
Epilepsy	542 (1.3)	2799 (1.0)	771 (1.9)	3860 (1.4)
Insomnia	2940 (7.2)	18 407 (6.5)	7351 (18.0)	45 227 (15.9)
Fatigue	2666 (6.5)	15 825 (5.6)	8561 (21.0)	50 351 (17.7)
Other sleep problems	583 (1.4)	3501 (1.2)	2772 (6.8)	15 878 (5.6)
Hemiplegia and paraplegia	131 (0.3)	816 (0.3)	235 (0.6)	1406 (0.5)
Drug abuse	297 (0.7)	1694 (0.6)	414 (1.0)	2357 (0.8)
Migraine	1320 (3.2)	8625 (3.0)	1839 (4.5)	11 999 (4.2)
Headache	2540 (6.2)	15 653 (5.5)	6102 (15)	37 602 (13.2)
Back or neck pain	12 225 (30.0)	79 108 (27.9)	21 123 (51.8)	138 554 (48.8)
Neuropathy	750 (1.8)	4766 (1.7)	2030 (5.0)	13 098 (4.6)
Meniere's disease	340 (0.8)	2353 (0.8)	471 (1.2)	3397 (1.2)
Restless leg syndrome	169 (0.4)	1088 (0.4)	610 (1.5)	3955 (1.4)
Chronic obstructive pulmonary disease	899 (2.2)	6327 (2.2)	2534 (6.2)	18 012 (6.3)
Asthma	3134 (7.7)	20 991 (7.4)	4375 (10.7)	29 822 (10.5)
Rhinitis	2556 (6.3)	16 617 (5.9)	5155 (12.6)	32 956 (11.6)
Gastroesophageal reflux disease or oesophagitis	2876 (7.1)	18 277 (6.4)	6141 (15.1)	39 437 (13.9)
Peptic or gastric ulcer	1122 (2.8)	6779 (2.4)	2530 (6.2)	15 724 (5.5)
Irritable bowel syndrome	210 (0.5)	1316 (0.5)	2328 (5.7)	15 277 (5.4)
Inflammatory bowel disease	1087 (2.7)	6692 (2.4)	2451 (6.0)	15 523 (5.5)
Intestinal surgery, colostomy, or ileostomy	1438 (3.5)	9515 (3.4)	3137 (7.7)	20 215 (7.1)
Liver disease	93 (0.2)	650 (0.2)	207 (0.6)	1312 (0.5)
Osteoarthritis	7925 (19.4)	50 644 (17.8)	14 627 (35.9)	94 681 (33.3)
Rheumatoid arthritis	486 (1.2)	3700 (1.3)	806 (2.0)	5799 (2.0)
Dermatitis	6986 (17.1)	45 613 (16.1)	13 364 (32.8)	88 331 (31.1)
Eczema	4015 (9.8)	26 696 (9.4)	8952 (22.0)	59 677 (21.0)
Psoriasis	1059 (2.6)	6856 (2.4)	1696 (4.2)	11 200 (3.9)
Urinary incontinence	1222 (3.0)	7186 (2.5)	3225 (7.9)	18 027 (6.3)
Renal disease or chronic kidney disease	457 (1.1)	3138 (1.1)	5817 (14.3)	37 981 (13.4)
Prostatism	1496 (3.7)	9176 (3.2)	3490 (8.6)	21 464 (7.6)
Cancer	3133 (7.7)	21 956 (7.7)	6307 (15.5)	44 567 (15.7)
History in 12 months before DEP				
Any falls	808 (2.0)	4391 (1.6)	808 (2.0)	4391 (1.6)
Any fractures	596 (1.5)	3693 (1.3)	596 (1.5)	3693 (1.3)
Mean (SD) doctor consultations	5.4 (6.3)	4.8 (5.9)	5.4 (6.3)	4.8 (5.9)

*Data missing for 9664 cases and 70 877 controls at the start of the DEP, and 1465 cases and 13 596 controls at the end of the DEP.
†Data missing for 22 940 cases and 159 721 controls at the start of the DEP, and 12 702 cases and 90 129 controls at the end of the DEP.
‡Data missing for 13 086 cases and 94 734 controls at the start of the DEP, and 4736 cases and 37 526 controls at the end of the DEP.
§Since first symptom or diagnosis of depression.

Table 2 | Crude and adjusted odds ratios of dementia by prescription of any, defined daily doses (DDDs), and total burden of anticholinergics measured with the Anticholinergic Cognitive Burden (ACB) score

			Odds ratio (95% CI)		
Exposure during DEP	No of cases (%)	No of controls (%)	Unadjusted	Adjusted at start of DEP*†	Adjusted at end of DEP*‡
Any use					
Prescriptions (ACB score):					
None	4295 (10.5)	36 329 (12.8)	1.00	1.00	1.00
1	36 437 (89.4)	247 406 (87.1)	1.25§ (1.21 to 1.29)	1.11§ (1.07 to 1.15)	1.10§ (1.06 to 1.15)
2	1429 (3.5)	7909 (2.8)	1.27§ (1.20 to 1.35)	1.10§ (1.03 to 1.17)	1.10§ (1.03 to 1.16)
3	14 453 (35.5)	86 403 (30.4)	1.27§ (1.24 to 1.30)	1.16§ (1.13 to 1.19)	1.11§ (1.08 to 1.14)
Number of DDDs (ACB score)					
1:					
0	4333 (10.6)	36 527 (12.9)	1.00	1.00	1.00
>0-13	3000 (7.4)	20 530 (7.2)	1.24§ (1.18 to 1.30)	1.16§ (1.11 to 1.22)	1.14§ (1.08 to 1.20)
14-89	2530 (6.2)	17 088 (6.0)	1.25§ (1.19 to 1.32)	1.15§ (1.09 to 1.21)	1.13§ (1.07 to 1.19)
90-364	4253 (10.4)	28 497 (10.0)	1.26§ (1.21 to 1.32)	1.12§ (1.07 to 1.18)	1.09§ (1.04 to 1.15)
365-1459	8549 (21.0)	56 607 (19.9)	1.28§ (1.23 to 1.33)	1.12§ (1.07 to 1.17)	1.10§ (1.05 to 1.15)
>1460	18 105 (44.4)	124 684 (43.9)	1.23§ (1.19 to 1.28)	1.05 (1.01 to 1.10)	1.05 (1.01 to 1.10)
2:					
0	39 341 (96.5)	276 024 (97.2)	1.00	1.00	1.00
>0-13	704 (1.7)	4301 (1.5)	1.15§ (1.06 to 1.25)	1.01 (0.93 to 1.10)	1.02 (0.94 to 1.11)
14-89	266 (0.7)	1533 (0.5)	1.22§ (1.07 to 1.39)	1.08 (0.94 to 1.23)	1.07 (0.94 to 1.23)
90-364	218 (0.5)	1035 (0.4)	1.48§ (1.28 to 1.72)	1.23§ (1.06 to 1.43)	1.20 (1.03 to 1.40)
365-1459	176 (0.4)	826 (0.3)	1.50§ (1.27 to 1.76)	1.23 (1.04 to 1.45)	1.18 (0.99 to 1.39)
>1460	65 (0.2)	214 (0.1)	2.15§ (1.63 to 2.83)	1.62§ (1.22 to 2.15)	1.57§ (1.18 to 2.09)
3:					
0	26 317 (64.5)	197 530 (69.6)	1.00	1.00	1.00
>0-13	5663 (13.9)	38 084 (13.4)	1.13§ (1.10 to 1.17)	1.07§ (1.04 to 1.11)	1.04 (1.01 to 1.08)
14-89	2440 (6.0)	15 154 (5.3)	1.23§ (1.17 to 1.28)	1.13§ (1.08 to 1.18)	1.07§ (1.02 to 1.12)
90-364	2786 (6.8)	15 462 (5.4)	1.37§ (1.31 to 1.43)	1.24§ (1.19 to 1.30)	1.17§ (1.12 to 1.22)
365-1459	2512 (6.2)	12 626 (4.4)	1.51§ (1.45 to 1.58)	1.35§ (1.29 to 1.42)	1.27§ (1.21 to 1.33)
>1460	1052 (2.6)	5077 (1.8)	1.59§ (1.49 to 1.71)	1.40§ (1.30 to 1.50)	1.31§ (1.22 to 1.41)
Average ACB score					
<0.1	9517 (23.3)	74 445 (26.2)	1.00	1.00	1.00
0.1-0.4	6084 (14.9)	41 528 (14.6)	1.15§ (1.11 to 1.19)	1.09§ (1.05 to 1.13)	1.07§ (1.03 to 1.11)
0.5-0.9	5781 (14.2)	40 413 (14.2)	1.12§ (1.08 to 1.16)	1.06§ (1.02 to 1.10)	1.06§ (1.02 to 1.10)
1.0-1.9	9030 (22.2)	62 348 (22.0)	1.14§ (1.10 to 1.17)	1.06§ (1.03 to 1.10)	1.07§ (1.01 to 1.09)
2.0-2.9	4914 (12.1)	33 113 (11.7)	1.17§ (1.13 to 1.21)	1.07§ (1.03 to 1.12)	1.07§ (1.02 to 1.12)
3.0-4.9	3874 (9.5)	23 954 (8.4)	1.28§ (1.23 to 1.33)	1.13§ (1.08 to 1.19)	1.12§ (1.07 to 1.18)
>5.0	1570 (3.9)	8132 (2.9)	1.53§ (1.44 to 1.62)	1.31§ (1.23 to 1.40)	1.28§ (1.19 to 1.36)

DEP=drug exposure period
*Adjusted for age, region, any falls, any fractures, and number of doctor consultations in the 12 months before the DEP. Also adjusted for the number of prescriptions during the DEP for the following drugs not rated as anticholinergic: benzodiazepines, z drugs, antidepressants, antinausea and antivertigo preparations, antiepileptics, and antiparkinson drugs.
†Adjusted for the following variables measured at the start of the DEP: body mass index, smoking status, harmful alcohol use, depression duration (0, 0-2, 2-5, 5-10, 10-20, and >20 years), and all diagnoses listed in table 1.
‡Adjusted for the following variables measured at the end of the DEP: body mass index, smoking status, harmful alcohol use, depression duration (0, 0-5, 5-10, 10-15, 15-20, and >20 years), and all diagnoses listed in table 1.
§P<0.01.

1.29) and 1.27 (1.09 to 1.48) respectively. However, for antidepressants with an ACB score of 1, the association with dementia increased for prescriptions given in periods closer to a diagnosis of dementia. Similarly, the negative association between gastrointestinal drugs and dementia was not seen for exposures 15-20 years before the index date.

Supplementary materials, appendix 4 details a further analysis of the associations between depression, antidepressants, and dementia incidence. Diagnosis of depression has no independent association with dementia incidence after adjusting for antidepressants and other covariates in the model. However, antidepressants were consistently associated with dementia; this affect was not attenuated by controlling for depression, and there was no interaction between depression severity and antidepressant drug use with respect to dementia incidence.

Sensitivity analyses

Excluding patients with a prescription for a drug with an ACB score of 2 or 3 in the 12 months before the DEP, hence restricting to new users, resulted in 5215 cases and 62 161 controls being excluded. This led to small reductions in the association between dementia incidence and any drug with an ACB score of 3 (odds ratio 1.07, 95% confidence interval 1.04 to 1.10) and any drug with an ACB score of 2 (1.12, 1.04 to 1.21) adjusted for covariates measured at the end of the DEP (see supplementary materials, table 3). No substantial changes were seen in the association between dementia incidence and specific classes of drugs used when restricted to new users. In particular, antidepressants and urologicals with an ACB score of 3 and antidepressants with an ACB score of 1 remained noticeably associated with dementia.

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Table 3 | Adjusted odds ratios of dementia by prescription of an anticholinergic drug by Anticholinergic Cognitive Burden (ACB) score and drug class

Drug class	No of cases (%)	No of controls (%)	Odds ratio (95% CI)	
			Adjusted at start of DEP*†	Adjusted at end of DEP*‡
ACB score of 1				
Analgesic	23 871 (58.6)	158 162 (55.7)	1.02 (1.00 to 1.05)	1.02 (0.99 to 1.04)
Antidepressant	5958 (14.6)	28 767 (10.1)	1.37§ (1.32 to 1.42)	1.25§ (1.20 to 1.30)
Antipsychotic	8051 (19.7)	50 079 (17.6)	1.05§ (1.02 to 1.08)	1.04 (1.01 to 1.07)
Cardiovascular	27 926 (68.5)	191 895 (67.6)	0.97 (0.94 to 0.99)	0.98 (0.95 to 1.01)
Gastrointestinal	10 845 (26.6)	71 814 (25.3)	0.97 (0.94 to 0.99)	0.96§ (0.93 to 0.99)
Respiratory	9385 (23.0)	62 787 (22.1)	0.99 (0.97 to 1.02)	0.99 (0.97 to 1.02)
Other	11 521 (28.3)	77 345 (27.2)	0.95§ (0.92 to 0.97)	0.95§ (0.92 to 0.98)
ACB score of 2				
Analgesic	385 (0.9)	2337 (0.8)	1.03 (0.92 to 1.15)	1.03 (0.92 to 1.16)
Antipsychotic	22 (0.1)	69 (0.0)	1.44 (0.87 to 2.36)	1.35 (0.82 to 2.23)
Antiparkinson	57 (0.1)	141 (0.0)	1.55§ (1.12 to 2.14)	1.32 (0.96 to 1.82)
Respiratory	19 (0.0)	123 (0.0)	0.89 (0.55 to 1.45)	0.83 (0.51 to 1.36)
Other	985 (2.4)	5454 (1.9)	1.07 (1.00 to 1.15)	1.09 (1.01 to 1.17)
ACB score of 3				
Antidepressant	8823 (21.6)	50 817 (17.9)	1.13§ (1.10 to 1.16)	1.11§ (1.08 to 1.14)
Antipsychotic	1036 (2.5)	5140 (1.8)	1.09 (1.02 to 1.18)	1.07 (1.00 to 1.16)
Gastrointestinal	1817 (4.5)	12 057 (4.2)	0.94 (0.89 to 0.99)	0.94 (0.89 to 0.99)
Antiparkinson	270 (0.7)	951 (0.3)	1.45§ (1.25 to 1.68)	1.29§ (1.11 to 1.50)
Respiratory	4002 (9.8)	25 195 (8.9)	1.04 (1.00 to 1.08)	1.03 (1.00 to 1.07)
Urological	3261 (8.0)	16 873 (5.9)	1.23§ (1.18 to 1.28)	1.18§ (1.13 to 1.23)
Other	284 (0.7)	1741 (0.6)	0.99 (0.87 to 1.13)	0.99 (0.87 to 1.13)

DEP=drug exposure period
*Adjusted for age, region, any falls, any fractures, and number of doctor consultations in the 12 months before the DEP. Also adjusted for the number of prescriptions during the DEP for the following drugs not rated as anticholinergic: benzodiazepines, z drugs, antidepressants, antinausea and antivertigo preparations, antiepileptics, and antiparkinson drugs.
†Adjusted for the following variables measured at the start of the DEP: body mass index, smoking status, harmful alcohol use, depression duration (0, 0-2, 2-5, 5-10, 10-20, and >20 years), and all diagnoses listed in table 1.
‡Adjusted for the following variables measured at the end of the DEP: body mass index, smoking status, harmful alcohol use, depression duration (0, 0-5, 5-10, 10-15, 15-20, and >20 years), and all diagnoses listed in table 1.
§P<0.01.

Findings remained similar when also analysed by more than 90 DDDs of exposure versus less, rather than any prescription versus none (results not shown).

Although there were differences in the number of drugs with an ACB score of 1 and 2 and drugs with an Anticholinergic Drug Scale (ADS) score of 1 and 2, the proportion of patients with a prescription for drugs with an ACB or ADS score of 3 were similar (see supplementary materials, table 4). There was good concordance between drugs with an ACB or ADS score of 3 (Cohen's kappa 0.91). Prescription of any drugs with an ADS score of 3 had a marginally lower association with dementia (odds ratio 1.08, 95% confidence interval 1.06 to 1.11) adjusted for covariates at the end of the DEP, than drugs with an ACB score of 3 (1.11, 1.08 to 1.14). However, when analysed by the drug class, the findings were very similar with the antidepressant, antiparkinson, and urological drugs with an ADS score of 3 and antidepressants with an ADS score of 1 consistently associated with greater dementia incidence (data not shown), but no association with other ADS classes.

Missing data

There were relatively high proportions of missing data for the body mass index, smoking, and alcohol variables. There was very little difference in any results when comparing estimates with and without adjustment for these variables among the main dataset and those with complete data (see supplementary materials, table 5), suggesting that our findings are not sensitive to missing data in these covariates.

Discussion

In this case-control study of older adults in the UK, there was a noticeable association between increasing total anticholinergic burden over the previous 4-20 years and incident dementia diagnosis. However, this dose-response effect was not seen for cumulative use of drugs with an Anticholinergic Cognitive Burden (ACB) score of 1 (possibly anticholinergic), and was only evident for certain classes of anticholinergic drugs. Antidepressants (predominantly amitriptyline, dosulepin, and paroxetine) and urologicals (predominantly oxybutynin and tolterodine) with an ABC score of 3 (definitely anticholinergic) were consistently associated with incident dementia. These relations were seen even for exposures 15-20 years before the diagnosis of dementia, suggesting that reverse causation or confounding with early dementia symptoms are less likely explanations for the effect. Prescription of gastrointestinal drugs with an ACB score of 3 was not positively associated with dementia in any of our analyses. Other antidepressants (predominantly selective serotonin reuptake inhibitors) with an ACB score of 1 were associated with dementia, but that association was greater for prescriptions close to

Table 4 | Adjusted odds ratios (OR) of dementia by prescription of anticholinergic drugs, by drug class, and by period before a diagnosis of dementia

	Exposure period (years before index date)								
	15-20*			10-15†			4-10‡		
Drug class	No of cases (n=10 684)	No of controls (n=74 145)	OR§ (95% CI)	No of cases (n=23 959)	No of controls (n=166 735)	OR§ (95% CI)	No of cases (n=40 770)	No of controls (n=283 933)	OR§ (95% CI)
Any use									
Prescriptions (ACB score):									
None	3638	27 905	1.00	5602	44 790	1.00	4492	38 579	1.00
1	6789	44 564	1.05 (1.00 to 1.10)	17 867	118 973	1.06¶ (1.02 to 1.10)	35 722	242 210	1.06¶ (1.02 to 1.09)
2	193	1057	1.07 (0.91 to 1.25)	493	2556	1.14¶ (1.03 to 1.26)	1054	5734	1.11¶ (1.03 to 1.18)
3	1972	11 321	1.17¶ (1.10 to 1.24)	5242	30 303	1.15¶ (1.10 to 1.19)	12 338	72 335	1.13¶ (1.10 to 1.15)
Any use by drug class									
Prescriptions (ACB score):									
None	3638	27 905	1.00	5602	44 790	1.00	4492	38 579	1.00
1:									
Analgesic	3638	22 914	1.06 (1.01 to 1.11)	9771	62 234	1.05¶ (1.02 to 1.08)	21 756	143 993	0.99 (0.96 to 1.01)
Antidepressant	262	1429	1.08 (0.93 to 1.24)	3813	24 345	1.18¶ (1.11 to 1.26)	5413	25 566	1.37¶ (1.32 to 1.42)
Antipsychotic	932	6032	0.99 (0.92 to 1.07)	2507	15 429	1.04 (0.99 to 1.09)	6392	39 642	1.03 (1.00 to 1.07)
Cardiovascular	3672	23 851	1.02 (0.97 to 1.08)	11 785	79 119	0.99 (0.95 to 1.02)	27 256	187 816	0.95¶ (0.92 to 0.97)
Gastrointestinal	1863	12 023	0.97 (0.92 to 1.03)	4447	28 709	0.98 (0.94 to 1.02)	8404	55 944	0.95¶ (0.92 to 0.98)
Respiratory	990	6658	0.96 (0.89 to 1.04)	2913	18 767	1.01 (0.97 to 1.06)	7784	52 560	0.98 (0.95 to 1.01)
Other	1230	8230	0.94 (0.88 to 1.02)	1396	7091	0.98 (0.94 to 1.02)	9792	66 244	0.91¶ (0.89 to 0.94)
2:									
Analgesic	64	358	1.09 (0.83 to 1.43)	102	654	0.92 (0.75 to 1.14)	254	1518	1.05 (0.91 to 1.20)
Antipsychotic	8	16	NA	10	28	NA	14	48	NA
Antiparkinson	<5	12	NA	17	22	NA	47	116	1.59 (1.11 to 2.28)
Respiratory	<5	26	NA	8	35	NA	12	75	NA
Other	120	675	0.99 (0.80 to 1.21)	363	1873	1.12 (1.00 to 1.26)	745	4056	1.07 (0.99 to 1.17)
3:									
Antidepressant	1155	6302	1.19¶ (1.10 to 1.29)	3237	17 828	1.16¶ (1.11 to 1.22)	7342	41 826	1.12¶ (1.08 to 1.15)
Antipsychotic	189	952	1.2 (1.00 to 1.42)	377	2024	0.98 (0.86 to 1.10)	781	3679	1.14¶ (1.04 to 1.23)
Gastrointestinal	273	1568	1.11 (0.97 to 1.28)	522	3453	0.93 (0.84 to 1.02)	1283	8721	0.91¶ (0.85 to 0.97)
Antiparkinson	29	146	1.29 (0.83 to 2.01)	104	379	1.54¶ (1.22 to 1.96)	230	786	1.56¶ (1.33 to 1.83)
Respiratory	524	3247	1.07 (0.97 to 1.18)	1228	7615	1.04 (0.97 to 1.10)	2839	17 807	1.03 (0.99 to 1.08)
Urological	207	995	1.27¶ (1.09 to 1.48)	810	4139	1.22¶ (1.13 to 1.32)	2870	14 654	1.23¶ (1.18 to 1.29)
Other	43	281	0.97 (0.70 to 1.34)	93	569	0.97 (0.78 to 1.21)	176	1051	1.02 (0.86 to 1.20)

ACB=Anticholinergic Cognitive Burden
*Including patients with ≥16 years of up to standard (UTS) data history before the index date.
†Including patients with ≥11 years of UTS data history before the index date.
‡Including patients with ≥6 years of UTS data history before the index date.
§Adjusted for age, region, number of prescriptions during the drug exposure period (DEP) for the following drugs not rated as anticholinergic: benzodiazepines, z drugs, antidepressants, antinausea and antivertigo preparations, antiepileptics, and antiparkinsons drugs. Also adjusted for the following variables measured at the start of the DEP: any falls, any fractures and number of doctor consultations in the 12 months before the DEP; body mass index; smoking status; harmful alcohol use; depression duration (0, 0-2, 2-5, 5-10, 10-20, and >20 years); and all diagnoses listed in table 1.
¶P<0.01.

dementia incidence, suggesting that reverse causation could be a possible explanation for this observed association. Other drugs with an ACB score of 1 were not associated with increased dementia incidence.

Strengths and weaknesses of the study

This is the first study to individually estimate the effect of classes of anticholinergic drugs with respect to dementia incidence. Our study used a large, population

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representative, primary care database that allowed a detailed analysis of the association between dementia incidence and prescriptions of different drugs classes up to 20 years before a diagnosis of dementia. However, there are several limitations to our approach.

In the UK, most diagnoses of dementia are made by memory services specialists. The diagnoses are then communicated back to primary care. Therefore, our cases are likely to represent genuine cases of dementia. Dementia codes in the Clinical Practice Research Datalink (CPRD) reflect diagnoses well with a positive predictive value of 95%.[23] However, dementia is known to be under diagnosed, with up to 50% of people with dementia undiagnosed at any time.[34] Hence it is possible that some of our controls have undiagnosed dementia or early cognitive impairment. This misclassification would shrink estimated effects towards the null (odds ratio of 1) but would not remove them completely. It is possible that surveillance bias influences the findings in that the patients who are prescribed anticholinergic drugs may be more likely to be diagnosed with dementia owing to their increased contact with health services. However, this effect would be observed across all drug classes and so is unlikely to account for our findings.

It is difficult to accurately assess the anticholinergic activity of each drug, and anticholinergic scales differ with respect to how they classify drugs.[29] However, there was good agreement between the Anticholinergic Drug Scale (ADS) and the ACB scale. Our findings were the same when using each scale. We do not know whether patients adhered to their prescribed drugs. Drugs obtained over-the-counter are not recorded in our data, hence we will have likely underestimated the use of certain antihistamines. Defined daily doses (DDDs) can be difficult to establish for certain drugs yet represent the best available method for comparing the levels of exposure of different drug classes. Our findings did not change when we instead analysed the number of prescriptions to quantify exposure (results not shown). DDDs also do not capture the relative anticholinergic activity across classes. Commonly used scales including the ACB scale typically assume that drugs with a score of 3 have three times the anticholinergic activity of those with a score of 1, but this is difficult to justify. Hence we stratified our results by drugs with an ACB score of 1, 2, or 3 in primary analysis to not enforce any particular relative anticholinergic activity, and separated by drug classes within those groups to avoid directly comparing DDDs across groups.

As in any observational study, unmeasured or residual confounding could underlie positive associations, and many causes of dementia are unknown. Primary care records do not hold detailed lifestyle or demographic information, but do include detailed records of diagnoses and symptoms that have allowed good confounding control. With respect to study design, our estimates generalise to those surviving at least four years after their initial anticholinergic exposure, and the nested case control design provides unbiased estimates of effects when compared with the equivalent cohort study.[35]

Strengths and weaknesses in relation to other studies

Many studies have linked anticholinergic drug use with concurrent or short term cognitive effects, but few have examined associations of long term anticholinergic exposure;[8] the latter tend to report positive associations.[12-15] Our findings are consistent with these studies, particularly a US cohort study of 3434 participants monitored over an average of seven years.[12] Anticholinergic antidepressants were linked to dementia incidence, consistent with our results, however, the authors did not test specific classes of the remaining anticholinergics. A US case-control study of 141 940 nursing home residents with depression found a greater adjusted odds ratio of 1.24 (95% confidence interval 1.20 to 1.28) for anticholinergic drugs use in the 90 days before a diagnosis of dementia based on administrative data.[15]

Our study uses a longer patient history in a larger sample of patients. This enables a much more granular disaggregation of the effects of specific drug classes in different periods before diagnosis, and in the depth of confounding control possible using complete primary care records, which enables exploration of alternative explanations for observed associations. Together these aspects substantially narrow the target of potential harm. Although set in the UK, our findings are likely generalisable to other developed countries.

Implications for clinicians and policymakers

The associations reported here are moderate (odds ratios for different exposures between 1.1 and 1.3), but given the high incidence of dementia they reflect an appreciable risk to patients. For example, the odds ratio for dementia associated with any use of antidepressants with an ACB score of 3 15-20 years before the index date is 1.19 (95% confidence interval 1.10 to 1.29). A typical patient aged 65-70 might normally expect a period incidence of dementia of around 10% over the next 15 years,[36] so this odds ratio would be consistent with an absolute risk increase of 2% (1% to 3%) over that period, corresponding to a number needed to harm of 50 (33 to 100). Possible explanations for our findings are that other actions of specific groups of anticholinergic drugs may underlie observed effects, or that the drugs are markers of prodromal symptoms or dementia risk factors. Alternatively, the class specific association we have observed may reflect a difference in the ability of different groups of anticholinergics to cross the blood-brain barrier.

Mechanistic evidence for a link between anticholinergic drugs and dementia incidence is limited, but neuropathological studies in humans and mice do support a role of anticholinergics affecting neurodegenerative pathology.[37 38] Most recently, a cross sectional analysis of Alzheimer's Disease Neuroimaging Initiative (ADNI) and Indiana Memory and Ageing Study (IMAS) data linked anticholinergic

drug use to reduced glucose metabolism and increased brain atrophy, and to future mild cognitive impairment or Alzheimer's disease incidence among cognitively normal participants (hazard ratio 2.47, P=0.01).[39] This study did not disaggregate subclasses of drugs. Evidence from anticholinergic cessation trials have not shown improvements in cognitive function, but these have been underpowered and focused on short term outcomes.[40]

Anticholinergic urological drugs, particularly oxybutynin, have been consistently associated with short term cognitive decline in randomised controlled trials,[8 41] so a long term risk of dementia is plausible. Lower urinary tract symptoms themselves have been linked to future dementia incidence and may be a symptom of early neurodegeneration.[42 43] To account for our finding, urinary incontinence would need to be a substantial risk factor for dementia diagnosed 15-20 years later.

Antidepressants (mainly selective serotonin reuptake inhibitors) with an ACB score of 1 were only associated with dementia close to the time of prescription. Conversely the finding of a constant association between dementia and antidepressants with an ACB score of 3 across the 20 years before dementia incidence, is more likely to represent a causal link. Although we carefully adjusted for depression diagnosis, severity, symptoms, and duration (see supplementary materials, appendix 4), residual confounding cannot be excluded. Depression has consistently been shown to be linked to increased dementia incidence in the short to medium term (up to 10 years). However, studies with longer follow-up periods have often failed to detect an association, or have reported weaker associations, between midlife depression and dementia in later life.[1 20] This suggests that residual confounding is unlikely to account for our observed association between antidepressants with an ACB score of 3 and dementia.

Patients with Parkinson's disease have an elevated risk of dementia;[44] anticholinergic antiparkinson drugs have previously been associated with greater cognitive decline.[45] This study provides further evidence that anticholinergic drugs should be avoided when treating patients with Parkinson's disease.

In each case (antidepressants, antiparkinsons, and urologicals with an ACB score of 3) a dose-response effect is seen with a smaller, but noticeable, positive association between dementia and recorded use of less than 90 DDDs (see supplementary materials, table 2). It is possible that in some cases these low exposures reflect a longer exposure that is not captured in the patients' current primary care record.

Previous research linking all anticholinergics to dementia incidence may have dissuaded some patients and clinicians from the use of anticholinergic antihistamine, cardiovascular, or gastrointestinal drugs. We find a slight negative association between gastrointenstinal drugs with an ACB score of 1 and 3 and dementia with an apparent dose-response effect, although there is no mechanistic explanation for this. Cardiovascular drugs with an ACB score of 1 were also negatively associated with dementia with prolonged exposure (odds ratio 0.95, 95% confidence interval 0.91 to 0.99; supplementary materials, table 2), suggesting their protective effect outweighs any possible harm associated with their anticholinergic properties. A small association between antihistamine use and dementia was observed that did not meet our threshold for statistical significance. Although very few patients (around 0.3% of the sample) are prescribed more than 365 DDDs of antihistamines in our study, those with fewer prescriptions may also have a substantial over-the-counter use that is not recorded. Patients who are prescribed more than 365 DDDs may comprise a lower socioeconomic status group for whom prescribed drugs are free of charge, hence preferred to over-the-counter drugs. Our results, although in need of independent confirmation particularly for antihistamines, should reassure these patients. Nevertheless, we do not dispute the possible short term harms of all anticholinergic drugs used among vulnerable groups, including short term cognitive impairment, and would advocate current guidance of vigilant use or avoidance among frail older people.

Considerations for future research

Adjusting for time varying confounders is difficult in a matched case-control study.[31 46] We measured covariates at the start and end of the drug exposure period (DEP). Since there was little difference between these estimates in most cases we are confident that the effect of time varying covariates does not considerably affect our findings. Secondly, to be certain that potential confounders preceded drug initiation and not vice versa, we further excluded patients who were prevalent users at the start of each DEP, again with little difference in results. We suggest that authors undertaking case-control studies comparing cumulative exposure over a long period carefully consider how time varying covariates and exposure before the period in which they are being directly measured might affect study findings. Future research into the potential harms of anticholinergics must consider differential effects of individual drug classes and their potentially different mechanisms of action. Carefully conducted prospective studies in specific cohorts of patients comparing the long term cognitive effects and neuropathological correlates of specific drug classes are needed.

Conclusion

Many people use anticholinergic drugs at some point in their lives, and many are prescribed to manage chronic conditions leading to potentially long exposures. There are robust associations between levels of anticholinergic antidepressants, antiparkinsons, and urologicals and the risk of a diagnosis of dementia up to 20 years after exposure. Other anticholinergics appear not to be linked to the risk of dementia, and risks remain uncertain for other drugs. Clinicians

should continue to be vigilant with respect to the use of anticholinergic drugs, and should consider the risk of long term cognitive effects, as well as short term effects, associated with specific drug classes when performing their risk-benefit analysis.

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Ethical approval: The study was approved by the Independent Scientific Advisory Committee for Clinical Practice Research Datalink (CPRD) research (protocol No 15_056R). No further ethical approval was required for the analysis of the data. CPRD has obtained ethical approval from a multicentre research ethics committee for all purely observational research using CPRD data.

Data sharing: Data from the Clinical Practice Research Datalink (CPRD) is available directly from CPRD. Full code lists are available from the corresponding author at k.richardson@uea.ac.uk.

Transparency: The lead author (KR) 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; and that any discrepancies from the study as planned and registered have been explained.

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Supplementary material: Additional information