**Supplementary Material**

**Appendix 1**

**CPRD medcodes, corresponding Read codes and Read terms used to define dementia**

|  |  |  |
| --- | --- | --- |
| **medcode**  | **Read code**  | **Read term** |
| 1350 | E00..12 | Senile/presenile dementia  |
| 1916 | E00..11 | Senile dementia  |
| 1917 | F110.00 | Alzheimer's disease  |
| 2882 | E00z.00 | Senile or presenile psychoses NOS |
| 4357 | Eu02z14 | [X] Senile dementia NOS  |
| 4693 | Eu02z00 | [X] Unspecified dementia  |
| 6578 | Eu01.00 | [X]Vascular dementia  |
| 7323 | E000.00 | Uncomplicated senile dementia  |
| 7572 | F116.00 | Lewy body disease  |
| 7664 | Eu00.00 | [X]Dementia in Alzheimer's disease  |
| 8195 | Eu00z11 | [X]Alzheimer's dementia unspec  |
| 8634 | E004.11 | Multi infarct dementia  |
| 8934 | Eu01200 | [X]Subcortical vascular dementia  |
| 9509 | Eu02300 | [X]Dementia in Parkinson's disease  |
| 9565 | Eu01.11 | [X]Arteriosclerotic dementia  |
| 11136 | F111.00 | Pick's disease  |
| 11175 | Eu01100 | [X]Multi-infarct dementia  |
| 11379 | Eu00112 | [X]Senile dementia,Alzheimer's type  |
| 12621 | Eu02.00 | [X]Dementia in other diseases classified elsewhere  |
| 15165 | E001.00 | Presenile dementia  |
| 15249 | E00y.00 | Other senile and presenile organic psychoses |
| 16797 | F110000 | Alzheimer's disease with early onset  |
| 18386 | E002000 | Senile dementia with paranoia  |
| 19393 | Eu01z00 | [X]Vascular dementia, unspecified  |
| 19477 | E004.00 | Arteriosclerotic dementia  |
| 21887 | E002100 | Senile dementia with depression  |
| 25386 | E041.00 | Dementia in conditions EC  |
| 25704 | Eu00011 | [X]Presenile dementia,Alzheimer's type  |
| 26270 | Eu02500 | [X]Lewy body dementia  |
| 27677 | E001300 | Presenile dementia with depression  |
| 27759 | Eu02z16 | [X] Senile dementia, depressed or paranoid type  |
| 27935 | Eu02z15 | [X] Senile psychosis NOS  |
| 28402 | Eu02000 | [X]Dementia in Pick's disease  |
| 29386 | Eu00z00 | [X]Dementia in Alzheimer's disease, unspecified  |
| 29512 | F112.00 | Senile degeneration of brain  |
| 30032 | E001200 | Presenile dementia with paranoia  |
| 30706 | Eu00200 | [X]Dementia in Alzheimer's dis, atypical or mixed type  |
| 31016 | Eu01300 | [X]Mixed cortical and subcortical vascular dementia  |
| 32057 | F110100 | Alzheimer's disease with late onset  |
| 33707 | E00..00  | Senile and presenile organic psychotic conditions |
| 34944 | Eu02z13 | [X] Primary degenerative dementia NOS  |
| 37014 | Eu02200 | [X]Dementia in Huntington's disease  |
| 37015 | E003.00 | Senile dementia with delirium  |
| 38438 | E001z00 | Presenile dementia NOS  |
| 38678 | Eu00100 | [X]Dementia in Alzheimer's disease with late onset  |
| 41089 | E002z00 | Senile dementia with depressive or paranoid features NOS  |
| 42279 | E004z00 | Arteriosclerotic dementia NOS  |
| 42602 | E001000 | Uncomplicated presenile dementia  |
| 43089 | E004000 | Uncomplicated arteriosclerotic dementia  |
| 43292 | E004300 | Arteriosclerotic dementia with depression  |
| 43346 | Eu00113 | [X]Primary degen dementia of Alzheimer's type, senile onset  |
| 44674 | E002.00 | Senile dementia with depressive or paranoid features  |
| 46488 | Eu01000 | [X]Vascular dementia of acute onset  |
| 46762 | Eu00111 | [X]Alzheimer's disease type 1  |
| 47619 | Eu02z12 | [X] Presenile psychosis NOS  |
| 48501 | Eu02z11 | [X] Presenile dementia NOS  |
| 49263 | Eu00000 | [X]Dementia in Alzheimer's disease with early onset  |
| 49513 | E001100 | Presenile dementia with delirium  |
| 51494 | E00y.11 | Presbyophrenic psychosis |
| 53446 | Eu04100 | [X]Delirium superimposed on dementia  |
| 54106 | Eu02100 | [X]Dementia in Creutzfeldt-Jakob disease  |
| 55313 | Eu01y00 | [X]Other vascular dementia  |
| 55467 | E004200 | Arteriosclerotic dementia with paranoia  |
| 55838 | Eu01111 | [X]Predominantly cortical dementia  |
| 56912 | E004100 | Arteriosclerotic dementia with delirium  |
| 59122 | Fyu3000 | [X]Other Alzheimer's disease  |
| 60059 | Eu00012 | [X]Primary degen dementia, Alzheimer's type, presenile onset  |
| 61528 | Eu00013 | [X]Alzheimer's disease type 2  |
| 62132 | E02y100 | Drug-induced dementia  |
| 64267 | Eu02y00 | [X]Dementia in other specified diseases classif elsewhere  |
| 109288 | A411000 |  |

**Appendix 2. Definition of covariates**

We extracted and coded the following covariates at the start and end of each patient’s Medication Exposure Period (MEP), unless stated otherwise, from the patient’s record:

*Diagnosis of cardiovascular and related diseases:* any previous diagnosis of diabetes, diabetes complications, hyperlipidemia, hypertension, stroke/ Transient Ischaemic Attack, congestive heart disease, heart failure, peripheral arterial disease, atrial fibrillation, angina, myocardial infarction, coronary artery operations, deep vein thrombosis.

*Depression*: Depression was measured in terms of its maximum severity (for diagnosed depression), the presence of depressive symptoms, and its duration. Maximum severity was defined as ‘mild’ ‘moderate’ or ‘severe’ using published classifications of Read codes for depression (1,2), with additional classification by members of the study team (KR, NS) for Read codes not included in those studies . The Read codes used for depression severity and depressive symptoms are given below. Duration is defined as the time between first record of diagnosis and the relevant cut-off date for measurement of covariates.

*Other potential dementia risk factors or correlates:* anxiety, anxiety symptoms, Parkinson's disease, severe mental illness, epilepsy, drug abuse, cancer, insomnia, sleep problems, migraine, headache, pain, neuropathy, Meniere's disease, restless leg syndrome

*Other indications for anticholinergics:* Chronic obstructive pulmonary disease, asthma, rhinitis, Gastroesophageal reflux disease, peptic/gastric ulcer, Irritable bowel syndrome, Inflammatory Bowel disease, intestinal surgery, liver disease, arthritis, dermatitis, eczema, psoriasis, incontinence, chronic kidney disease, or prostatism.

*Other factors:* GP practice region (Scotland, Northern Ireland, Wales and 10 health regions of England), smoking status (never, former, current or unknown), body mass index (<20, 20-24.9, 25-29.9, 30+ kg/m2, or missing), and problematic alcohol use (categorised as more than 49 units per week for men and more than 35 units per week for women, or missing). In the 12 months prior to the DEP: any falls, any fractures, and number of GP consultations.

*Other medication:* Number of prescriptions during the DEP of other medications rated without anticholinergic activity from the following classes: benzodiazepines (ATC N05BA, N05CD, N03AE), z-drugs (ATC N05CF), antidepressants (ATC N06A), antinausea and antivertigo preparations (ATC N07C, A03F), antiepileptics (ATC N03), and anti-Parkinson drugs (ATC N04).

**References**

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2. Coupland C, Hill T, Morriss R, Moore M, Arthur A, Hippisley-Cox J. Antidepressant use and risk of cardiovascular outcomes in people aged 20 to 64: cohort study using primary care database. BMJ. 2016 Mar 22;352:i1350.

**Appendix 3. CPRD medcodes, corresponding Read codes and Read terms used to define depression severity and depressive symptoms**

|  |  |  |  |
| --- | --- | --- | --- |
| **medcode** | **Read code** | **Read term** | **Depression severity** |
| 595 | E112.14 | Endogenous depression  | Severe |
| 1055 | E135.00  | Agitated depression | Severe |
| 2560 | E11..12 | Depressive psychoses | Severe |
| 5879 | E112.11 | Agitated depression  | Severe |
| 6932 | E113.11 | Endogenous depression - recurrent  | Severe |
| 8478 | E130.00  | Reactive depressive psychosis | Severe |
| 9667 | Eu32200 | [X]Severe depressive episode without psychotic symptoms  | Severe |
| 11329 | Eu33311 | [X]Endogenous depression with psychotic symptoms  | Severe |
| 12099 | Eu32300 | [X]Severe depressive episode with psychotic symptoms  | Severe |
| 15099 | E113.00 | Recurrent major depressive episode  | Severe |
| 16861 | Eu33315 | [X]Recurrent severe episodes of psychotic depression | Severe |
| 16861 | Eu33315 | [X]Recurrent severe episodes of psychotic depression  | Severe |
| 17770 | E130.11 | Psychotic reactive depression | Severe |
| 22806 | Eu32212 | [X]Single episode major depression w'out psychotic symptoms  | Severe |
| 24112 | Eu32313 | [X]Single episode of psychotic depression  | Severe |
| 24117 | Eu32311 | [X]Single episode of major depression and psychotic symptoms  | Severe |
| 24171 | E113400 | Recurrent major depressive episodes, severe, with psychosis  | Severe |
| 25563 | E113z00 | Recurrent major depressive episode NOS  | Severe |
| 25697 | E113300 | Recurrent major depressive episodes, severe, no psychosis  | Severe |
| 28863 | Eu32314 | [X]Single episode of reactive depressive psychosis  | Severe |
| 29784 | Eu33300 | [X]Recurrent depress disorder cur epi severe with psyc symp  | Severe |
| 31757 | Eu33314 | [X]Recurr severe episodes/psychogenic depressive psychosis  | Severe |
| 32159 | E112400 | Single major depressive episode, severe, with psychosis  | Severe |
| 32941 | Eu33313 | [X]Recurr severe episodes/major depression+psychotic symptom  | Severe |
| 33469 | Eu33200 | [X]Recurr depress disorder cur epi severe without psyc sympt  | Severe |
| 33469 | Eu33200 | [X]Recurr depress disorder cur epi severe without psyc sympt | Severe |
| 34390 | E112000 | Single major depressive episode, unspecified  | Severe |
| 35671 | E113000 | Recurrent major depressive episodes, unspecified  | Severe |
| 37764 | Eu33316 | [X]Recurrent severe episodes/reactive depressive psychosis | Severe |
| 37764 | Eu33316 | [X]Recurrent severe episodes/reactive depressive psychosis  | Severe |
| 41989 | Eu32211 | [X]Single episode agitated depressn w'out psychotic symptoms  | Severe |
| 52678 | Eu32312 | [X]Single episode of psychogenic depressive psychosis  | Severe |
| 98414 | Eu32700 | [X]Major depression, severe without psychotic symptoms  | Severe |
| 98417 | Eu32800 | [X]Major depression, severe with psychotic symptoms  | Severe |
| 101153 | Eu32A00 | [X]Recurr major depr ep, severe with psych, psych in remiss  | Severe |
| 324 | E2B..00 | Depressive disorder NEC | Moderate |
| 2970 | Eu32z00 | [X]Depressive episode, unspecified  | Moderate |
| 3292 | Eu33.00 | [X]Recurrent depressive disorder  | Moderate |
| 4323 | E2B1.00  | Chronic depression | Moderate |
| 4639 | Eu32.00 | [X]Depressive episode  | Moderate |
| 6482 | E113700 | Recurrent depression  | Moderate |
| 6546 | E112.12 | Endogenous depression first episode  | Moderate |
| 6950 | E112.13 | Endogenous depression first episode  | Moderate |
| 7011 | E112z00 | Single major depressive episode NOS  | Moderate |
| 9183 | E11z200 | Masked depression | Moderate |
| 9211 | Eu32100 | [X]Moderate depressive episode  | Moderate |
| 10610 | E112.00 | Single major depressive episode  | Moderate |
| 10720 | Eu32y11 | [X]Atypical depression  | Moderate |
| 11252 | Eu33212 | [X]Major depression, recurrent without psychotic symptoms  | Moderate |
| 11329 | Eu33211 | [X]Endogenous depression without psychotic symptoms  | Moderate |
| 11913 | Eu41200 | [X]Mixed anxiety and depressive disorder Moderate | Moderate |
| 14709 | E113200 | Recurrent major depressive episodes, moderate  | Moderate |
| 15155 | E112200 | Single major depressive episode, moderate  | Moderate |
| 15219 | E112300 | Single major depressive episode, severe, without psychosis  | Moderate |
| 15220 | Eu34114 | [X]Persistant anxiety depression  | Moderate |
| 22116 | Eu33400 | [X]Recurrent depressive disorder, currently in remission  | Moderate |
| 27491 | E11y200 | Atypical depressive disorder  | Moderate |
| 28248 | Eu32z13 | [X]Prolonged single episode of reactive depression  | Moderate |
| 29520 | Eu33100 | [X]Recurrent depressive disorder, current episode moderate  | Moderate |
| 29520 | Eu33100 | [X]Recurrent depressive disorder, current episode moderate | Moderate |
| 31757 | Eu33214 | [X]Vital depression, recurrent without psychotic symptoms  | Moderate |
| 36616 | Eu33z11 | [X]Monopolar depression NOS  | Moderate |
| 43324 | E112500 | Single major depressive episode, partial or unspec remission  | Moderate |
| 44300 | Eu33z00 | [X]Recurrent depressive disorder, unspecified  | Moderate |
| 47731 | Eu33y00 | [X]Other recurrent depressive disorders  | Moderate |
| 56273 | E113500 | Recurrent major depressive episodes,partial/unspec remission  | Moderate |
| 59386 | Eu32213 | [X]Single episode vital depression w'out psychotic symptoms  | Moderate |
| 98252 | Eu32600 | [X]Major depression, moderately severe  | Moderate |
| 101054 | Eu32900 | [X]Single major depr ep, severe with psych, psych in remiss  | Moderate |
| 543 | Eu32z11 | [X]Depression NOS  | Mild |
| 655 | E200300 | Anxiety with depression | Mild |
| 1131 | E204.00 | Neurotic depression reactive type | Mild |
| 1533 | E290.00 | Brief depressive reaction  | Mild |
| 2716 | 1465.00  | H/O: depression | Mild |
| 2972 | E2B0.00  | Postviral depression | Mild |
| 3291 | Eu32z12 | [X]Depressive disorder NOS  | Mild |
| 5987 | Eu32z14 | [X] Reactive depression NOS  | Mild |
| 6854 | Eu32y00 | [X]Other depressive episodes  | Mild |
| 7604 | Eu32.13 | [X]Single episode of reactive depression  | Mild |
| 7737 | Eu34113 | [X]Neurotic depression  | Mild |
| 7749 | Eu41211 | [X]Mild anxiety depression Mild | Mild |
| 7953 | Eu34100 | [X]Dysthymia  | Mild |
| 8584 | Eu34111 | [X]Depressive neurosis  | Mild |
| 8826 | Eu33.15 | [X]SAD - Seasonal affective disorder  | Mild |
| 8851 | Eu33.11 | [X]Recurrent episodes of depressive reaction  | Mild |
| 8902 | Eu33.13 | [X]Recurrent episodes of reactive depression  | Mild |
| 9055 | Eu32.11 | [X]Single episode of depressive reaction  | Mild |
| 10290 | Eu34112 | [X]Depressive personality disorder  | Mild |
| 10455 | E211200 | Depressive personality disorder | Mild |
| 10667 | Eu32400 | [X]Mild depression  | Mild |
| 10825 | E118.00  | Seasonal affective disorder | Mild |
| 11717 | Eu32000 | [X]Mild depressive episode  | Mild |
| 12399 | 9H90.00 | Depression annual review | Mild |
| 16506 | E112100 | Single major depressive episode, mild  | Mild |
| 16632 | E291.00  | Prolonged depressive reaction | Mild |
| 18510 | Eu32.12 | [X]Single episode of psychogenic depression  | Mild |
| 19696 | Eu33.12 | [X]Recurrent episodes of psychogenic depression  | Mild |
| 28756 | Eu33.14 | [X]Seasonal depressive disorder  | Mild |
| 29342 | E113100 | Recurrent major depressive episodes, mild  | Mild |
| 29784 | Eu33000 | [X]Recurrent depressive disorder, current episode mild  | Mild |
| 42931 | 9HA0.00 | On depression register | Mild |
| 55384 | E113600 | Recurrent major depressive episodes, in full remission  | Mild |
| 56609 | Eu32y12 | [X]Single episode of masked depression NOS  | Mild |
| 57409 | E112600 | Single major depressive episode, in full remission | Mild |
| 98346 | Eu32500 | [X]Major depression, mild  | Mild |
| 1449 | 1B1J.00 | Emotional problem  | Depressive symptoms |
| 1908 | 2257.00 | O/E – depressed | Depressive symptoms |
| 1996 | 1B17.00 | Depressed  | Depressive symptoms |
| 2639 | E204.11 | Postnatal depression | Depressive symptoms |
| 2775 | E290000 | Grief reaction  | Depressive symptoms |
| 3489 | E11z100 | Rebound mood swings | Depressive symptoms |
| 3502 | 1B1J.11 | Emotional upset | Depressive symptoms |
| 4824 | 1B17.11 | C/O - feeling depressed  | Depressive symptoms |
| 4979 | Eu53012 | [X]Postpartum depression NOS | Depressive symptoms |
| 6021 | 1BO..00 | Mood swing | Depressive symptoms |
| 7382 | R007z14 | [D]Work stress | Depressive symptoms |
| 8928 | 1BT..11 | Low mood | Depressive symptoms |
| 9796 | 1B1U.00 | Symptoms of depression | Depressive symptoms |
| 10015 | 1BT..00 | depressed mood | Depressive symptoms |
| 10438 | 1B1U.11 | Depressive symptoms | Depressive symptoms |
| 10535 | Eu43012 | [[X]Acute reaction to stress | Depressive symptoms |
| 10734 | E290011 | Bereavement reaction  | Depressive symptoms |
| 11098 | Eu43.00 | [X]Reaction to severe stress, and adjustment disorders | Depressive symptoms |
| 11607 | Eu43000 | [X]Acute stress reaction | Depressive symptoms |
| 12122 | 9H91.00 | Depression medication review | Depressive symptoms |
| 12416 | 1S4..00 | Mood observations | Depressive symptoms |
| 13307 | Eu53011 | [X]Postnatal depression NOS | Depressive symptoms |
| 13307 | Eu53011 | [X]Postnatal depression NOS | Depressive symptoms |
| 15665 | E292z00 | Adjustment reaction with disturbance of other emotion NOS | Depressive symptoms |
| 19054 | Eu3y111 | [X]Recurrent brief depressive episodes | Depressive symptoms |
| 19439 | 212S.00 | Depression resolved | Depressive symptoms |
| 21753 | Eu43y00 | [X]Other reactions to severe stress | Depressive symptoms |
| 23808 | Eu4..00 | [X]Neurotic, stress - related and somoform disorders | Depressive symptoms |
| 23869 | E284.00 | Stress reaction causing mixed disturbance of emotion/conduct | Depressive symptoms |
| 24212 | E292.00 | Adjustment reaction, predominant disturbance other emotions | Depressive symptoms |
| 25435 | 1BQ..00 | Loss of capacity for enjoyment | Depressive symptoms |
| 26028 | 1BT..12 | sad mood | Depressive symptoms |
| 26138 | E28z.00 | Acute stress reaction NOS | Depressive symptoms |
| 29527 | R007z13 | [D]Postoperative depression  | Depressive symptoms |
| 29707 | E283z00 | Other acute stress reaction NOS | Depressive symptoms |
| 30405 | 9H92.00 | Depression interim review | Depressive symptoms |
| 30483 | 8CAa.00 | Patient given advice about management of depression | Depressive symptoms |
| 30583 | 9k4..00 | Depression - enhanced services administration | Depressive symptoms |
| 31515 | Eu43z00 | [X]Reaction to severe stress, unspecified | Depressive symptoms |
| 32841 | 8HHq.00 | Referral for guided self-help for depression | Depressive symptoms |
| 32845 | Eu92000 | [X]Depressive conduct disorder  | Depressive symptoms |
| 36246 | E290z00 | Brief depressive reaction NOS  | Depressive symptoms |
| 38640 | E283.00 | Other acute stress reactions | Depressive symptoms |
| 41599 | E2C4.00 | Mixed disturbance of conduct and emotion | Depressive symptoms |
| 44848 | 8BK0.00 | Depression management programme | Depressive symptoms |
| 45603 | E294.00 | Adjustment reaction with disturbance emotion and conduct | Depressive symptoms |
| 48349 | 1S40.00 | Dysphoric mood | Depressive symptoms |
| 48588 | E292y00 | Adjustment reaction with mixed disturbance of emotion | Depressive symptoms |
| 53148 | 1BU..00 | Loss of hope for the future | Depressive symptoms |
| 56924 | E292400 | Adjustment reaction with anxious mood | Depressive symptoms |
| 59869 | 1BP0.00 | Loss of interest in previously enjoyable activity | Depressive symptoms |
| 65435 | 9k40.00 | Depression - enhanced service completed | Depressive symptoms |
| 91580 | Eu92.11 | [X]Emotional behavioural problems | Depressive symptoms |
| 96995 | 9kQ..00 | On full dose long term treatment depression - enh serv admin | Depressive symptoms |
| 100977 | 1JJ..00 | Suspected depression | Depressive symptoms |
| 103677 | Eu32B00 | [X]Antenatal depression  | Depressive symptoms |

eFigure1 – Selection of 40,770 patients with dementia and 283,933 controls from the Clinical Practice Research Datalink.



eTable 1. Frequency of prescriptions during the drug exposure period according to Anticholinergic Cognitive Burden (ACB) score and drug class. Drugs representing more than 1% of the prescriptions within each ACB level are shown, or the most prevalent drug within each subgroup where this represents fewer than 1% of prescriptions. Shaded areas indicate no drug within that group was prescribed during the course of the study.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  **ACB1 (25,122,902 prescriptions)** |  | **ACB2 (132,731 prescriptions)** |  | **ACB3 (1,793,505 prescriptions)** |
| **Class** | **Drug** | **%** |  | **Drug** | **%** |  | **Drug** | **%** |
| Antidepressant | Citalopram | 1% |  |  |  |  | Amitriptyline | 29% |
|  |  |  |  |  |  |  | Dosulepin | 16% |
|  |  |  |  |  |  |  | Paroxetine | 8% |
|  |  |  |  |  |  |  | Lofepramine | 2% |
|  |  |  |  |  |  |  | Clomipramine | 2% |
|  |  |  |  |  |  |  | Imipramine | 2% |
|  |  |  |  |  |  |  | Trimipramine | 2% |
|   |   |   |   |   |   |   | Nortriptyline | 1% |
| Gastrointestinal | Ranitidine | 2% |  |  |  |  | Hyoscine | 1% |
|  |  |  |  |  |  |  | Dicycloverine | 1% |
|   |   |   |   |   |   |   | Atropine | 1% |
| Respiratory | Ipratropium | 0.6% |  | Cyproheptadine | 0.7% |  | Chlorphenamine | 4% |
|  |  |  |  |  |  |  | Hydroxyzine | 2% |
|   |   |   |   |   |   |   | Promethazine | 1% |
| Antipsychotic | Prochlorperazine | 1% |  | Zuclopenthixol  | 1% |  | Trifluoperazine | 2% |
|  |  |  |  |  |  |  | Olanzapine | 2% |
|  |  |  |  |  |  |  | Chlorpromazine | 1% |
|   |   |   |   |   |   |   | Thioridazine | 1% |
| Parkinsonian |   |   |   | Amantadine  | 2% |   | Procyclidine | 1% |
| Urological |  |  |  |  |  |  | Tolterodine | 7% |
|  |  |  |  |  |  |  | Oxybutynin | 7% |
|   |   |   |   |   |   |   | Solifenacin | 1% |
| Analgesic | CODEINE | 6% |  | Nefopam  | 6% |  |  |  |
|  | Dextropropoxyphene | 4% |  | Pethidine  | 2% |  |  |  |
|  | Dihydrocodeine | 3% |  |  |  |  |  |  |
|   | Tramadol | 1% |   |   |   |   |   |   |
| Cardiovascular | Bendroflumethiazide | 13% |  |  |  |  |  |  |
|  | Atenolol | 11% |  |  |  |  |  |  |
|  | Furosemide | 6% |  |  |  |  |  |  |
|  | Ramipril | 5% |  |  |  |  |  |  |
|  | Lisinopril | 4% |  |  |  |  |  |  |
|  | Isosorbide | 4% |  |  |  |  |  |  |
|  | Warfarin | 4% |  |  |  |  |  |  |
|  | Nifedipine | 3% |  |  |  |  |  |  |
|  | Doxazosin | 3% |  |  |  |  |  |  |
|  | Digoxin | 2% |  |  |  |  |  |  |
|  | Enalapril | 2% |  |  |  |  |  |  |
|  | Perindopril | 2% |  |  |  |  |  |  |
|  | Amiloride | 2% |  |  |  |  |  |  |
|   | Glyceryl Trinitrate | 2% |   |   |   |   |   |   |
| Other | Prednisolone | 2% |  | Carbamazepine | 87% |  | Methocarbamol | 0.4% |
|   | Diazepam | 1% |   |   |   |   |   |   |

eTable 2. Adjusted odds ratios of dementia by number of DDDs of anticholinergic medications by drug class and ACB score

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Drug class | Cases (n=40,770)n (%) | Controls (283,933)n (%) | Adjusted for covariates measured at start of DEPaOR (95% CI) | Adjusted for covariates measured at end of DEPaOR (95% CI) |
| Analgesic |  |  |  |  |
| 0 | 16,899 (41.4%) | 125,771 (44.3%) | 1 | 1 |
| >0-13 | 6,581 (16.1%) | 45,258 (15.9%) | 1.03 (1.00 to 1.07) | 1.02 (0.99 to 1.05) |
| 14-89 | 8,166 (20.0%) | 55,924 (19.7%) | 1.00 (0.97 to 1.03) | 1.00 (0.97 to 1.03) |
| 90-364 | 5,216 (12.8%) | 33,483 (11.8%) | 1.03 (0.99 to 1.07) | 1.04 (1.00 to 1.08) |
| 365-1459 | 3,293 (8.1%) | 20,172 (7.1%) | 1.04 (1.00 to 1.09) | 1.06 (1.01 to 1.11) |
| 1460+ | 615 (1.5%) | 3,325 (1.2%) | 1.12 (1.02 to 1.23) | 1.16\* (1.05 to 1.27) |
| Antidepressant |  |  |  |  |
| 0 | 34,812 (85.4%) | 255,166 (89.9%) | 1 | 1 |
| >0-13 | 114 (0.3%) | 0,713 (0.3%) | 1.05 (0.86 to 1.28) | 0.99 (0.81 to 1.21) |
| 14-89 | 2,103 (5.2%) | 10,967 (3.9%) | 1.29\* (1.23 to 1.36) | 1.19\* (1.13 to 1.25) |
| 90-364 | 1,481 (3.6%) | 7,222 (2.5%) | 1.36\* (1.28 to 1.44) | 1.23\* (1.16 to 1.31) |
| 365-1459 | 1,552 (3.8%) | 6,883 (2.4%) | 1.47\* (1.39 to 1.57) | 1.34\* (1.26 to 1.43) |
| 1460+ | 708 (1.7%) | 2,982 (1.1%) | 1.55\* (1.42 to 1.69) | 1.47\* (1.34 to 1.60) |
| Antipsychotic |  |  |  |  |
| 0 | 32,719 (80.3%) | 233,854 (82.4%) | 1 | 1 |
| >0-13 | 6,453 (15.8%) | 41,234 (14.5%) | 1.04 (1.01 to 1.07) | 1.03 (1.00 to 1.06) |
| 14-89 | 1,102 (2.7%) | 6,195 (2.2%) | 1.10\* (1.02 to 1.17) | 1.09 (1.01 to 1.16) |
| 90-364 | 359 (0.9%) | 1,977 (0.7%) | 1.09 (0.97 to 1.23) | 1.07 (0.95 to 1.20) |
| 365-1459 | 108 (0.3%) | 0,542 (0.2%) | 1.11 (0.90 to 1.38) | 1.09 (0.88 to 1.36) |
| 1460+ | 29 (0.1%) | 0,131 (0.0%) | 1.04 (0.68 to 1.59) | 1.03 (0.67 to 1.57) |
| Cardiovascular |  |  |  |  |
| 0 | 12,844 (31.5%) | 92,038 (32.4%) | 1 | 1 |
| >0-13 | 713 (1.7%) | 4,550 (1.6%) | 1.00 (0.92 to 1.09) | 0.99 (0.91 to 1.07) |
| 14-89 | 1,863 (4.6%) | 11,912 (4.2%) | 1.03 (0.98 to 1.09) | 1.03 (0.97 to 1.09) |
| 90-364 | 2,625 (6.4%) | 17,242 (6.1%) | 1.01 (0.96 to 1.06) | 1.01 (0.96 to 1.06) |
| 365-1459 | 6,802 (16.7%) | 46,285 (16.3%) | 0.98 (0.94 to 1.01) | 0.98 (0.95 to 1.02) |
| 1460+ | 15,923 (39.1%) | 111,906 (39.4%) | 0.93\* (0.90 to 0.96) | 0.95\* (0.91 to 0.99) |
| Gastro-intestinal |  |  |  |  |
| 0 | 29,925 (73.4%) | 212,119 (74.7%) | 1 | 1 |
| >0-13 | 2,995 (7.3%) | 19,201 (6.8%) | 1.03 (0.98 to 1.07) | 1.01 (0.97 to 1.06) |
| 14-89 | 3,592 (8.8%) | 24,251 (8.5%) | 0.95\* (0.91 to 0.99) | 0.94\* (0.90 to 0.98) |
| 90-364 | 2,216 (5.4%) | 15,138 (5.3%) | 0.92\* (0.88 to 0.97) | 0.92\* (0.87 to 0.96) |
| 365-1459 | 1,607 (3.9%) | 10,409 (3.7%) | 0.96 (0.91 to 1.01) | 0.96 (0.90 to 1.01) |
| 1460+ | 435 (1.1%) | 2,815 (1.0%) | 0.94 (0.85 to 1.05) | 0.95 (0.86 to 1.06) |
| Respiratory |  |  |  |  |
| 0 | 31,385 (77.0%) | 221,146 (77.9%) | 1 | 1 |
| >0-13 | 1,507 (3.7%) | 10,163 (3.6%) | 1.01 (0.95 to 1.07) | 1.02 (0.96 to 1.08) |
| 14-89 | 4,702 (11.5%) | 31,037 (10.9%) | 1.01 (0.98 to 1.05) | 1.00 (0.97 to 1.04) |
| 90-364 | 1,515 (3.7%) | 10,357 (3.6%) | 0.95 (0.89 to 1.00) | 0.95 (0.89 to 1.00) |
| 365-1459 | 1,095 (2.7%) | 7,363 (2.6%) | 0.97 (0.91 to 1.04) | 0.98 (0.92 to 1.05) |
| 1460+ | 566 (1.4%) | 3,867 (1.4%) | 0.94 (0.86 to 1.04) | 0.96 (0.87 to 1.05) |
| Other |  |  |  |  |
| 0 | 29,249 (71.7%) | 206,588 (72.8%) | 1 | 1 |
| >0-13 | 2,653 (6.5%) | 17,447 (6.1%) | 0.98 (0.93 to 1.03) | 0.97 (0.93 to 1.02) |
| 14-89 | 5,013 (12.3%) | 33,590 (11.8%) | 0.95\* (0.92 to 0.99) | 0.95 (0.92 to 0.99) |
| 90-364 | 2,182 (5.4%) | 14,688 (5.2%) | 0.93\* (0.88 to 0.98) | 0.94 (0.89 to 0.99) |
| 365-1459 | 1,362 (3.3%) | 9,441 (3.3%) | 0.92\* (0.86 to 0.97) | 0.91\* (0.86 to 0.97) |
| 1460+ | 311 (0.8%) | 2,179 (0.8%) | 0.86 (0.76 to 0.97) | 0.86 (0.76 to 0.98) |
| ACB2 |  |  |  |  |
| Analgesic |  |  |  |  |
| 0 | 40,385 (99.1%) | 281,596 (99.2%) | 1 | 1 |
| >0-13 | 116 (0.3%) | 0,832 (0.3%) | 0.89 (0.73 to 1.08) | 0.89 (0.73 to 1.09) |
| 14-89 | 208 (0.5%) | 1,189 (0.4%) | 1.10 (0.94 to 1.27) | 1.10 (0.95 to 1.28) |
| 90-364 | 39 (0.1%) | 0,208 (0.1%) | 1.13 (0.79 to 1.59) | 1.12 (0.79 to 1.59) |
| 365+ | 22 (0.1%) | 0,108 (0.0%) | 1.21 (0.76 to 1.93) | 1.21 (0.76 to 1.93) |
| Antipsychotic |  |  |  |  |
| 0 | 40,748 (99.9%) | 283,864 (100.0%) | 1 | 1 |
| >0-89 | 6 (0.0%) | 0,024 (0.0%) | 1.11 (0.45 to 2.75) | 0.92 (0.36 to 2.33) |
| 90+ | 16 (0.0%) | 0,045 (0.0%) | 1.62 (0.90 to 2.92) | 1.61 (0.89 to 2.91) |
| Parkinsonian |  |  |  |  |
| 0 | 40,713 (99.9%) | 283,792 (100.0%) | 1 | 1 |
| >0-89 | 20 (0.0%) | 0,063 (0.0%) | 1.43 (0.85 to 2.40) | 1.33 (0.79 to 2.23) |
| 90-364 | 19 (0.0%) | 0,037 (0.0%) | 1.80 (1.02 to 3.17) | 1.47 (0.84 to 2.59) |
| 365+ | 18 (0.0%) | 0,041 (0.0%) | 1.48 (0.84 to 2.62) | 1.18 (0.67 to 2.08) |
| Respiratory |  |  |  |  |
| 0 | 40,751 (100.0%) | 283,810 (100.0%) | 1 | 1 |
| >0-13 | 6 (0.0%) | 0,041 (0.0%) | 0.89 (0.37 to 2.11) | 0.80 (0.34 to 1.93) |
| 14+ | 13 (0.0%) | 0,082 (0.0%) | 0.89 (0.49 to 1.61) | 0.85 (0.47 to 1.53) |
| Other  |  |  |  |  |
| 0 | 39,785 (97.6%) | 278,479 (98.1%) | 1 | 1 |
| >0-13 | 424 (1.0%) | 2,499 (0.9%) | 1.02 (0.92 to 1.14) | 1.05 (0.94 to 1.17) |
| 14-89 | 218 (0.5%) | 1,338 (0.5%) | 0.97 (0.84 to 1.12) | 0.99 (0.85 to 1.15) |
| 90-364 | 152 (0.4%) | 0,773 (0.3%) | 1.17 (0.98 to 1.39) | 1.17 (0.97 to 1.40) |
| 365-1459 | 143 (0.4%) | 0,674 (0.2%) | 1.26 (1.05 to 1.52) | 1.23 (1.01 to 1.48) |
| 1460+ | 48 (0.1%) | 0,170 (0.1%) | 1.58\* (1.14 to 2.20) | 1.56\* (1.12 to 2.17) |
| ACB3 |  |  |  |  |
| Antidepressant |  |  |  |  |
| 0 | 31,947 (78.4%) | 233,116 (82.1%) | 1 | 1 |
| >0-13 | 3,389 (8.3%) | 21,235 (7.5%) | 1.08\* (1.04 to 1.13) | 1.07\* (1.02 to 1.11) |
| 14-89 | 1,505 (3.7%) | 8,976 (3.2%) | 1.07 (1.01 to 1.14) | 1.05 (0.99 to 1.12) |
| 90-364 | 1,775 (4.4%) | 9,682 (3.4%) | 1.16\* (1.10 to 1.23) | 1.14\* (1.08 to 1.21) |
| 365-1459 | 1,498 (3.7%) | 7,732 (2.7%) | 1.24\* (1.17 to 1.31) | 1.22\* (1.14 to 1.29) |
| 1460+ | 656 (1.6%) | 3,192 (1.1%) | 1.30\* (1.18 to 1.42) | 1.29\* (1.18 to 1.41) |
| Antipsychotic |  |  |  |  |
| 0 | 39,734 (97.5%) | 278,793 (98.2%) | 1 | 1 |
| >0-13 | 413 (1.0%) | 2,356 (0.8%) | 0.98 (0.88 to 1.09) | 0.96 (0.86 to 1.07) |
| 14-89 | 243 (0.6%) | 1,175 (0.4%) | 1.11 (0.96 to 1.28) | 1.10 (0.95 to 1.27) |
| 90-364 | 194 (0.5%) | 800 (0.3%) | 1.31\* (1.12 to 1.54) | 1.29\* (1.09 to 1.52) |
| 365-1459 | 134 (0.3%) | 601 (0.2%) | 1.20 (0.99 to 1.46) | 1.16 (0.95 to 1.42) |
| 1460+ | 52 (0.1%) | 208 (0.1%) | 1.31 (0.96 to 1.80) | 1.32 (0.96 to 1.82) |
| Gastro-intestinal |  |  |  |  |
| 0 | 38,953 (95.5%) | 271,876 (95.8%) | 1 | 1 |
| >0-13 | 1,205 (3.0%) | 8,052 (2.8%) | 0.95 (0.90 to 1.02) | 0.95 (0.89 to 1.01) |
| 14-89 | 454 (1.1%) | 2,977 (1.0%) | 0.91 (0.82 to 1.00) | 0.91 (0.82 to 1.01) |
| 90-364 | 101 (0.2%) | 717 (0.3%) | 0.80 (0.65 to 0.99) | 0.82 (0.66 to 1.02) |
| 365+ | 57 (0.1%) | 311 (0.1%) | 1.09 (0.82 to 1.46) | 1.12 (0.84 to 1.49) |
| Parkinsonian |  |  |  |  |
| 0 | 40,500 (99.3%) | 282,982 (99.7%) | 1 | 1 |
| >0-13 | 30 (0.1%) | 125 (0.0%) | 1.29 (0.95 to 1.74) | 1.19 (0.88 to 1.61) |
| 14-89 | 60 (0.1%) | 207 (0.1%) | 1.40 (0.94 to 2.07) | 1.27 (0.86 to 1.89) |
| 90-364 | 65 (0.2%) | 220 (0.1%) | 1.44 (1.08 to 1.92) | 1.27 (0.95 to 1.70) |
| 365-1459 | 88 (0.2%) | 301 (0.1%) | 1.56\* (1.22 to 2.01) | 1.35 (1.05 to 1.74) |
| 1460+ | 27 (0.1%) | 98 (0.0%) | 1.61 (1.04 to 2.50) | 1.39 (0.89 to 2.18) |
| Respiratory |  |  |  |  |
| 0 | 36,768 (90.2%) | 258,738 (91.1%) | 1 | 1 |
| >0-13 | 1,997 (4.9%) | 12,966 (4.6%) | 1.02 (0.97 to 1.08) | 1.02 (0.97 to 1.07) |
| 14-89 | 1,511 (3.7%) | 9,321 (3.3%) | 1.05 (1.00 to 1.12) | 1.05 (0.99 to 1.11) |
| 90-364 | 293 (0.7%) | 1,809 (0.6%) | 1.02 (0.90 to 1.15) | 1.01 (0.89 to 1.15) |
| 365-1459 | 169 (0.4%) | 893 (0.3%) | 1.18 (1.00 to 1.40) | 1.18 (1.00 to 1.40) |
| 1460+ | 32 (0.1%) | 206 (0.1%) | 1.01 (0.69 to 1.47) | 1.01 (0.70 to 1.48) |
| Urological |  |  |  |  |
| 0 | 37,509 (92.0%) | 267,060 (94.1%) | 1 | 1 |
| >0-13 | 295 (0.7%) | 1,810 (0.6%) | 1.06 (0.94 to 1.20) | 1.02 (0.90 to 1.15) |
| 14-89 | 1,167 (2.9%) | 6,514 (2.3%) | 1.15\* (1.08 to 1.23) | 1.10\* (1.03 to 1.17) |
| 90-364 | 773 (1.9%) | 3,891 (1.4%) | 1.27\* (1.18 to 1.38) | 1.21\* (1.12 to 1.31) |
| 365-1459 | 800 (2.0%) | 3,550 (1.3%) | 1.41\* (1.30 to 1.53) | 1.35\* (1.24 to 1.46) |
| 1460+ | 226 (0.6%) | 1,108 (0.4%) | 1.28\* (1.11 to 1.48) | 1.24\* (1.07 to 1.44) |
| Other |  |  |  |  |
| 0 | 40,483 (99.3%) | 282,179 (99.4%) | 1 | 1 |
| >0-13 | 83 (0.2%) | 488 (0.2%) | 1.06 (0.84 to 1.35) | 1.04 (0.82 to 1.32) |
| 14-89 | 165 (0.4%) | 1,109 (0.4%) | 0.89 (0.75 to 1.05) | 0.89 (0.76 to 1.06) |
| 90-364 | 36 (0.1%) | 144 (0.1%) | 1.52 (1.05 to 2.20) | 1.55 (1.07 to 2.24) |

DEP, drug exposure period; DDD, defined daily dose; OR, odds ratio, aOR, adjusted odds ratio; CI confidence interval; ACB Anticholinergic cognitive burden

\* p<0.01

eTable 3. Adjusted odds ratios of dementia by any new prescription of a probably or potently anticholinergic medication and by drug class

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Cases (n=35,555) | Controls (n=221,772) | Measured at start of DEP | Measured at end of DEP |
| Any use during DEP | n (%) | n (%) | aOR (95% CI) | aOR (95% CI) |
| Any use by ACB score |  |  |  |  |
| No prescription | 3,791 (10.7%) | 28,866 (13.0%) | 1 | 1 |
| Any ACB 1 | 31,463 (88.5%) | 191,183 (86.2%) | 1.12\* (1.08 to 1.16) | 1.11\* (1.07 to 1.16) |
| New ACB 2 | 912 (2.6%) | 4,594 (2.1%) | 1.11\* (1.03 to 1.20) | 1.12\* (1.04 to 1.21) |
| New ACB 3 | 10,163 (28.6%) | 55,534 (25.0%) | 1.13\* (1.09 to 1.16) | 1.07\* (1.04 to 1.10) |
| Any use by ACB score and class |  |  |  |  |
| No prescription | 3,791 (10.7%) | 28,866 (13.0%) | 1 | 1 |
| Any ACB1 |  |  |  |  |
| Analgesic | 20,056 (56.4%) | 119,509 (53.9%) | 1.02 (1.00 to 1.05) | 1.02 (0.99 to 1.05) |
| Antidepressant | 4,468 (12.6%) | 19,010 (8.6%) | 1.39\* (1.34 to 1.45) | 1.26\* (1.20 to 1.32) |
| Antipsychotic | 6,534 (18.4%) | 36,702 (16.5%) | 1.05\* (1.02 to 1.09) | 1.04 (1.01 to 1.07) |
| Cardiovascular | 24,092 (67.8%) | 148,297 (66.9%) | 0.97 (0.94 to 1.00) | 0.98 (0.95 to 1.02) |
| Gastro-intestinal | 8,870 (24.9%) | 53,297 (24.0%) | 0.96\* (0.93 to 0.99) | 0.95\* (0.93 to 0.98) |
| Respiratory | 7,853 (22.1%) | 47,517 (21.4%) | 0.99 (0.96 to 1.02) | 0.95\* (0.92 to 0.98) |
| Other | 9,470 (26.6%) | 57,341 (25.9%) | 0.95\* (0.92 to 0.98) | 0.99 (0.96 to 1.02) |
| New ACB2 |  |  |  |  |
| Analgesic | 286 (0.8%) | 1,510 (0.7%) | 1.08 (0.95 to 1.23) | 1.09 (0.96 to 1.24) |
| Antipsychotic | 6 (0.0%) | 12 (0.0%) | NA | NA |
| Parkinsonian | 39 (0.1%) | 83 (0.0%) | 1.55 (1.04 to 2.30) | 1.32 (0.88 to 1.96) |
| Respiratory | 13 (0.0%) | 77 (0.0%) | 0.89 (0.49 to 1.61) | 0.85 (0.47 to 1.54) |
| Other | 591 (1.7%) | 3,019 (1.4%) | 1.07 (0.98 to 1.18) | 1.10 (1.00 to 1.21) |
| New ACB3 |  |  |  |  |
| Antidepressant | 5,708 (16.1%) | 30,035 (13.5%) | 1.10\* (1.06 to 1.14) | 1.08\* (1.04 to 1.11) |
| Antipsychotic | 503 (1.4%) | 2,230 (1.0%) | 1.14 (1.03 to 1.27) | 1.12 (1.01 to 1.25) |
| Gastro-intestinal | 1,296 (3.6%) | 7,854 (3.5%) | 0.93 (0.88 to 0.99) | 0.93 (0.87 to 0.99) |
| Parkinsonian | 91 (0.3%) | 283 (0.1%) | 1.32 (1.03 to 1.69) | 1.16 (0.90 to 1.49) |
| Respiratory | 3,114 (8.8%) | 17,752 (8.0%) | 1.04 (1.00 to 1.09) | 1.04 (0.99 to 1.08) |
| Urological | 2,239 (6.3%) | 10,630 (4.8%) | 1.22\* (1.16 to 1.28) | 1.17\* (1.11 to 1.23) |
| Other | 220 (0.6%) | 1,169 (0.5%) | 1.03 (0.89 to 1.19) | 1.03 (0.89 to 1.20) |

DEP, drug exposure period; aOR, adjusted odds ratio; CI confidence interval; ACB Anticholinergic cognitive burden

\* p<0.01

eTable 4. Adjusted odds ratios of dementia by prescription of an anticholinergic medication as measured by the Anticholinergic Drug Scale and by drug class

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Cases (n=40,770) | Controls (n=283,933) | Measured at start of DEP | Measured at end of DEP |
| Drug class | n (%) | n (%) | aOR (95% CI) | aOR (95% CI) |
| Any use by ADS score |  |  |  |  |
| No prescription | 14,585 (35.8%) | 114,814 (40.4%) | 1 | 1 |
| ADS1 | 21,074 (51.7%) | 135,248 (47.6%) | 1.07\* (1.04 to 1.09) | 1.03 (1.01 to 1.06) |
| ADS2 | 7,038 (17.3%) | 45,301 (16.0%) | 0.98 (0.95 to 1.01) | 0.96 (0.93 to 0.99) |
| ADS3 | 13,203 (32.4%) | 79,114 (27.9%) | 1.13\* (1.10 to 1.16) | 1.08\* (1.06 to 1.11) |
| Any use by ADS score and class |  |  |  |  |
| No prescription | 14,585 (35.8%) | 114,814 (40.4%) | 1 | 1 |
| ADS1 |  |  |  |  |
| Analgesic | 5,275 (12.9%) | 33,364 (11.8%) | 0.96 (0.93 to 1.00) | 0.97 (0.93 to 0.00) |
| Antidepressant | 6,061 (14.9%) | 29,393 (10.4%) | 1.34\* (1.30 to 1.39) | 1.22\* (1.18 to 1.27) |
| Antipsychotic | 7,602 (18.6%) | 47,934 (16.9%) | 1.03 (1.00 to 1.06) | 1.02 (0.99 to 1.05) |
| Cardiovascular | 4,320 (10.6%) | 27,358 (9.6%) | 1.02 (0.98 to 1.06) | 1.02 (0.98 to 1.06) |
| Gastro-intestinal | 832 (2.0%) | 5,513 (1.9%) | 0.96 (0.89 to 1.04) | 0.96 (0.89 to 1.04) |
| Respiratory | 3,206 (7.9%) | 21,246 (7.5%) | 1.01 (0.97 to 1.05) | 1.00 (0.96 to 1.04) |
| Other  | 7,240 (17.8%) | 49,734 (17.5%) | 0.94\* (0.91 to 0.97) | 0.94\* (0.92 to 0.97) |
| ADS2 |  |  |  |  |
| Antipsychotic | 367 (0.9%) | 1,707 (0.6%) | 1.12 (1.00 to 1.26) | 1.10 (0.97 to 1.24) |
| Gastro-intestinal | 5,820 (14.3%) | 39,251 (13.8%) | 0.94\* (0.91 to 0.97) | 0.93\* (0.90 to 0.96) |
| Other  | 1,314 (3.2%) | 6,688 (2.4%) | 1.10\* (1.04 to 1.18) | 1.07 (1.00 to 1.14) |
| ADS3 |  |  |  |  |
| Antidepressant | 7,778 (19.1%) | 45,295 (16.0%) | 1.10\* (1.07 to 1.14) | 1.09\* (1.06 to 1.12) |
| Antipsychotic | 649 (1.6%) | 3,247 (1.1%) | 1.02 (0.93 to 1.12) | 1.01 (0.92 to 1.10) |
| Gastro-intestinal | 921 (2.3%) | 6,176 (2.2%) | 0.90\* (0.84 to 0.97) | 0.91 (0.85 to 0.98) |
| Parkinsonian | 270 (0.7%) | 951 (0.3%) | 1.48\* (1.28 to 1.72) | 1.28\* (1.10 to 1.49) |
| Respiratory  | 4,281 (10.5%) | 26,921 (9.5%) | 1.02 (0.98 to 1.06) | 1.01 (0.98 to 1.05) |
| Urological | 3,236 (7.9%) | 16,750 (5.9%) | 1.24\* (1.19 to 1.29) | 1.17\* (1.12 to 1.23) |

DEP, drug exposure period; OR, odds ratio, aOR, adjusted odds ratio; CI confidence interval; ADS Anticholinergic drug scale

\* p<0.01

etable 5a. Adjusted odds ratios of dementia by prescription of a potent anticholinergic by drug class, by adjustment for BMI, smoking and alcohol abuse and by patients with complete data. Adjustments made for covariates as measured at the start of the drug exposure period.

|  |  |
| --- | --- |
|  | Adjusted for covariates measured at the start of the drug exposure period |
|  | All patients (40,770 cases, 283,933 controls) | Patients without missing data at start of DEP (15,214 cases, 48,486 controls) |
| ACB score and drug class | Fully adjusted model | Unadjusted for alcohol abuse, smoking, BMI | Fully adjusted model | Unadjusted for alcohol abuse, smoking, BMI |
| aOR (95% CI) | aOR (95% CI) | aOR (95% CI) | aOR (95% CI) |
| **Any use by ACB score**  |  |  |  |  |
| No prescriptions | 1 | 1 | 1 | 1 |
| ACB 1 prescription | 1.11\* (1.07 to 1.15) | 1.11\* (1.07 to 1.15) | 1.08 (1.01 to 1.16) | 1.07 (1.00 to 1.15) |
| ACB 2 prescription | 1.10\* (1.03 to 1.17) | 1.10\* (1.03 to 1.16) | 1.13 (1.01 to 1.26) | 1.13 (1.01 to 1.26) |
| ACB 3 prescription | 1.16\* (1.13 to 1.19) | 1.16\* (1.13 to 1.19) | 1.16\* (1.11 to 1.21) | 1.16\* (1.11 to 1.21) |
|  |  |  |  |  |
| No prescription | 1 | 1 | 1 | 1 |
| ACB1 |  |  |  |  |
| Analgesic | 1.02 (1.00 to 1.05) | 1.02 (0.99 to 1.04) | 1.02 (0.97 to 1.06) | 1.01 (0.96 to 1.05) |
| Antidepressant | 1.37\* (1.32 to 1.42) | 1.37\* (1.32 to 1.42) | 1.43\* (1.34 to 1.52) | 1.42\* (1.34 to 1.51) |
| Antipsychotic | 1.05\* (1.02 to 1.08) | 1.05\* (1.02 to 1.08) | 1.08\* (1.02 to 1.14) | 1.08\* (1.02 to 1.13) |
| Cardiovascular | 0.97 (0.94 to 0.99) | 0.96 (0.94 to 0.99) | 0.94 (0.90 to 0.99) | 0.93\* (0.88 to 0.97) |
| Gastro-intestinal | 0.97 (0.94 to 0.99) | 0.97 (0.94 to 0.99) | 0.98 (0.94 to 1.03) | 0.98 (0.94 to 1.03) |
| Respiratory | 0.99 (0.97 to 1.02) | 1.00 (0.97 to 1.02) | 0.97 (0.93 to 1.02) | 0.98 (0.93 to 1.03) |
| Other | 0.95\* (0.92 to 0.97) | 0.95\* (0.92 to 0.97) | 0.94 (0.90 to 0.99) | 0.94 (0.90 to 0.99) |
| ACB2 |  |  |  |  |
| Analgesic | 1.03 (0.92 to 1.15) | 1.03 (0.92 to 1.15) | 1.02 (0.82 to 1.26) | 1.01 (0.82 to 1.25) |
| Antipsychotic | 1.44 (0.87 to 2.36) | 1.43 (0.87 to 2.35) | 1.13 (0.40 to 3.17) | 1.12 (0.40 to 3.15) |
| Parkinsonian | 1.55\* (1.12 to 2.14) | 1.56\* (1.13 to 2.15) | 1.23 (0.68 to 2.25) | 1.26 (0.69 to 2.29) |
| Respiratory | 0.89 (0.55 to 1.45) | 0.90 (0.55 to 1.46) | 0.74 (0.30 to 1.82) | 0.76 (0.31 to 1.86) |
| Other | 1.07 (1.00 to 1.15) | 1.07 (1.00 to 1.15) | 1.13 (0.99 to 1.28) | 1.13 (0.99 to 1.28) |
| ACB3 |  |  |  |  |
| Antidepressant | 1.13\* (1.10 to 1.16) | 1.13\* (1.10 to 1.16) | 1.18\* (1.12 to 1.24) | 1.18\* (1.12 to 1.24) |
| Antipsychotic | 1.09 (1.02 to 1.18) | 1.09 (1.02 to 1.18) | 1.01 (0.88 to 1.17) | 1.01 (0.88 to 1.17) |
| Gastro-intestinal | 0.94 (0.89 to 0.99) | 0.94 (0.89 to 0.99) | 0.94 (0.86 to 1.03) | 0.94 (0.86 to 1.04) |
| Parkinsonian | 1.45\* (1.25 to 1.68) | 1.44\* (1.24 to 1.68) | 1.47\* (1.10 to 1.97) | 1.46\* (1.09 to 1.95) |
| Respiratory | 1.04 (1.00 to 1.08) | 1.04 (1.00 to 1.08) | 1.03 (0.97 to 1.11) | 1.03 (0.96 to 1.10) |
| Urological | 1.23\* (1.18 to 1.28) | 1.23\* (1.18 to 1.28) | 1.26\* (1.17 to 1.36) | 1.26\* (1.17 to 1.35) |
| Other | 0.99 (0.87 to 1.13) | 0.99 (0.87 to 1.12) | 0.96 (0.77 to 1.19) | 0.96 (0.77 to 1.19) |

DEP, drug exposure period; OR, odds ratio, aOR, adjusted odds ratio; CI, confidence interval; ACB, Anticholinergic Cognitive Burden score; BMI, body mass index

\* p<0.01

etable 5b. Adjusted odds ratios of dementia by prescription of a potent anticholinergic by drug class, by adjustment for BMI, smoking and alcohol abuse and by patients with complete data. Adjustments made for covariates as measured at the end of the drug exposure period.

|  |  |
| --- | --- |
|  | Adjusted for covariates measured at the start of the drug exposure period |
|  | All patients (40,770 cases, 283,933 controls) | Patients without missing data at start of DEP (15,214 cases, 48,486 controls) |
| ACB score and drug class | Fully adjusted model | Unadjusted for alcohol abuse, smoking, BMI | Fully adjusted model | Unadjusted for alcohol abuse, smoking, BMI |
| aOR (95% CI) | aOR (95% CI) | aOR (95% CI) | aOR (95% CI) |
| **Any use by ACB score**  |  |  |  |  |
| No prescriptions | 1 | 1 | 1 | 1 |
| ACB 1 prescription | 1.10\* (1.06 to 1.15) | 1.12\* (1.07 to 1.16) | 1.07 (1.01 to 1.13) | 1.05 (1.00 to 1.11) |
| ACB 2 prescription | 1.10\* (1.03 to 1.16) | 1.09\* (1.02 to 1.16) | 1.09 (1.01 to 1.18) | 1.09 (1.01 to 1.17) |
| ACB 3 prescription | 1.11\* (1.08 to 1.14) | 1.10\* (1.08 to 1.13) | 1.09\* (1.06 to 1.13) | 1.09\* (1.05 to 1.12) |
| **Any use by ACB score and class** |  |  |  |  |
| No prescription | 1 | 1 | 1 | 1 |
| ACB1 |  |  |  |  |
| Analgesic | 1.02 (0.99 to 1.04) | 1.00 (0.98 to 1.03) | 1.01 (0.98 to 1.04) | 0.99 (0.96 to 1.02) |
| Antidepressant | 1.25\* (1.20 to 1.30) | 1.25\* (1.20 to 1.30) | 1.22\* (1.16 to 1.28) | 1.22\* (1.16 to 1.28) |
| Antipsychotic | 1.04 (1.01 to 1.07) | 1.04 (1.01 to 1.07) | 1.05\* (1.02 to 1.09) | 1.05\* (1.02 to 1.09) |
| Cardiovascular | 0.98 (0.95 to 1.01) | 0.97 (0.94 to 1.00) | 0.97 (0.93 to 1.01) | 0.94 (0.91 to 0.98) |
| Gastro-intestinal | 0.96\* (0.93 to 0.99) | 0.96 (0.94 to 0.99) | 0.97 (0.94 to 1.01) | 0.97 (0.94 to 1.01) |
| Respiratory | 0.99 (0.97 to 1.02) | 1.00 (0.97 to 1.02) | 1.00 (0.97 to 1.04) | 1.00 (0.97 to 1.04) |
| Other | 0.95\* (0.92 to 0.98) | 0.95\* (0.92 to 0.97) | 0.95\* (0.91 to 0.98) | 0.94\* (0.91 to 0.98) |
| ACB2 |  |  |  |  |
| Analgesic | 1.03 (0.92 to 1.16) | 1.02 (0.91 to 1.14) | 1.04 (0.91 to 1.19) | 1.02 (0.89 to 1.17) |
| Antipsychotic | 1.35 (0.82 to 2.23) | 1.32 (0.80 to 2.18) | 1.65 (0.84 to 3.27) | 1.58 (0.80 to 3.12) |
| Parkinsonian | 1.32 (0.96 to 1.82) | 1.37 (1.00 to 1.89) | 1.40 (0.93 to 2.10) | 1.47 (0.97 to 2.21) |
| Respiratory | 0.83 (0.51 to 1.36) | 0.88 (0.54 to 1.44) | 0.75 (0.42 to 1.33) | 0.82 (0.46 to 1.45) |
| Other | 1.09 (1.01 to 1.17) | 1.09 (1.01 to 1.17) | 1.07 (0.98 to 1.18) | 1.07 (0.97 to 1.17) |
| ACB3 |  |  |  |  |
| Antidepressant | 1.11\* (1.08 to 1.14) | 1.11\* (1.07 to 1.14) | 1.11\* (1.07 to 1.16) | 1.11\* (1.07 to 1.15) |
| Antipsychotic | 1.07 (1.00 to 1.16) | 1.07 (0.99 to 1.15) | 1.01 (0.91 to 1.11) | 1.00 (0.91 to 1.10) |
| Gastro-intestinal | 0.94 (0.89 to 0.99) | 0.94 (0.89 to 0.99) | 0.95 (0.89 to 1.01) | 0.95 (0.89 to 1.02) |
| Parkinsonian | 1.29\* (1.11 to 1.50) | 1.29\* (1.11 to 1.50) | 1.31\* (1.07 to 1.59) | 1.31\* (1.08 to 1.59) |
| Respiratory | 1.03 (1.00 to 1.07) | 1.03 (0.99 to 1.07) | 1.04 (0.99 to 1.08) | 1.03 (0.99 to 1.08) |
| Urological | 1.18\* (1.13 to 1.23) | 1.17\* (1.12 to 1.22) | 1.16\* (1.10 to 1.22) | 1.16\* (1.09 to 1.22) |
| Other | 0.99 (0.87 to 1.13) | 0.98 (0.86 to 1.12) | 1.01 (0.87 to 1.17) | 1.00 (0.86 to 1.16) |

DEP, drug exposure period; OR, odds ratio, aOR, adjusted odds ratio; CI, confidence interval; ACB, Anticholinergic Cognitive Burden score; BMI, body mass index

\* p<0.01

**Appendix 4. Extended analysis of the association between antidepressants, depression and dementia**

**Aim**

To further document the association between antidepressants, depression and dementia shown in tables 3 and 4, in particular to test the possibility that the apparent link between dementia and anti-depressant use is induced by residual confounding by depression.

**Method**

Depression was recoded into a five-level variable corresponding to the maximum recorded depression severity in a participants’ available history up to the end of the drug exposure period as “No record”, “Depressive symptoms”, “Mild Depression”, “Moderate Depression” and “Severe Depression”.

The relationship between depression and anticholinergic antidepressant use during the DEP was tabulated. Several conditional logistic regression models were then estimated with incident dementia as the outcome variable and the following predictors:

1. Depression only
2. Depression and all other covariates.
3. All anti-depressants only
4. Depression and all anti-depressants.
5. Depression, all anti-depressants, and all other covariates

Anti-depressants are coded in categories corresponding to levels of exposure during the DEP. ACB1 and ACB3 are coded by DDDs, ACB0 antidepressants are coded by number of prescriptions.

Finally, models were estimated including the main effects of antidepressants, depression and all covariates as well as the interaction between antidepressants and depression. The effect of ACB3 antidepressants was derived at each level of depression by combining the relevant main effect and interaction term and was tabulated.

This analysis was then repeated restricted to the exposures 15-20 years before index date and confounders measured up to 15 years before index date. Here the antidepressant variables are coded as binary (present or absent).

**Results**

There is a strong relationship between ACB3 antidepressants and recorded depression. 11% of the population with no depression have been prescribed an ACB3 antidepressant compared to 61% of those with a record of severe depression (table e6).

In univariable analysis depression is associated with dementia incidence, with that association attenuated by 50% after adjusting for covariates (not including the use of antidepressants). Each antidepressant class is associated with dementia with this association not being substantially affected by including covariates. When depression and antidepressants are both included in the model, there is no longer an independent effect of depression, but the effect of antidepressants remains essentially unaffected. Each antidepressant group (ACB0, ACB1 and ACB3) is independently associated with dementia incidence (table e7). This pattern is repeated when exposures and covariates are only measured up to 15 years before index date, except here only ACB3 antidepressants are independently associated with dementia, while ACB0 and ACB1 antidepressants are not (table e8).

The association between ACB3 antidepressants and dementia incidence is not systematically affected by recorded depression severity (table e9).

|  |  |
| --- | --- |
|  | Maximum recorded depression N(%) |
|  | No record | Symptoms only | Mild | Moderate | Severe | All |
| Total | 259,406 (100%) | 13,003 (100%) | 17,181 (100%) | 30,253 (100%) | 4,860 (100%) | 324,703 (100%) |
| ACB3 Anticholinergics (DDD) |  |  |  |  |  |  |
|  0 | 229,617 (89%) | 8,566 (66%) | 10,169 (59%) | 14,829 (49%) | 1,882 (39%) | 265,063 (82%) |
|  1-29 | 16,270 (6%) | 1,885 (15%) | 2,249 (13%) | 3,746 (12%) | 474 (10%) | 24,624 (8%) |
|  30-89 | 4,861 (2%) | 912 (7%) | 1,360 (8%) | 2,898 (10%) | 450 (9%) | 10,481 (3%) |
|  90-364 | 4,854 (2%) | 841 (6%) | 1,469 (9%) | 3,612 (12%) | 681 (14%) | 11,457 (4%) |
|  365-1459 | 3,072 (1%) | 619 (5%) | 1,373 (8%) | 3,369 (11%) | 797 (16%) | 9,230 (3%) |
|  1460+ | 732 (0%) | 180 (1%) | 561 (3%) | 1,799 (6%) | 576 (12%) | 3,848 (1%) |

Table e6. Relationship between maximum recorded depression severity and DDDs of ACB3 antidepressants during the DEP.

|  |  |
| --- | --- |
|  | Terms included in model |
|  | Depression only | Depression + covariates | Antidepressants only | Depression + Antidepressants | Full model |
|  | aOR (se) | aOR (se) | aOR (se) | aOR (se) | aOR (se) |
| Depression severity |  |  |  |  |  |
|  None | 1 | 1 |  | 1 | 1 |
|  Symptoms | 1.26\* (0.03) | 1.15\* (0.03) |   | 1.11\* (0.03) | 1.06 (0.03) |
|  Mild | 1.34\* (0.03) | 1.20\* (0.03) |   | 1.12\* (0.03) | 1.08\* (0.03) |
|  Moderate | 1.35\* (0.02) | 1.18\* (0.02) |   | 1.09\* (0.02) | 1.03 (0.02) |
|  Severe | 1.48\* (0.06) | 1.24\* (0.05) |   | 1.09 (0.05) | 1.02 (0.04) |
| ACB3 antidepressants (DDD) |  |  |  |  |  |
|  0 |  |  | 1 | 1 | 1 |
|  1-29 |   |   | 1.12\* (0.02) | 1.11\* (0.02) | 1.07\* (0.02) |
|  30-89 |   |   | 1.12\* (0.03) | 1.09\* (0.03) | 1.06 (0.03) |
|  90-364 |   |   | 1.21\* (0.03) | 1.18\* (0.03) | 1.15\* (0.03) |
|  365-1459 |   |   | 1.29\* (0.04) | 1.25\* (0.04) | 1.21\* (0.04) |
|  1460+ |   |   | 1.37\* (0.06) | 1.31\* (0.06) | 1.28\* (0.06) |
| ACB0 antidepressants (number of prescriptions) |  |  |  |  |  |
|  0 |  |  | 1 | 1 | 1 |
|  1 |   |   | 1.03 (0.06) | 1.01 (0.06) | 0.98 (0.06) |
|  2 |   |   | 1.19\* (0.06) | 1.17\* (0.06) | 1.13 (0.06) |
|  3-10 |   |   | 1.26\* (0.08) | 1.22\* (0.08) | 1.18\* (0.07) |
|  10-50 |   |   | 1.36\* (0.16) | 1.31 (0.15) | 1.26 (0.15) |
| ACB1 antidepressants (DDD) |  |  |  |  |  |
|  0 |  |  | 1 | 1 | 1 |
|  1-29 |   |   | 1.11 (0.11) | 1.07 (0.11) | 1.01 (0.10) |
|  30-89 |   |   | 1.33\* (0.03) | 1.27\* (0.03) | 1.23\* (0.03) |
|  90-364 |   |   | 1.42\* (0.04) | 1.35\* (0.04) | 1.28\* (0.04) |
|  365-1459 |   |   | 1.55\* (0.05) | 1.47\* (0.05) | 1.39\* (0.04) |
|  1460+ |   |   | 1.62\* (0.07) | 1.54\* (0.07) | 1.49\* (0.07) |

DDD – defined daily dose; aOR – adjusted odds ratio; se – standard error; \* p<0.01

Table e7. Association between DDDs/number of prescriptions of antidepressant use and maximum recorded depression before index date and dementia incidence estimated in different conditional logistic regression models.

|  |  |  |
| --- | --- | --- |
|  |  | Terms included in model |
|  |  | Depression only | Depression and covariates | Antidepr. only | Antidepr. and covariates | Full model |
|   |   | aOR (se) | aOR (se) | aOR (se) | aOR (se) | aOR (se) |
| Depression severity |  |  |  |  |  |  |
|  | Symptoms | 1.19 (0.14) | 1.09 (0.13) |  |  | 1.08 (0.13) |
|  | Mild | 1.12 (0.07) | 1.05 (0.07) |  |  | 1.01 (0.07) |
|  | Moderate | 1.19\* (0.04) | 1.10\* (0.04) |  |  | 1.03 (0.04) |
|  | Severe | 1.35\* (0.15) | 1.23 (0.14) |  |  | 1.13 (0.13) |
| Use of any antidepressant |  |  |  |  |  |  |
|  | ACB3 antidepressants |  |  | 1.29\* (0.05) | 1.21\* (0.05) | 1.19\* (0.05) |
|  | ACB1 antidepressants |  |  | 1.15 (0.08) | 1.08 (0.08) | 1.07 (0.08) |
|   | ACB0 antidepressants |   |   | 1.04 (0.11) | 0.93 (0.10) | 0.92 (0.10) |

DDD – defined daily dose; aOR – adjusted odds ratio; se – standard error; \* p<0.01

Table e8. Association between antidepressants and maximum recorded depression severity 15-20 years before index date and dementia incidence estimated using different conditional logistic regression models.

|  |  |  |
| --- | --- | --- |
|  | Complete data | Exposures 15-20 years before index date |
|  | aOR (95% CI) | aOR (95% CI) |
| Overall | 1.11 (1.08-1.14) | 1.19 (1.10-1.30) |
| Depression |  |  |
| None | 1.13 (1.09-1.18) | 1.23 (1.10-1.37) |
| Symptoms | 0.92 (0.83-1.03) | 1.23 (0.67-2.27) |
| Mild | 1.10 (1.01-1.20) | 0.99 (0.75-1.30) |
| Moderate | 1.11 (1.04-1.19) | 1.15 (1.01-1.31) |
| Severe | 1.11 (0.95-1.31) | 1.50 (0.96-2.36) |

aOR – adjusted odds ratio; se – standard error

Table e9. Effect of ACB3 Antidepressants on dementia incidence by highest level of recorded depressive disorder, estimated using an interaction term between depression and ACB3 antidepressant use, both for the complete data and restricted to exposures occurring 15-20 years before index date.