



**Trends in the prevalence of antipsychotic drug use among patients with Alzheimer's disease treated with antidementia drugs in the community in the UK: a cohort study**

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**Abstract**

**OBJECTIVE:**

To investigate the pattern and trends of use of psychotropic drugs in dementia including subjects taking antidementia medication.

**DESIGN:**

Cohort study with incident dementia patients formed in the United Kingdom Clinical Practice Research Datalink.

**PARTICIPANTS:**

Patients with incident dementia, between 1995 and 2011 and a reference non-dementia cohort matched on age, gender and date of dementia diagnosis. Two subcohorts included new users of acetylcholinesterase inhibitors (AChEIs) and memantine.

The study endpoint was use of psychotropic medications (antipsychotics, antidepressants, hypnotics and anxiolytics) up to 10 years before and 4 years after dementia diagnosis, and for up to 5 years before and one year after first use of AChEI or memantine.

**RESULTS:**

50,349 patients with incident dementia diagnosis and 50,349 matched controls, 10794 first-time users of AChEI and 669 of memantine. The mean prevalence of antipsychotic use from 1995-2011 on diagnosis of dementia was 12.5%, decreasing from 19.9% in 1995 to 7.4% in 2011. There was an increase in antidepressant use (10.7% to 26.3%) and a small increase in anxiolytic use. The matched cohort showed a lower use of antipsychotics and anxiolytics but a rise in antidepressant use (5.9% to 13.4%). Both groups showed a decrease in hypnotic use. 10.6% of AChEI and 26.3% of memantine users were prescribed antipsychotics, 34.1% and 26.3% antidepressants, 13.2% and 4.1% anxiolytics and 18.4% and 8.3% hypnotics. The slopes for monthly use of antipsychotics were positive in the year leading up to AChEI and memantine use; after treatment initiation the slope for AChEI users continued to increase but at a reduced rate whereas antipsychotic use declined for memantine users.

**CONCLUSIONS:**

The marked reduction in antipsychotic use in dementia is to be welcomed whilst there was a steady increase in antidepressant use. There was a decline in antipsychotic use after initiation of memantine.

## Article summary

### Article focus

- Antipsychotic medications (APs) have frequently been prescribed as the first-line pharmacological treatment approach for neuropsychiatric symptoms in Alzheimer's disease and other dementias (AD) but their use has been associated with several risk concerns
- To describe the pattern and trends of use of AP, antidepressants, hypnotics and anxiolytics in AD and in patients treated with antidementia medications, i.e. acetylcholinesterase inhibitors (AChEIs) and memantine in primary care in the UK.

### Key messages

- The mean prevalence of AP use on the first recording of a dementia was 12.5%, decreasing markedly from 19.9% in 1995 to 7.4% in 2011. In contrast, there was a steady increase in the use of antidepressants (10.7% to 26.3%) and a small increase in the use of anxiolytics.
- AP use in patients with a first dementia diagnosis between 2005 and 2011 increased from 2.2% 10 years prior to the dementia diagnosis to 5.1% one year preceding the dementia diagnosis and 11.1% at the time of entering the dementia diagnosis on the Clinical Practice Research Datalink (CPRD).
- The monthly use of AP increased in the year leading up to the first AChEI or memantine use; after treatment initiation the monthly use for those prescribed AChEIs continued to increase but at a reduced rate whereas antipsychotic use declined for those prescribed memantine.

### Strengths and limitations of this study

- The Clinical Practice Research Datalink (CPRD) is the largest primary care database in the world, containing the longitudinal records for up to 20 years of over 3 million patients
- There may have been a trend towards diagnosing AD at an earlier stage of the AD because of the increasing awareness despite the fact that the mean age at the time of the first AD diagnosis was stable over the entire study period.

- APs and antidementia drugs prescribed exclusively by hospital specialists are not completely recorded in CPRD

**Introduction**

Functional deficits and neuropsychiatric/behavioural symptoms contribute significantly to the disabilities associated with Alzheimer’s disease (AD). Up to 90% of patients with AD will experience neuropsychiatric symptoms such as hallucinations, delusions, aggressive behaviour, agitation, and affective disturbances during the course of their disease. [1,2] These symptoms can be amongst the most distressing aspects of AD, increasing caregiver burden, contributing to poor patient quality of life, and often triggering the transfer to institutional care. [1,3,4] In a survey of carers by Alzheimer Europe, behavioural symptoms including agitation, aggression, and irritability were cited more often than cognitive symptoms as the most problematic symptoms of AD (50% versus 45%). [1]

Antipsychotic medications (APs) have frequently been prescribed as the first-line pharmacological treatment approach for neuropsychiatric symptoms in AD and other dementias but their use has been associated with several serious concerns. Treatment with APs has been shown to raise the risk of adverse events including cerebrovascular events, somnolence, and extrapyramidal symptoms as well as accelerated cognitive decline. [5-7] Furthermore, APs are associated with an increased mortality risk in elderly patients with and without AD. [7-9]

Only the atypical antipsychotic risperidone has use in AD included in its licensed indications within the European Community. This licence followed a review in 2008 and is restricted to “the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate

to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others". [10] In the UK risperidone is included within the Black Triangle Scheme that identifies medicines whose safety profiles are monitored intensively; healthcare professionals are asked to report via the Yellow Card Scheme all suspected side-effects that occur in the treatment of elderly people with dementia.

The US Food and Drug Administration (FDA) has issued warnings against the use of atypical APs in patients with dementia [11] and, in 2008, the UK Department of Health commissioned an independent report on the use of antipsychotic medication in people with dementia. [12] This report concluded that APs appear to have only a limited positive effect but can cause significant harm to people with dementia – including an additional 1,800 deaths and 1,620 cerebrovascular adverse events in the UK per year. [12] Although APs may offer benefit to some patients, the report generally recommended “reducing the use of antipsychotic drugs for people with dementia.” [12] The French High Authority for Health (HAS) raised similar concerns, criticising the excessive prescribing of APs to patients with AD. [13]

There is some evidence that the currently available anti-dementia agents – memantine and the acetylcholinesterase inhibitors (AChEIs) have beneficial effects on behavioural disturbances in AD, and they are generally well tolerated [14-18] although the 12-week CALM-AD trial was unable to show that the AChEI donepezil was more effective than placebo in treating agitation in patients with AD. [19] Furthermore, a retrospective study in France has shown that there was an apparent increasing trend of AP use before the initiation of memantine therapy and that memantine stabilized the proportion of AP users. [20] In the United States, a study using national Veterans Affairs data has examined changes in atypical and conventional antipsychotic use in outpatients with dementia from 1999 through 2007. [21] Use of atypical antipsychotics began to decline significantly in 2003, and after the Food and Drug Administration advisory warning in 2005 a further significant decline was evident.

The aim of the current study was to investigate the pattern and trends of use of psychotropic drugs (i.e., antipsychotics, antidepressants, hypnotics and anxiolytics) and their association with use of AChEIs (donepezil, galantamine, or rivastigmine) and memantine to better understand their use in primary care in the UK.

**Methods**

An observational cohort study was carried out using data from the UK Clinical Practice Research Datalink (CPRD), until 1st April 2012 known as the General Practice Research Database. Participating general practitioners (GPs) currently contribute data on more than 5 million patients and are broadly representative of the UK population in terms of age, gender and region. [22] The CPRD comprises data on patient demographics, medical diagnoses, all GP prescriptions (electronic issue), referrals to secondary care, and hospital discharge reports. Prescription information includes date of prescription, drug substance, daily dose, daily quantity and number of packs/pack size. Dispensing information is not available. GP practices are required to meet defined quality standards before they can contribute to the CPRD.

**Study population and study design**

The study population consisted of patients in the CPRD at least 60 years of age and with at least three years history in the CPRD before a first diagnosis of dementia between 1 January 1995 and 30 June 2011. Dementia was defined by a Read medical code for Alzheimer’s disease, vascular dementia or other dementia. A control cohort was generated by randomly selecting for each dementia patient, one control, matched on gender and year of birth but without a recording of dementia during the entire observational period. The date of the first diagnosis of dementia was defined as the index day in the dementia cohort, and the same date

was taken as the index day for the matched control. Matched controls were also required to have a minimum of 3 years in the CPRD prior to the index day.

Two subcohorts were created by the first-time use of AChEI or memantine from 2003 to 2011 (with the index day based on first drug use rather than on first diagnosis of dementia) to assess the use of psychotropic medications in association with antidementia medication. The date of the first prescription for an AChEI or memantine was defined as the index day for the subcohort analyses. Patients with both AChEI and memantine prescriptions were not analysed further. As some patients were given antidementia medications before the first recording of a dementia diagnosis, patients on AChEI and memantine were required to have a minimum of one year in the CPRD prior to the first use of an antidementia medication.

The study endpoint was the use of psychotropic medications (APs, antidepressants, anxiolytics and hypnotics). Use of any psychotropic medication was identified from recordings by the GP.

First, the prevalence of psychotropic drug use was assessed by its exposure status on the date of the first recording of a dementia diagnosis or index day of the respective matched controls for the complete study period of 1995 to 2011.

To investigate the temporal relationship between the use of psychotropic drugs in association with the first dementia diagnosis the study cohort was restricted to those with a first dementia diagnosis between 2005 and 2011 to estimate the prevalence of psychotropic use up to 10 years before and up to 4 years after the index day.

Psychotropic use in the AChEI and memantine subcohorts was assessed for up to 5 years before and up to one year after first use of AChEI or memantine.

**Data analysis**

For each prescription of a psychotropic drug, a prescription-specific duration was calculated from the number of tablets prescribed combined with the dosing instructions and adding a grace period of 30 days. The 30-day grace period was used to allow for any residual effect of the drug or any remaining medication due to a lack of compliance. The prescription-specific duration was used to calculate the exposure prevalence of each psychotropic drug class per week of the observational period. The prevalence of AP and antidepressant use attributable to dementia was estimated by subtracting the prevalence of APs and antidepressants in the matched cohort from the respective prevalence of the dementia cohort. The weekly or monthly prevalence was described using binomial regression and the method of generalized estimating equations [23] and for the antidementia drug use shown as the slope of the fitted regression line for the year before and separately for the year after first use. All analyses were performed with STATA Intercooled Version 11.2 (StataCorp LP). The study protocol was approved by the Independent Scientific Advisory Committee for GPRD research.

**Results**

**Dementia cohort**

A total of 50,349 patients with a first-time diagnosis of dementia were identified in the CPRD between 1995 and June 2011. The mean age of dementia patients was 82.0 years with 34.6% males. There was an increasing trend over time for patients with dementia to be seen by a specialist, i.e. psychiatrists, geriatricians or neurologists, from 25.5% in 1995 to 64.7% in 2011.

At the time of the first dementia diagnosis between 1995 and 2011, 12.5% were given antipsychotics, 22.1% antidepressants, 4.5% anxiolytics and 9.8% hypnotics. The age at first



dementia diagnosis increased from 81.7 to 82.5 years and the proportion of men from 34.6% to 37.6% from 1995 to 2011, Table 1. Over the years 1995 to 2011, the prevalence of AP use on the day of the first dementia diagnosis decreased from 19.9% to 7.4%. There was a steady increase in antidepressant use (10.7% to 26.3%), a small increase in anxiolytic use (2.7% to 4.0%), and a decrease in hypnotic use (13.0% to 7.9%). The matched cohort without dementia showed a nearly constant use of antipsychotics and anxiolytics during the entire study period, a small decrease in the use of hypnotics, but also an increase in the use of antidepressants (5.9% to 13.4%), Figures 1a-b.

In patients with a first dementia diagnosis between 2005 and 2011 and with up to 10 years of medical history, antipsychotic use was 2.2% 10 years prior to the dementia diagnosis and increased linearly up until one year preceding the dementia diagnosis to 5.1%; on the date of the dementia diagnosis it was 11.1% and then it increased to 18.7% after a further 4 years. In the matched cohort and during the same period antipsychotic use was nearly constant ranging between 1.7% and 2.6%, Figure 2a. A similar pattern was observed in the use of antidepressants. For patients with a dementia diagnosis, antidepressant use increased from 7.2% 10 years before and 18.6% one year before the dementia diagnosis, to 24.7% on the date of the diagnosis, and to 31.6% four years after the dementia diagnosis, compared to 10.1%, and 11.4% for the matched cohort for the same time period, Figure 2b. Anxiolytics and hypnotic use only started to increase noticeably in the year before the dementia diagnosis, Figure 2c-d.

### **AChEI and/or memantine subcohort**

Within the dementia cohort, 10,794 patients were treated with an AChEI, 669 with memantine and 379 with both an AChEI and memantine. The mean duration of dementia at first prescription was 0.7 years in the AChEI group, 1.4 years in the memantine group and 2.6

years in the AChEI and memantine group. Age and gender were comparable in the AChEI and memantine subgroups, but patients on both AChEI and memantine were younger and more often males. Memantine users were more likely to have a record of a referral to a psychiatrist/geriatrician in the 182 days before the first prescription compared to AChEI users (67.9% vs. 60.7%). A total of 17.8% of first-time users of memantine were recorded as having been given AChEI previously, Table 1.

During the 5-year period prior to the index prescribing of memantine or AChEI each of the 4 classes of psychotropic drugs was more frequently prescribed in the memantine group compared to the AChEI group, Table 1 and Figure 3a-d. On the index day, 26.2% of memantine and 10.6% of AChEI patients were prescribed antipsychotics, 34.1% and 26.3% respectively were prescribed antidepressants, 13.2% and 4.1% anxiolytics and 18.4% and 8.3% hypnotics, Table 1.

The slope for all classes of antipsychotics and antidepressants were positive in the 12 months leading up to memantine and AChEI use but steeper in the memantine cohort, i.e. antipsychotics: memantine 0.69 versus AChEIs 0.36; antidepressants: memantine 0.56 versus AChEIs 0.47, Table 2. There was an acute increase of antipsychotic and antidepressant medication at the start of memantine and AChEI use respectively. The sharp increase was more prominent among memantine users, Figure 4a-b, suggesting that they had more behavioural issues at this point. Following use of AChEI the slopes for use of all classes of antipsychotics and antidepressants continued to increase over the next year but at a reduced rate, i.e. 0.13 for antipsychotics, 0.27 for antidepressants. In contrast, in the year following first memantine use, there was a stabilisation in antidepressant use (slope -0.02) and a declining use of both atypical and typical antipsychotic medication (slope -0.22), Table 2. However, levels of antipsychotic and antidepressant use did not return to the levels before either memantine or AChEI use, Figure 4a-b. Although the prevalence of anxiolytic and

hypnotic drug use was higher in the memantine cohort, the slopes for anxiolytics were 0.22 and -0.12 in the year before and after memantine use compared to 0.06 and 0.01 before and after AChEI use. Hypnotic use showed a similar pattern, Table 2 and Figure 4c-d. The slope for use of all psychotropic drugs showed a statistically significant change in the year before and after use of AChEI and memantine.

## Discussion

The mean prevalence of AP use over the period 1995-2011 on the day the first recording of a dementia diagnosis was noted was 12.5%, decreasing markedly from 19.9% in 1995 to 7.4% in 2011. This reduction is to be welcomed given the concerns about the over-prescription of APs and probably reflects on the increased publicity about the excessive prescribing [12] and the risks of their use versus their limited benefits.

In contrast there was a steady increase in the use of antidepressants (10.7% to 26.3%) and a small increase in the use of anxiolytics. The matched non-dementia cohort showed a lower but nearly constant use of antipsychotics and anxiolytics but also showed a rise in antidepressant use (5.9% to 13.4%). Both groups showed a decrease in the use of hypnotics.

Antipsychotic use in patients with a first dementia diagnosis between 2005 and 2011 increased from 2.2% 10 years prior to the dementia diagnosis to 5.1% one year preceding the dementia diagnosis and 11.1% at the time of entering the dementia diagnosis on the CPRD.

In the same period and compared to non-dementia there was also an excess use of antidepressants increasing from 7.2% to 18.6% among people with dementia.

Neuropsychiatric symptoms are common in dementia but increasing attention is being paid to their occurrence in the prodromal stages leading up to dementia. In a population-based study, the most common neuropsychiatric symptoms in people with Mild Cognitive Impairment

(MCI) were apathy, depression, agitation, delusions, hallucinations and sleep impairment.

[26] In MCI patients, neuropsychiatric symptoms were associated with a higher risk of dementia onset. Depression in MCI has also been reported to double the risk of dementia.

[27] The increasing prescription of psychotropic medication in the years before the diagnosis of dementia may therefore be reflecting the symptomatology that often precedes the development and diagnosis of dementia; it may also reflect a tendency to switch from prescribing an antipsychotic drug to an antidepressant.

Although still lower than might have been expected, referral to specialists was noted to increase over the period 1995 to 2011. This may partly reflect the way information is collected in the CPRD but probably mainly reflects the lack of licensed drug treatments in 1995 (donepezil being the first to become available in 1997) and the large increase since then in the number of memory clinics and old age psychiatrists. Memantine users were more likely to have a record of referral to a psychiatrist or geriatrician in the 182 days before the first prescription than AChEI users. The NICE guidance on the use of these drugs in the treatment of AD, first issued in 2001, has always recommended that treatment should be initiated by a specialist and prescribing taken over by general practitioners as part of a shared care protocol. [25]. It is likely therefore that drug treatment may have been initiated a few months before the first date that it was noted on the GPRD when the initial prescription has been provided by the specialist. Some GPs may have initiated treatment but it is less likely that they would have initiated treatment with memantine during this time given the initial recommendation of NICE in 2006 about the compound. Practice also varies across the UK such that in some areas GPs are advised that they should not prescribe these compounds at all, in which case prescribing remains with the specialist and would not be noted on the CPRD.

For the subcohorts treated with antidementia drugs, there were far greater numbers who received an AChEI in comparison with either memantine alone or in combination with an

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3 AChEI, reflecting the somewhat restricted use of memantine during this time as a result of  
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5 not being recommended by NICE in 2006 (subsequently altered in the revised guidance of  
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7 2011), [25]. The mean duration of dementia at first prescription was less for an AChEI (0.7  
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9 years) than either memantine (1.4 years) or the combination of an AChEI with memantine  
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11 (2.6 years). The AChEIs are usually the first drugs to be used and are approved for use in  
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13 mild to moderate AD whereas memantine is approved for moderate to severe AD so it would  
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15 be predicted that memantine would be used later in the course of the illness. This would also  
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17 explain the sharper rise in the use of antidepressants and antipsychotic medication at the  
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19 commencement of memantine therapy compared with AChEI therapy; patients with more  
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21 advanced disease would be expected to display more behavioural and psychological  
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23 symptoms.  
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28 The four classes of psychotropic drugs were more frequently prescribed in the memantine  
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30 group than in the AChEI group not only on the index day but also in the 5 years prior to  
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32 prescribing. In addition, whilst the slopes for monthly use of antipsychotics and  
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34 antidepressants were positive in the year leading up to either AChEI or memantine use, the  
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36 slope was steeper in the memantine cohort. There was also an acute increase in antipsychotic  
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38 and antidepressant medication at the start of antidementia drug therapy but again this was  
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40 more prominent for the patients initiated on memantine. More memantine patients were  
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42 taking anxiolytics and hypnotics on the index date than AChEI patients, which may reflect an  
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44 increase in behavioural problems such as anxiety and sleep disturbance in patients who are  
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46 then started on memantine. This suggests that there may be differences in the type of patient  
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48 selected to receive memantine. Memantine has been shown to have a beneficial effect on the  
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50 behavioural and psychological symptoms of dementia (BPSD) in clinical trials [15, 16] and a  
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52 Cochrane Review meta-analysis showed that AD patients taking memantine were less likely  
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54 to develop agitation. [28] Thus, patients may be selected to receive memantine partly because  
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of behavioural issues that are reflected in the higher levels of prescribing of psychotropic drugs at the time the memantine is initiated.

There are also differences after the initiation of either AChEIs or memantine. For AChEI users the slopes for antipsychotic and antidepressant use continued to increase but at a reduced rate whereas for memantine users there was a stabilisation in antidepressant use and a decline in the use of atypical and typical antipsychotic medication. This supports the idea that memantine may reduce behavioural problems such as agitation and reduce or delay the need to prescribe antipsychotic medication.

The data for antidepressant and antipsychotic use after initiation of memantine are similar to the results from the French National Health Care Database where the onset of memantine therapy was associated with a stabilisation of psychotropic drug use. [20]

**Strengths and limitations**

This study has used the extensive data provided within the CPRD to examine the use of psychotropic drugs, and particularly antipsychotic medication in people with dementia including those receiving treatment with antidementia drugs (AChEIs and/or memantine).

Although the numbers receiving memantine are considerably lower than those receiving AChEIs, this reflects the prescribing pattern over the period studied and also that the NICE Guidance on drug treatment for AD did not formally recommend memantine until its most recent review. [25]

It is plausible that patients were diagnosed at an earlier stage of the AD because of the increasing awareness about dementia and from 1997 onwards the availability of drug treatments for people with mild to moderate AD. As behaviours such as agitation and aggression become more common as the disease becomes more severe [29] and the use of antipsychotics tends to increase, the apparent decrease in use of AP in our study could have

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3 resulted from the earlier diagnosis of AD. In this case, we would have overestimated the  
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5 reduction of AP use. However, the fact that the mean age at the time of the first AD diagnosis  
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7 was stable over the entire study period does not support this alternative explanation.  
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11 The evaluation of the duration of AD treatment and of the use of psychotropic drugs in this  
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13 analysis is based on drugs prescribed or recorded by GPs. The use of AD medications and of  
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15 psychotropic drugs is assumed to start on the date of the recording of the respective  
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17 medication but we may have missed initial prescriptions where this was provided to the  
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19 patient directly by a specialist and not recorded by the GP although subsequent prescriptions  
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21 may be issued and recorded by the GP. Antidementia drugs prescribed exclusively by  
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23 hospital specialists will not be fully captured by the GP and there are areas in the UK where  
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25 all prescriptions for anti-dementia drugs are still only issued by specialists.  
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## 28 29 30 **Conclusions**

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32 Over the period 1995-2011, there has been a marked reduction in the prevalence of  
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34 antipsychotic drug use on the day that a diagnosis of dementia was first noted by GPs. In  
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36 contrast there was a steady increase in antidepressant use, a small increase in anxiolytic use  
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38 and a decrease in hypnotic use. Antipsychotic use did increase over the 10 years prior to the  
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40 dementia diagnosis with a more marked increase in the year before the dementia diagnosis on  
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42 the CPRD. Antidepressant use increased exponentially over the 10 years prior to the dementia  
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44 diagnosis. Psychotropic drugs were more frequently prescribed in the memantine treated  
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46 subgroup than in the AChEI subgroup not only on the index day but also in the 5 years prior  
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48 to prescribing. The slopes for use of antipsychotics and antidepressants were positive in the  
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50 year leading up to either AChEI or memantine use; the slope was steeper in the cohort  
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52 eventually started on memantine with an immediate increase at the start of antidementia drug  
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54 therapy that was again more prominent for patients initiated on memantine suggesting that  
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this cohort was experiencing more behavioural and psychological symptoms and likely to have more advanced dementia.

There were also differences between the subcohorts after the initiation of antedementia drugs. For AChEI users the slopes for antipsychotic and antidepressant use continued to increase but at a reduced rate whereas for memantine users there was a stabilisation in antidepressant use and a decline in the use of atypical and typical antipsychotic medication.



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**Contributorship:**

CM and RJ conceived of and designed the study. SR and CM performed the statistical analyses. CM, SR and RJ interpreted the results. CM and RJ drafted the manuscript. All authors revised the manuscript for intellectual content, and read and approved the final manuscript.

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**Conflict of interest:**

Yes, I will upload an ICMJE conflicts of interest form for each author of this manuscript.

**Data sharing:**

No additional data are available.

**Table 1: Characteristics of patients in dementia cohort and subset treated with memantine, AChEI and the combination of memantine and AChEI**

	Complete dementia cohort	Dementia cohort	Dementia cohort	Matched control cohort	Memantine subcohort	AChEI subcohort	Memantine plus AChEI subcohort
Study period	1995 to 2011	1995	2011	1995 to 2011	2003 to 2011	2003 to 2011	2003 to 2011
Total	50439	879	3108	50439	669	10794	379
Males	17432 (34.6)	304 (34.6)	1170 (37.6)	17432 (34.6)	243 (36.3)	3855 (35.7)	156 (41.2)
Age mean ± SD	82.0±7.3	81.7±7.3	82.5±7.4	82.0±7.3	79.9±7.5	79.4±7.0	76.4±7.1
Median age	83	82	83	83	80	80	77
Age 60 to 64	896 (1.8)	9 (1.0)	48 (1.5)	896 (1.8)	25 (3.7)	324 (3.0)	16 (4.2)
65 to 69	2058 (4.1)	50 (5.7)	118 (3.8)	2058 (4.1)	43 (6.4)	670 (6.2)	52 (13.7)
70 to 74	4798 (9.5)	89 (10.1)	287 (9.2)	4798 (9.5)	77 (11.5)	1502 (13.9)	73 (19.3)
75 to 80	9610 (19.1)	161 (18.3)	510 (16.4)	9610 (19.1)	150 (22.4)	2608 (24.2)	111 (29.3)
80 to 84	13383 (26.5)	243 (27.6)	812 (26.1)	13383 (26.5)	194 (29.0)	3112 (28.8)	76 (20.1)
85 to 90	12414 (24.6)	206 (23.4)	817 (26.3)	12414 (24.6)	118 (17.6)	1978 (18.3)	41 (10.8)
≥90	7280 (14.4)	121 (13.8)	516 (16.6)	7280 (14.4)	62 (9.3)	600 (5.6)	10 (2.6)
First recording of dementia after index prescription of antdementia drug (%)					38 (5.7)	948 (8.8)	14 (3.7)
Duration of dementia at time of first use of antdementia drug (mean years ± SD)					1.4±1.7	0.7±1.1	2.7±2.0
Referral to specialist* in previous 6 months	25205 (50.0)	224 (25.5)	2010 (64.7)	1265 (2.5)	454 (67.9)	6549 (60.7)	173 (45.6)

Previous use of memantine					0 (0.0)	9 (0.1)	35 (9.2)
Previous use of AChEI					119 (17.8)	0 (0.0)	342 (90.2)
<b>Use of antipsychotics at or before index day</b>							
Index day	6289 (12.5)	175 (19.9)	231 (7.4)	1322 (2.6)	175 (26.2)	1143 (10.6)	89 (23.5)
1 to 182 days	7394 (14.7)	197 (22.4)	300 (9.7)	2439 (4.8)	182 (27.2)	1325 (12.3)	108 (28.5)
183 to 365 days	4950 (9.8)	135 (15.4)	225 (7.2)	2403 (4.8)	128 (19.1)	906 (8.4)	80 (21.1)
1 to 2 years	5329 (10.6)	123 (14.0)	256 (8.2)	3218 (6.4)	122 (18.2)	930 (8.6)	67 (17.7)
2 to 3 years	4792 (9.5)	105 (11.9)	246 (7.9)	3157 (6.3)	89 (13.7)	783 (7.5)	43 (11.5)
3 to 4 years	4353 (8.6)	99 (11.3)	234 (7.5)	2937 (5.8)	78 (12.6)	677 (6.8)	32 (8.7)
4 to 5 years	3685 (8.0)	63 (8.3)	225 (7.6)	2583 (5.6)	58 (9.7)	611 (6.5)	25 (7.1)
≥5 years	7298 (17.3)	43 (7.6)	603 (21.0)	5983 (14.2)	111 (19.6)	1440 (16.4)	65 (19.1)
<b>Use of antidepressants at or before index day</b>							
Index day	11164 (22.1)	94 (10.7)	817 (26.3)	4981 (9.9)	228 (34.1)	2843 (26.3)	134 (35.4)
1 to 182 days	13165 (26.1)	129 (14.7)	922 (29.7)	6189 (12.3)	239 (35.7)	3130 (29.0)	142 (37.5)
183 to 365 days	11204 (22.2)	107 (12.2)	801 (25.8)	5807 (11.5)	201 (30.0)	2832 (26.2)	127 (33.5)
1 to 2 years	11284 (22.4)	115 (13.1)	782 (25.2)	6417 (12.7)	209 (31.2)	2716 (25.2)	129 (34.0)
2 to 3 years	10014 (19.9)	107 (12.2)	667 (21.5)	5970 (11.8)	177 (27.2)	2234 (21.4)	109 (29.1)
3 to 4 years	8912 (17.7)	87 (9.9)	618 (19.9)	5535 (11.0)	142 (22.9)	1897 (19.0)	94 (25.6)
4 to 5 years	7420 (16.1)	70 (9.2)	524 (17.6)	4800 (10.4)	120 (20.1)	1534 (16.3)	73 (20.7)
≥5 years	9565 (22.7)	43 (7.6)	809 (28.2)	7164 (17.0)	158 (28.0)	2149 (24.4)	102 (29.9)
<b>Use of anxiolytics at or before index day</b>							
Index day	2265 (4.5)	24 (2.7)	123 (4.0)	1327 (2.6)	88 (13.2)	444 (4.1)	51 (13.5)
1 to 182 days	3304 (6.6)	36 (4.1)	188 (6.0)	2075 (4.1)	116 (17.3)	668 (6.2)	67 (17.7)

183 to 365 days	2506 (5.0)	24 (2.7)	132 (4.2)	1988 (3.9)	87 (13.0)	593 (5.5)	42 (11.1)
1 to 2 years	2901 (5.8)	41 (4.7)	159 (5.1)	2354 (4.7)	89 (13.3)	646 (6.0)	46 (12.1)
2 to 3 years	2778 (5.5)	52 (5.9)	159 (5.1)	2356 (4.7)	75 (11.5)	541 (5.2)	46 (12.3)
3 to 4 years	2698 (5.4)	49 (5.6)	146 (4.7)	2295 (4.6)	65 (10.5)	509 (5.1)	40 (10.9)
4 to 5 years	2448 (5.3)	44 (5.8)	146 (4.9)	2014 (4.4)	60 (10.1)	461 (4.9)	29 (8.2)
≥5 years	4624 (11.0)	26 (4.6)	387 (13.5)	3904 (9.3)	108 (19.1)	1024 (11.6)	60 (17.6)
<b>Use of hypnotics at or before index day</b>							
Index day	4935 (9.8)	114 (13.0)	246 (7.9)	3662 (7.3)	123 (18.4)	899 (8.3)	75 (19.8)
1 to 182 days	6287 (12.5)	137 (15.6)	317 (10.2)	4559 (9.0)	145 (21.7)	1066 (9.9)	87 (23.0)
183 to 365 days	5267 (10.4)	115 (13.1)	275 (8.8)	4437 (8.8)	131 (19.6)	916 (8.5)	68 (17.9)
1 to 2 years	5690 (11.3)	129 (14.7)	322 (10.4)	4913 (9.7)	128 (19.1)	980 (9.1)	64 (16.9)
2 to 3 years	5472 (10.8)	127 (14.4)	288 (9.3)	4872 (9.7)	97 (14.9)	901 (8.6)	53 (14.1)
3 to 4 years	5266 (10.4)	128 (14.6)	293 (9.4)	4732 (9.4)	84 (13.6)	859 (8.6)	47 (12.8)
4 to 5 years	4669 (10.1)	106 (13.9)	271 (9.1)	4198 (9.1)	66 (11.1)	777 (8.2)	37 (10.5)
≥5 years	6611 (15.7)	71 (12.5)	489 (17.1)	5832 (13.9)	123 (21.8)	1296 (14.7)	70 (20.5)

\*Referrals to psychiatrist, geriatrician or neurologist; index day: day of first diagnosis of dementia in dementia cohort, respective day in the matched control cohort, or day of first use of memantine or an acetylcholinesterase inhibitor (AChEIs)



Table 2: Summary results: slope of the fitted regression line for the prevalence of concomitant psychotropic treatment in year before and after first use of memantine, 2005 to 2011

	Memantine			AChEI		
	Slope 12 months before	Slope 12 months after	Slope difference (95% CI)	Slope 12 months before	Slope 12 months after	Slope difference (95% CI)
<b>Antipsychotics</b>	<b>0.69</b>	<b>-0.22</b>	<b>0.91 (0.73, 1.09)</b>	<b>0.36</b>	<b>0.13</b>	<b>0.23 (0.20, 0.26)</b>
Atypical antipsychotics	0.6	-0.19	0.79 (0.62, 0.96)	0.3	0.1	0.20 (0.18, 0.23)
Typical antipsychotics	0.12	-0.09	0.21 (0.12, 0.30)	0.06	0.03	0.04 (0.02, 0.05)
<b>Antidepressants</b>	<b>0.56</b>	<b>-0.02</b>	<b>0.58 (0.38, 0.79)</b>	<b>0.47</b>	<b>0.27</b>	<b>0.19 (0.14, 0.24)</b>
Tricyclic antidepressants	0.05	-0.17	0.22 (0.13, 0.31)	0	0.03	-0.04 (-0.06, -0.01)
SSRI	0.33	0.01	0.33 (0.15, 0.50)	0.34	0.15	0.20 (0.16, 0.24)
Other antidepressants	0.22	0.06	0.16 (0.04, 0.28)	0.17	0.1	0.07 (0.05, 0.09)
<b>Anxiolytics</b>	<b>0.22</b>	<b>-0.12</b>	<b>0.34 (0.21, 0.48)</b>	<b>0.06</b>	<b>0.01</b>	<b>0.04 (0.02, 0.06)</b>
<b>Hypnotics</b>	<b>0.16</b>	<b>-0.26</b>	<b>0.42 (0.26, 0.59)</b>	<b>0.11</b>	<b>0</b>	<b>0.11 (0.08, 0.14)</b>

Figure 1a-b: Prevalence of psychotropic drug use in dementia and matched control cohort by year at the time of first dementia diagnosis or index day, 1995 to 2011

Figure 1a: Dementia cohort

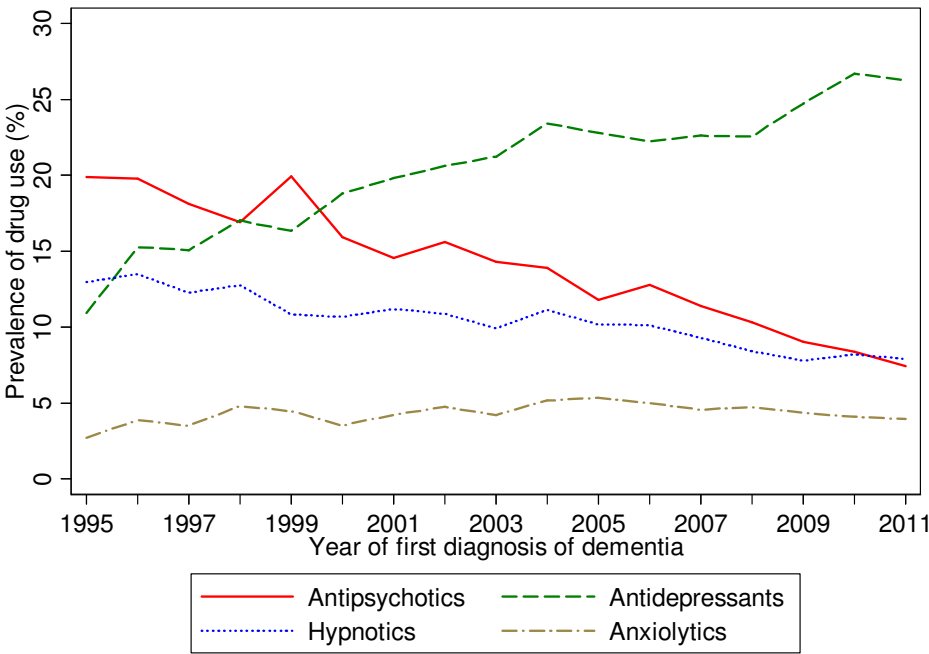


Figure 1b: Control cohort

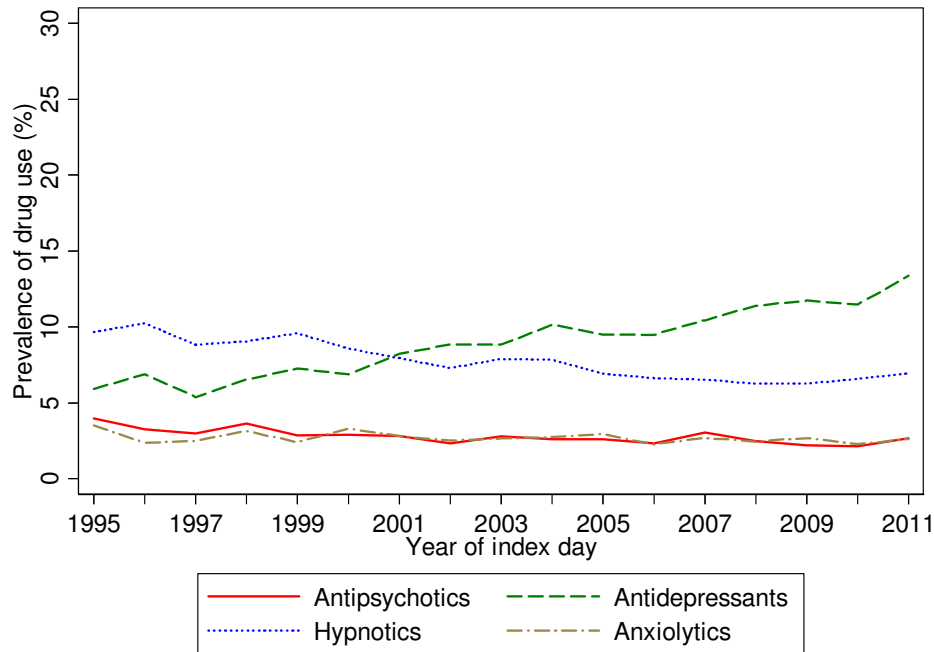
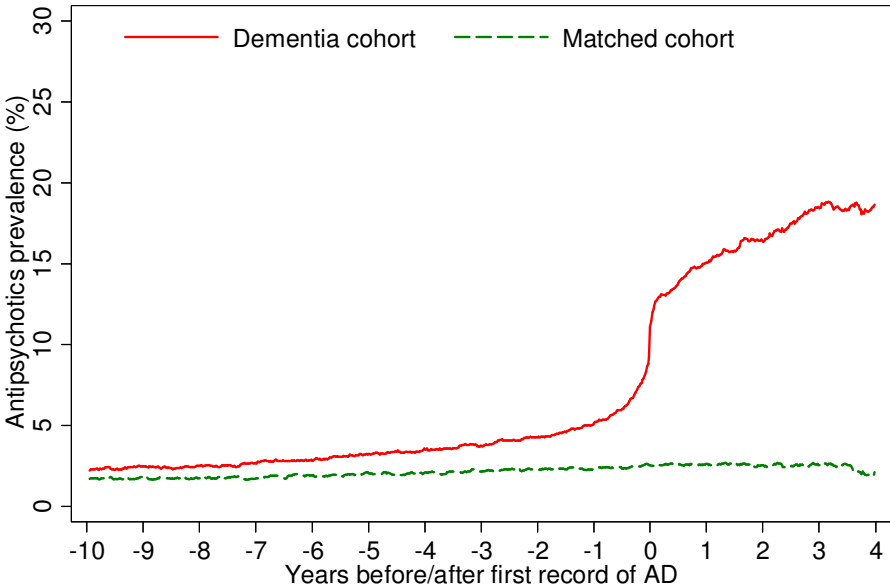


Figure 2a-d: Prevalence of psychotropic use in dementia cohort and in matched control cohort before and after the first dementia diagnosis for 2005 to 2011 cohort

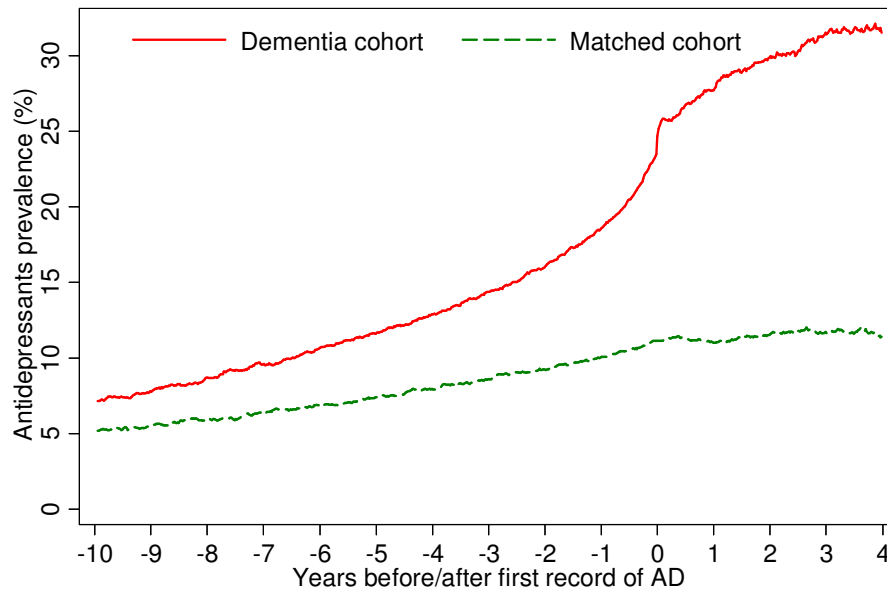
Figure 2a: Prevalence of antipsychotic use



Dem:	15619	20777	25476	29113	30803	30803	11073	3252
Ref:	16371	21347	25914	29333	30803	30803	15998	6721

Antipsychotics: typical antipsychotics (phenothiazines, butyrophenones, diphenylbutylpiperidines, thioxanthenes and substituted benzamides), and atypical antipsychotics (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone and zotepine).

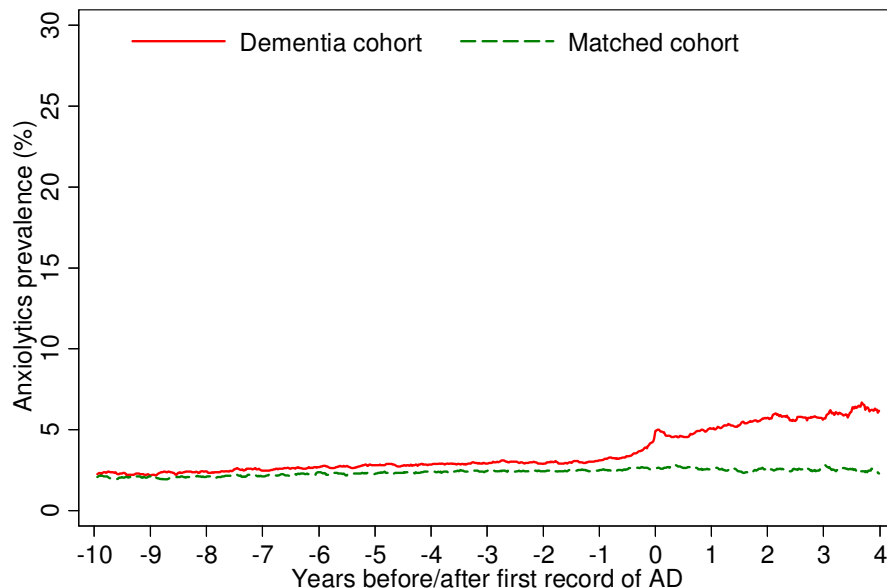
**Figure 2b: Prevalence of antidepressant use**



Dem:	15619	20777	25476	29113	30803	30803	11073	3252
Ref:	16371	21347	25914	29333	30803	30803	15998	6721

Antidepressants: tricyclic and related antidepressants, selective serotonin re-uptake inhibitors (SSRI) and other antidepressants.

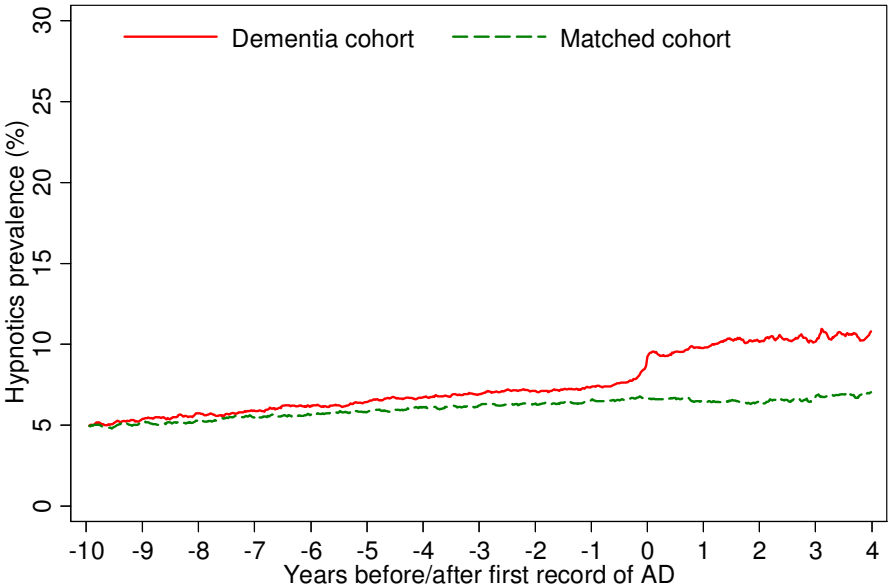
**Figure 2c: Prevalence of anxiolytic use**



Dem:	15619	20777	25476	29113	30803	30803	11073	3252
Ref:	16371	21347	25914	29333	30803	30803	15998	6721

Anxiolytics: buspirone, chlordiazepoxide, diazepam, hydroxyzine and lorazepam.

Figure 2d: Prevalence of hypnotic use



Dem:	15619	20777	25476	29113	30803	30803	11073	3252
Ref:	16371	21347	25914	29333	30803	30803	15998	6721

Hypnotics: clomethiazole, chloral betaine, loperazolam, lormetazepam, nitrazepam, promethazine, temazepam, zaleplon, zolpidem and zopiclone.

**Figure 3a-d: Prevalence of psychotropic drug use in AChEI and memantine (Mem) subcohort in the 5 years preceding the first prescription (index day), excluding patients without a previous prescription for the other compound, AChEI or memantine, 2003 to 2011.**

**Figure 3a: Prevalence of antipsychotic use in AChEI and memantine subcohort**

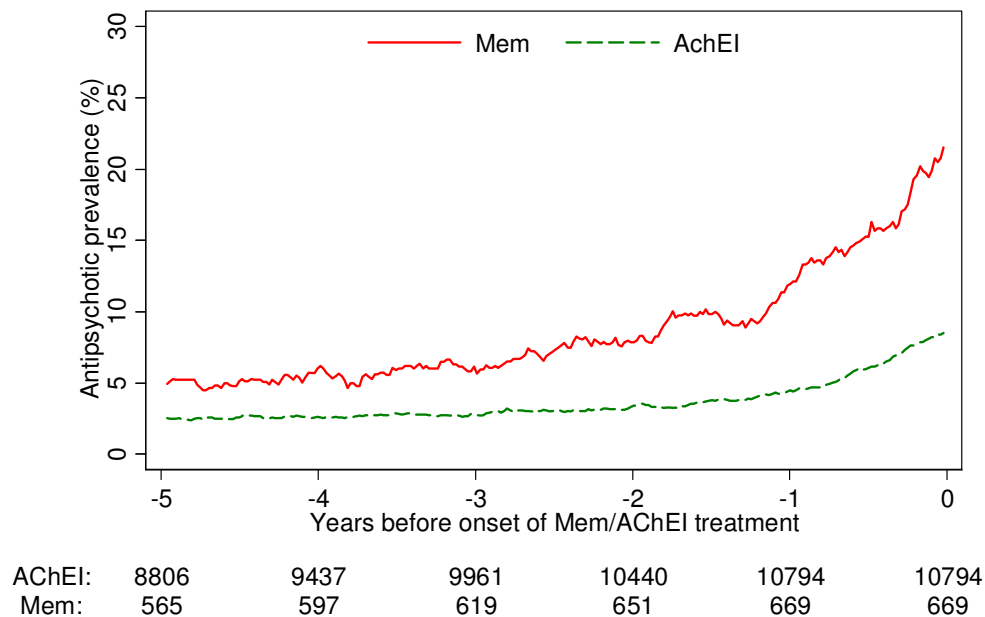


Figure 3b: Prevalence of antidepressant use in AChEI and memantine subcohort

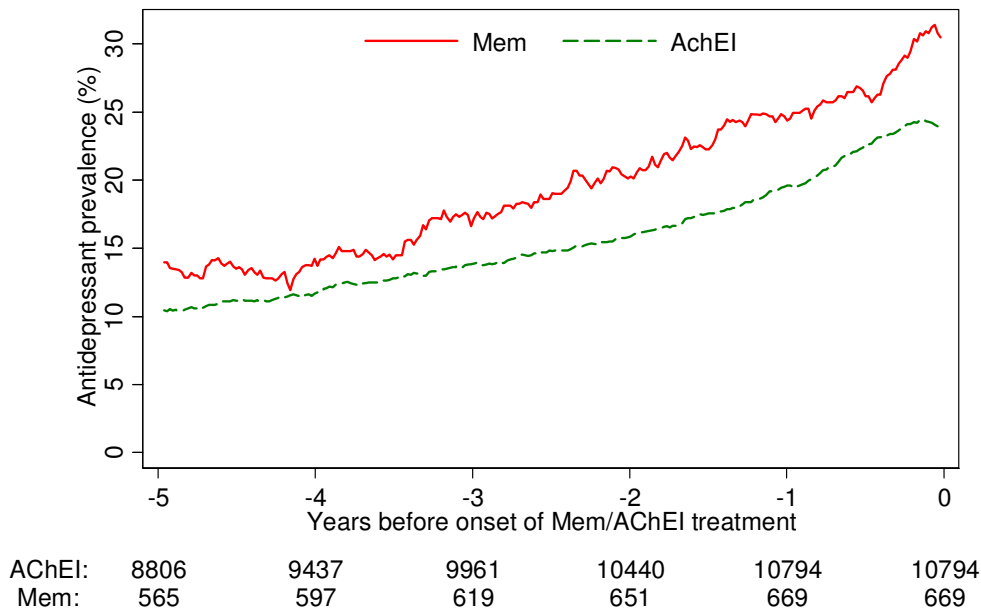
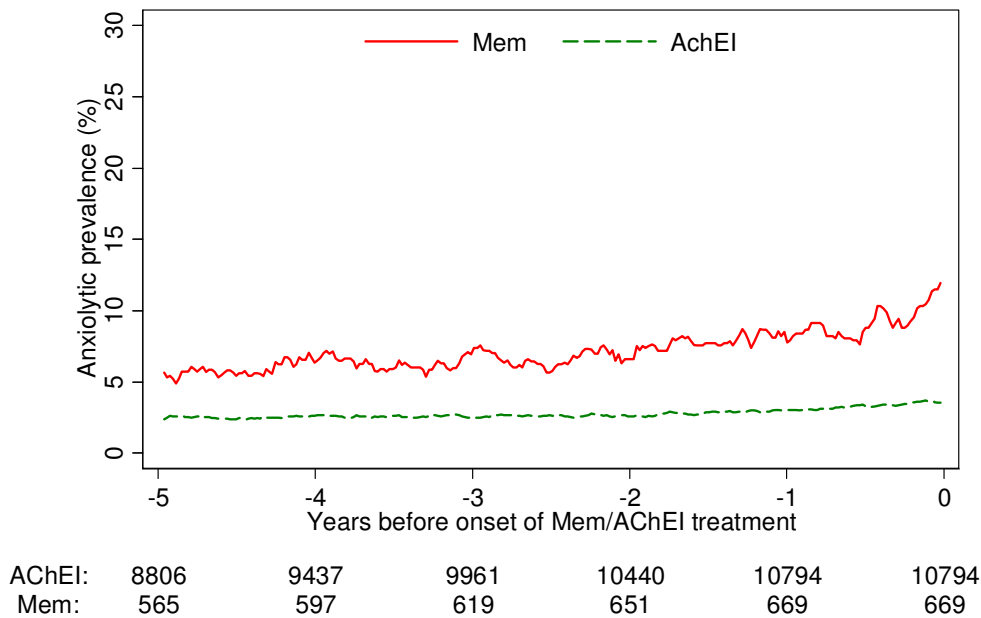
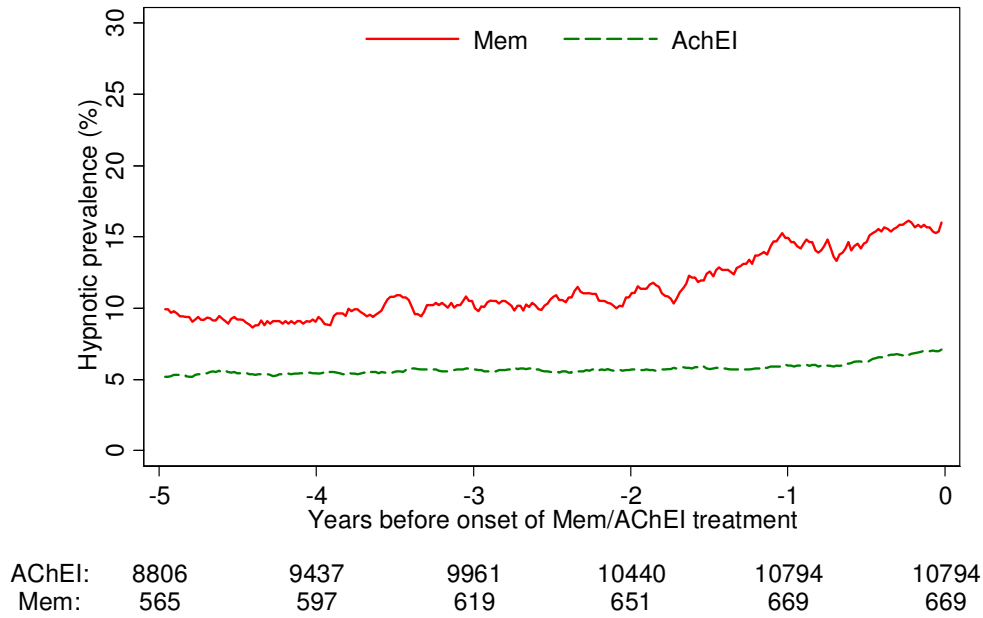


Figure 3c: Prevalence of anxiolytic use in AChEI and memantine subcohort





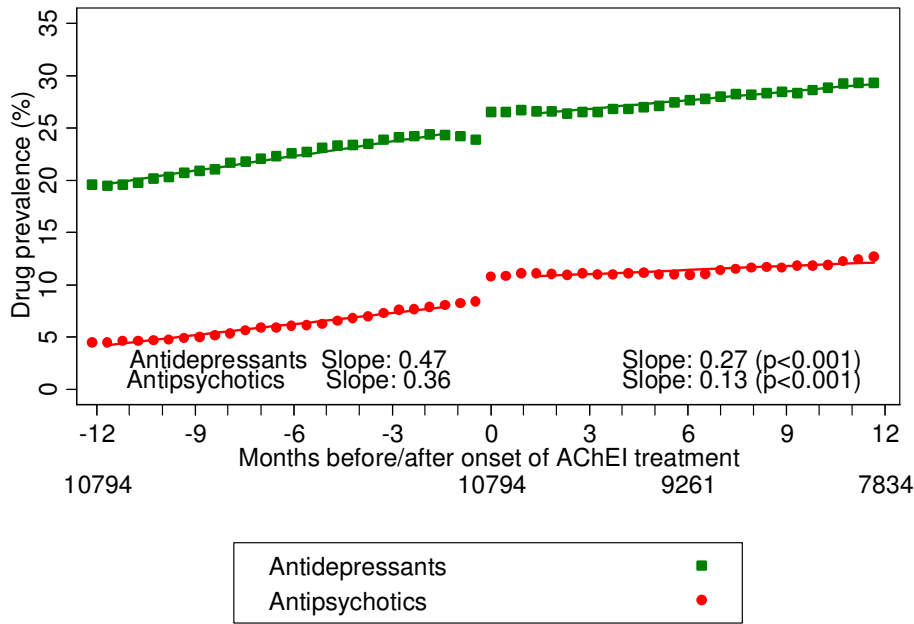
**Figure 3d: Prevalence of hypnotic use in AChEI and memantine subcohort**



review only

Figure 4a-d: Prevalence of antipsychotic and antidepressant use in the year before and after first use of AChEI and memantine, excluding patients without a previous prescription for the other compound, AChEI or memantine).

Figure 4a: Prevalence of antipsychotic and antidepressant use among AChEI users.



**Figure 4b: Prevalence of antipsychotic and antidepressant use among memantine users.**

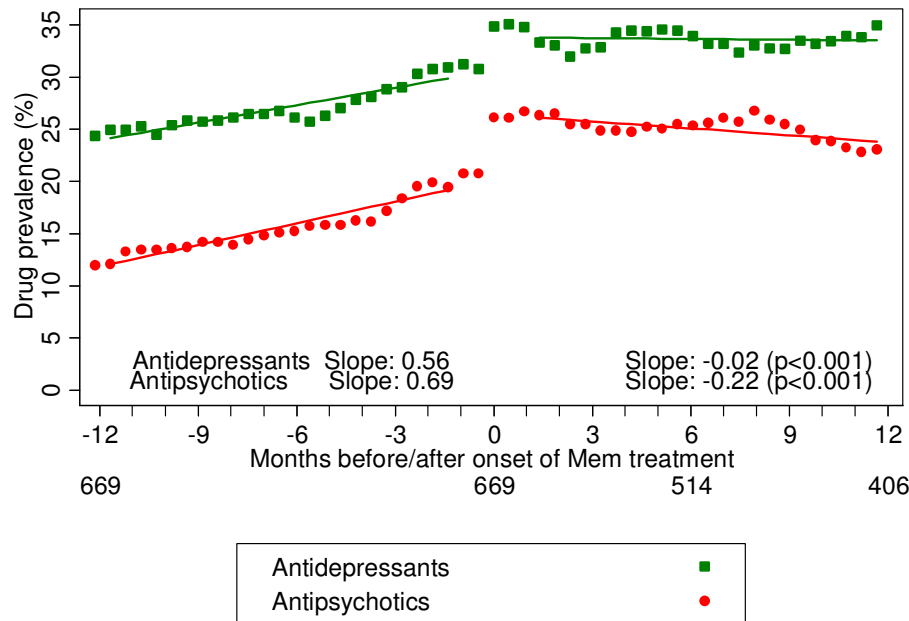


Figure 4c: Prevalence of anxiolytic and hypnotic use among AChEI users.

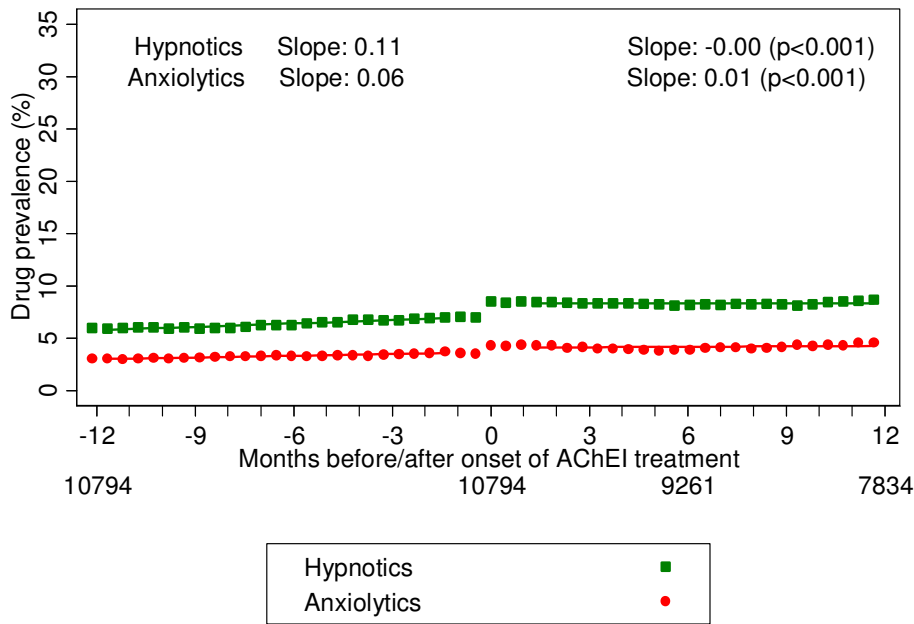
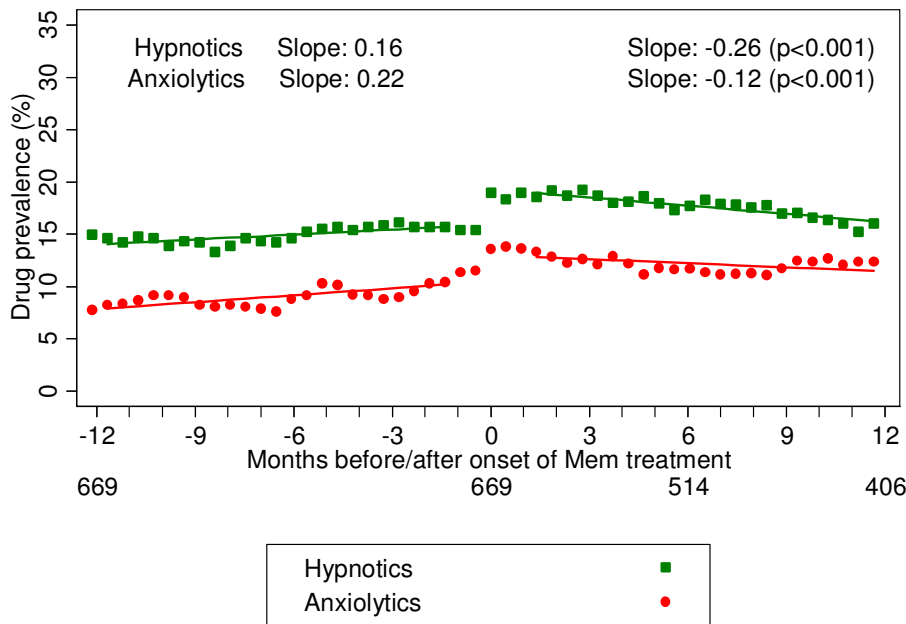
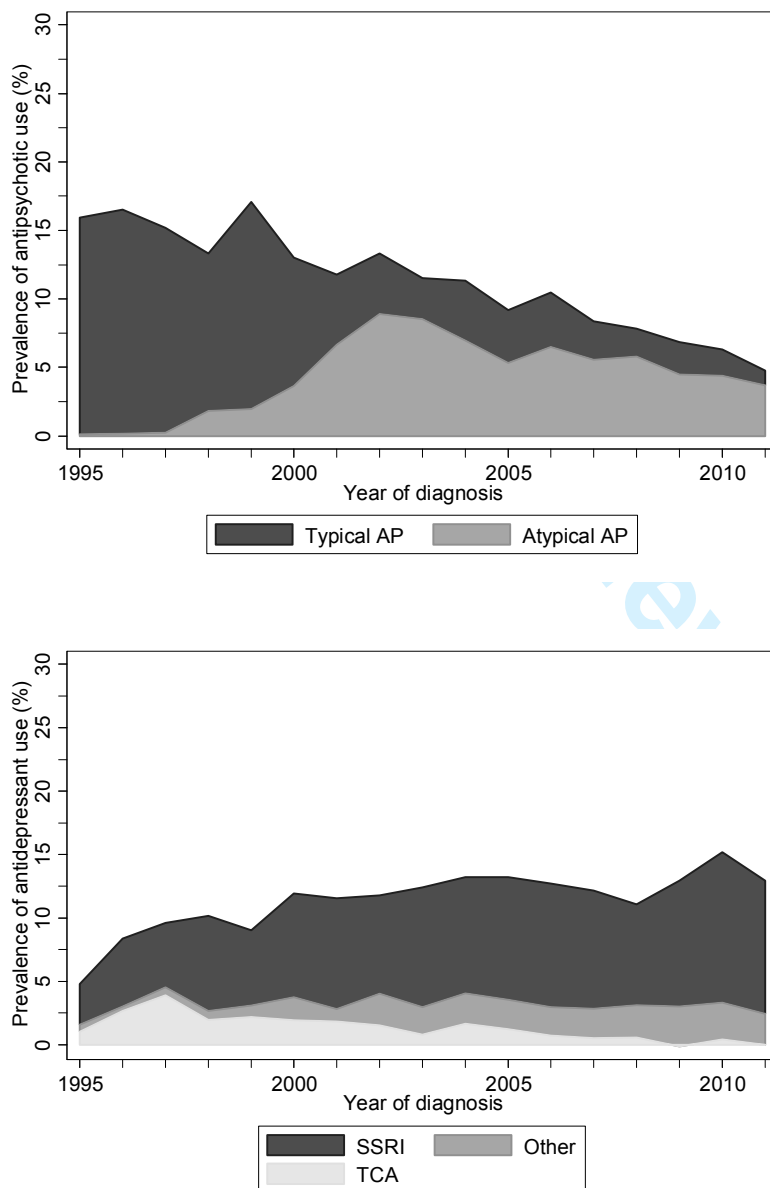


Figure 4d: Prevalence of anxiolytic and hypnotic use among memantine users.

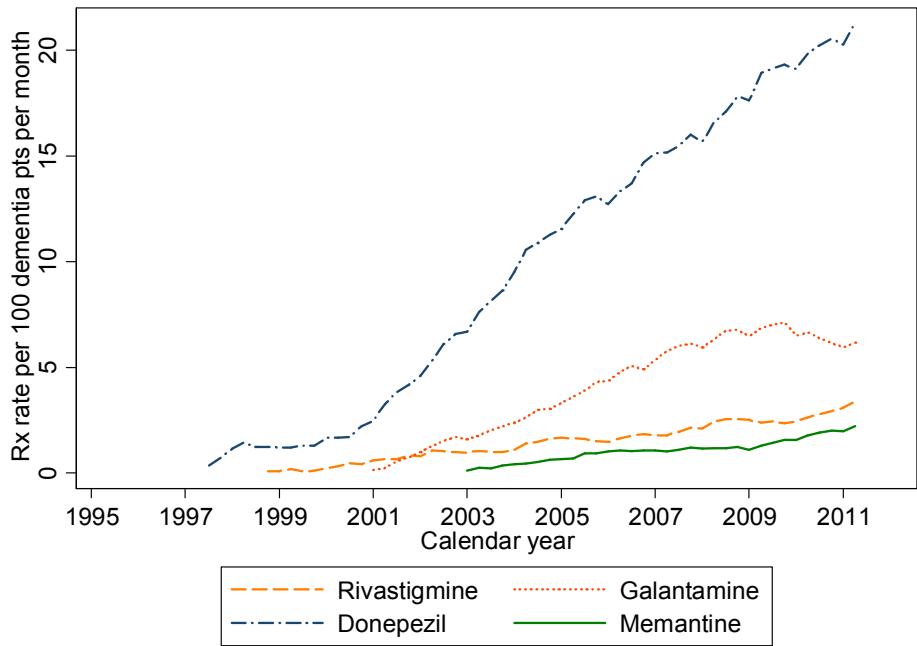


## Supplementary data

**Supplement Figure 1: Proportion of antipsychotics (above) and of antidepressants (below) attributable to dementia at the time of first diagnosis of dementia by type of antipsychotic, 1995 to 2011**



Supplement Figure 2: Monthly prevalence of use of antidementia drugs per 100 dementia patients since 1995





**Trends in the prevalence of antipsychotic drug use among patients with Alzheimer's disease and other dementias including those treated with antidementia drugs in the community in the UK: a cohort study**

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Secondary Subject Heading:	Medical management, Geriatric medicine, Pharmacology and therapeutics, Mental health, Neurology
Keywords:	Dementia < NEUROLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Toxicity < THERAPEUTICS

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**Abstract**

**OBJECTIVE:**

To investigate the pattern and trends of use of psychotropic drugs in dementia including subjects taking antidementia medication.

**DESIGN:**

Cohort study with incident dementia patients formed in the United Kingdom Clinical Practice Research Datalink.

**PARTICIPANTS:**

Patients with incident dementia, between 1995 and 2011 and a reference non-dementia cohort matched on age, gender and date of dementia diagnosis. Two subcohorts included new users of acetylcholinesterase inhibitors (AChEIs) and memantine.

The study endpoint was use of psychotropic medications (antipsychotics, antidepressants, hypnotics and anxiolytics) up to 10 years before and 4 years after dementia diagnosis, and for up to 5 years before and one year after first use of AChEI or memantine.

**RESULTS:**

50,349 patients with incident dementia diagnosis and 50,349 matched controls, 10794 first-time users of AChEI and 669 of memantine. The mean prevalence of antipsychotic use from 1995-2011 on diagnosis of dementia was 12.5%, decreasing from 19.9% in 1995 to 7.4% in 2011. There was an increase in antidepressant use (10.7% to 26.3%) and a small increase in anxiolytic use. The matched cohort showed a lower use of antipsychotics and anxiolytics but a rise in antidepressant use (5.9% to 13.4%). Both groups showed a decrease in hypnotic use. 10.6% of AChEI and 26.3% of memantine users were prescribed antipsychotics, 34.1% and 26.3% antidepressants, 13.2% and 4.1% anxiolytics and 18.4% and 8.3% hypnotics. The slopes for monthly use of antipsychotics were positive in the year leading up to AChEI and memantine use; after treatment initiation the slope for AChEI users continued to increase but at a reduced rate whereas antipsychotic use declined for memantine users.

**CONCLUSIONS:**

The marked reduction in antipsychotic use in dementia is to be welcomed whilst there was a steady increase in antidepressant use. There was a decline in antipsychotic use after initiation of memantine.



## Article summary

### Article focus

- Antipsychotic medications (APs) have frequently been prescribed as the first-line pharmacological treatment approach for neuropsychiatric symptoms in Alzheimer's disease and other dementias (AD) but their use has been associated with several risk concerns
- To describe the pattern and trends of use of AP, antidepressants, hypnotics and anxiolytics in AD and in patients treated with antidementia medications, i.e. acetylcholinesterase inhibitors (AChEIs) and memantine in primary care in the UK.

### Key messages

- The mean prevalence of AP use on the first recording of a dementia was 12.5%, decreasing markedly from 19.9% in 1995 to 7.4% in 2011. In contrast, there was a steady increase in the use of antidepressants (10.7% to 26.3%) and a small increase in the use of anxiolytics.
- AP use in patients with a first dementia diagnosis between 2005 and 2011 increased from 2.2% 10 years prior to the dementia diagnosis to 5.1% one year preceding the dementia diagnosis and 11.1% at the time of entering the dementia diagnosis on the Clinical Practice Research Datalink (CPRD).
- The monthly use of AP increased in the year leading up to the first AChEI or memantine use; after treatment initiation the monthly use for those prescribed AChEIs continued to increase but at a reduced rate whereas antipsychotic use declined for those prescribed memantine.

### Strengths and limitations of this study

- The Clinical Practice Research Datalink (CPRD) is the largest primary care database in the world, containing the longitudinal records for up to 20 years of over 3 million patients
- There may have been a trend towards diagnosing AD at an earlier stage of the AD because of the increasing awareness despite the fact that the mean age at the time of the first AD diagnosis was stable over the entire study period.

- APs and antidementia drugs prescribed exclusively by hospital specialists are not completely recorded in CPRD

Introduction

Functional deficits and neuropsychiatric/behavioural symptoms contribute significantly to the disabilities associated with Alzheimer’s disease (AD). Up to 90% of patients with AD will experience neuropsychiatric symptoms such as hallucinations, delusions, aggressive behaviour, agitation, and affective disturbances during the course of their disease. [1,2] These symptoms can be amongst the most distressing aspects of AD, increasing caregiver burden, contributing to poor patient quality of life, and often triggering the transfer to institutional care. [1,3,4] In a survey of carers by Alzheimer Europe, behavioural symptoms including agitation, aggression, and irritability were cited more often than cognitive symptoms as the most problematic symptoms of AD (50% versus 45%). [1]

Antipsychotic medications (APs) have frequently been prescribed as the first-line pharmacological treatment approach for neuropsychiatric symptoms in AD and other dementias but their use has been associated with several serious concerns. Treatment with APs has been shown to raise the risk of adverse events including cerebrovascular events, somnolence, and extrapyramidal symptoms as well as accelerated cognitive decline. [5-7] Furthermore, APs are associated with an increased mortality risk in elderly patients with and without AD. [7-9]

Only the atypical antipsychotic risperidone has use in AD included in its licensed indications within the European Community. This licence followed a review in 2008 and is restricted to “the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate

to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others". [10] In the UK risperidone is included within the Black Triangle Scheme that identifies medicines whose safety profiles are monitored intensively; healthcare professionals are asked to report via the Yellow Card Scheme all suspected side-effects that occur in the treatment of elderly people with dementia.

The US Food and Drug Administration (FDA) has issued warnings against the use of atypical APs in patients with dementia [11] and, in 2008, the UK Department of Health commissioned an independent report on the use of antipsychotic medication in people with dementia. [12] This report concluded that APs appear to have only a limited positive effect but can cause significant harm to people with dementia – including an additional 1,800 deaths and 1,620 cerebrovascular adverse events in the UK per year. [12] Although APs may offer benefit to some patients, the report generally recommended “reducing the use of antipsychotic drugs for people with dementia.” [12] The French High Authority for Health (HAS) raised similar concerns, criticising the excessive prescribing of APs to patients with AD. [13]

There is some evidence that the currently available anti-dementia agents – memantine and the acetylcholinesterase inhibitors (AChEIs) have beneficial effects on behavioural disturbances in AD, and they are generally well tolerated [14-18] although the 12-week CALM-AD trial was unable to show that the AChEI donepezil was more effective than placebo in treating agitation in patients with AD. [19] Furthermore, a retrospective study in France has shown that there was an apparent increasing trend of AP use before the initiation of memantine therapy and that memantine stabilized the proportion of AP users. [20] In the United States, a study using national Veterans Affairs data has examined changes in atypical and conventional antipsychotic use in outpatients with dementia from 1999 through 2007. [21] Use of atypical antipsychotics began to decline significantly in 2003, and after the Food and Drug Administration advisory warning in 2005 a further significant decline was evident.

The aim of the current study was to investigate the pattern and trends of use of psychotropic drugs (i.e., antipsychotics, antidepressants, hypnotics and anxiolytics) and their association with use of AChEIs (donepezil, galantamine, or rivastigmine) and memantine to better understand their use in primary care in the UK.

**Methods**

An observational cohort study was carried out using data from the UK Clinical Practice Research Datalink (CPRD), until 1st April 2012 known as the General Practice Research Database. Participating general practitioners (GPs) currently contribute data on more than 5 million patients and are broadly representative of the UK population in terms of age, gender and region. [22] The CPRD comprises data on patient demographics, medical diagnoses, all GP prescriptions (electronic issue), referrals to secondary care, and hospital discharge reports. Prescription information includes date of prescription, drug substance, daily dose, daily quantity and number of packs/pack size. Dispensing information is not available. GP practices are required to meet defined quality standards before they can contribute to the CPRD.

**Study population and study design**

The study population consisted of patients in the CPRD at least 60 years of age and with at least three years history in the CPRD before a first diagnosis of dementia between 1 January 1995 and 30 June 2011. Dementia was defined by a Read medical code for Alzheimer’s disease, vascular dementia or other dementia. A control cohort was generated by randomly selecting for each dementia patient, one control, matched on gender and year of birth but without a recording of dementia during the entire observational period. The date of the first diagnosis of dementia was defined as the index day in the dementia cohort, and the same date

was taken as the index day for the matched control. Matched controls were also required to have a minimum of 3 years in the CPRD prior to the index day.

Two subcohorts were created by the first-time use of AChEI or memantine from 2003 to 2011 (with the index day based on first drug use rather than on first diagnosis of dementia) to assess the use of psychotropic medications in association with antidementia medication. The date of the first prescription for an AChEI or memantine was defined as the index day for the subcohort analyses. Patients with both AChEI and memantine prescriptions were not analysed further. As some patients were given antidementia medications before the first recording of a dementia diagnosis, patients on AChEI and memantine were required to have a minimum of one year in the CPRD prior to the first use of an antidementia medication.

The study endpoint was the use of psychotropic medications (APs, antidepressants, anxiolytics and hypnotics). Use of any psychotropic medication was identified from recordings by the GP.

First, the prevalence of psychotropic drug use was assessed by its exposure status on the date of the first recording of a dementia diagnosis or index day of the respective matched controls for the complete study period of 1995 to 2011.

To investigate the temporal relationship between the use of psychotropic drugs in association with the first dementia diagnosis the study cohort was restricted to those with a first dementia diagnosis between 2005 and 2011 to estimate the prevalence of psychotropic use up to 10 years before and up to 4 years after the index day.

Psychotropic use in the AChEI and memantine subcohorts was assessed for up to 5 years before and up to one year after first use of AChEI or memantine.

**Data analysis**

For each prescription of a psychotropic drug, a prescription-specific duration was calculated from the number of tablets prescribed combined with the dosing instructions and adding a grace period of 30 days. The 30-day grace period was used to allow for any residual effect of the drug or any remaining medication due to a lack of compliance. The prescription-specific duration was used to calculate the exposure prevalence of each psychotropic drug class per week of the observational period. The prevalence of AP and antidepressant use attributable to dementia was estimated by subtracting the prevalence of APs and antidepressants in the matched cohort from the respective prevalence of the dementia cohort. The weekly or monthly prevalence was described using binomial regression and the method of generalized estimating equations [23] and for the antidementia drug use shown as the slope of the fitted regression line for the year before and separately for the year after first use. All analyses were performed with STATA Intercooled Version 11.2 (StataCorp LP). The study protocol was approved by the Independent Scientific Advisory Committee for GPRD research.

**Results**

**Dementia cohort**

A total of 50,349 patients with a first-time diagnosis of dementia were identified in the CPRD between 1995 and June 2011. The mean age of dementia patients was 82.0 years with 34.6% males. There was an increasing trend over time for patients with dementia to be seen by a specialist, i.e. psychiatrists, geriatricians or neurologists, from 25.5% in 1995 to 64.7% in 2011.

At the time of the first dementia diagnosis between 1995 and 2011, 12.5% were given antipsychotics, 22.1% antidepressants, 4.5% anxiolytics and 9.8% hypnotics. The age at first

dementia diagnosis increased from 81.7 to 82.5 years and the proportion of men from 34.6% to 37.6% from 1995 to 2011, Table 1. Over the years 1995 to 2011, the prevalence of AP use on the day of the first dementia diagnosis decreased from 19.9% to 7.4%. There was a steady increase in antidepressant use (10.7% to 26.3%), a small increase in anxiolytic use (2.7% to 4.0%), and a decrease in hypnotic use (13.0% to 7.9%). The matched cohort without dementia showed a nearly constant use of antipsychotics and anxiolytics during the entire study period, a small decrease in the use of hypnotics, but also an increase in the use of antidepressants (5.9% to 13.4%), Figures 1a-b.

In patients with a first dementia diagnosis between 2005 and 2011 and with up to 10 years of medical history, antipsychotic use was 2.2% 10 years prior to the dementia diagnosis and increased linearly up until one year preceding the dementia diagnosis to 5.1%; on the date of the dementia diagnosis it was 11.1% and then it increased to 18.7% after a further 4 years. In the matched cohort and during the same period antipsychotic use was nearly constant ranging between 1.7% and 2.6%, Figure 2a. A similar pattern was observed in the use of antidepressants. For patients with a dementia diagnosis, antidepressant use increased from 7.2% 10 years before and 18.6% one year before the dementia diagnosis, to 24.7% on the date of the diagnosis, and to 31.6% four years after the dementia diagnosis, compared to 10.1%, and 11.4% for the matched cohort for the same time period, Figure 2b. Anxiolytics and hypnotic use only started to increase noticeably in the year before the dementia diagnosis, Figure 2c-d.

### **AChEI and/or memantine subcohort**

Within the dementia cohort, 10,794 patients were treated with an AChEI, 669 with memantine and 379 with both an AChEI and memantine. The mean duration of dementia at first prescription was 0.7 years in the AChEI group, 1.4 years in the memantine group and 2.6



years in the AChEI and memantine group. Age and gender were comparable in the AChEI and memantine subgroups, but patients on both AChEI and memantine were younger and more often males. Memantine users were more likely to have a record of a referral to a psychiatrist/geriatrician in the 182 days before the first prescription compared to AChEI users (67.9% vs. 60.7%). A total of 17.8% of first-time users of memantine were recorded as having been given AChEI previously, Table 1.

During the 5-year period prior to the index prescribing of memantine or AChEI each of the 4 classes of psychotropic drugs was more frequently prescribed in the memantine group compared to the AChEI group, Table 1 and Figure 3a-d. On the index day, 26.2% of memantine and 10.6% of AChEI patients were prescribed antipsychotics, 34.1% and 26.3% respectively were prescribed antidepressants, 13.2% and 4.1% anxiolytics and 18.4% and 8.3% hypnotics, Table 1.

The slope for all classes of antipsychotics and antidepressants were positive in the 12 months leading up to memantine and AChEI use but steeper in the memantine cohort, i.e. antipsychotics: memantine 0.69 versus AChEIs 0.36; antidepressants: memantine 0.56 versus AChEIs 0.47, Table 2. There was an acute increase of antipsychotic and antidepressant medication at the start of memantine and AChEI use respectively. The sharp increase was more prominent among memantine users, Figure 4a-b, suggesting that they had more behavioural issues at this point. Following use of AChEI the slopes for use of all classes of antipsychotics and antidepressants continued to increase over the next year but at a reduced rate, i.e. 0.13 for antipsychotics, 0.27 for antidepressants. In contrast, in the year following first memantine use, there was a stabilisation in antidepressant use (slope -0.02) and a declining use of both atypical and typical antipsychotic medication (slope -0.22), Table 2. However, levels of antipsychotic and antidepressant use did not return to the levels before either memantine or AChEI use, Figure 4a-b. Although the prevalence of anxiolytic and



hypnotic drug use was higher in the memantine cohort, the slopes for anxiolytics were 0.22 and -0.12 in the year before and after memantine use compared to 0.06 and 0.01 before and after AChEI use. Hypnotic use showed a similar pattern, Table 2 and Figure 4c-d. The slope for use of all psychotropic drugs showed a statistically significant change in the year before and after use of AChEI and memantine.

## Discussion

The mean prevalence of AP use over the period 1995-2011 on the day the first recording of a dementia diagnosis was noted was 12.5%, decreasing markedly from 19.9% in 1995 to 7.4% in 2011. This reduction is to be welcomed given the concerns about the over-prescription of APs and probably reflects on the increased publicity about the excessive prescribing [12] and the risks of their use versus their limited benefits.

In contrast there was a steady increase in the use of antidepressants (10.7% to 26.3%) and a small increase in the use of anxiolytics. The matched non-dementia cohort showed a lower but nearly constant use of antipsychotics and anxiolytics but also showed a rise in antidepressant use (5.9% to 13.4%). Both groups showed a decrease in the use of hypnotics.

Antipsychotic use in patients with a first dementia diagnosis between 2005 and 2011 increased from 2.2% 10 years prior to the dementia diagnosis to 5.1% one year preceding the dementia diagnosis and 11.1% at the time of entering the dementia diagnosis on the CPRD.

In the same period and compared to non-dementia there was also an excess use of antidepressants increasing from 7.2% to 18.6% among people with dementia.

Neuropsychiatric symptoms are common in dementia but increasing attention is being paid to their occurrence in the prodromal stages leading up to dementia. In a population-based study, the most common neuropsychiatric symptoms in people with Mild Cognitive Impairment

(MCI) were apathy, depression, agitation, delusions, hallucinations and sleep impairment.

[26] In MCI patients, neuropsychiatric symptoms were associated with a higher risk of dementia onset. Depression in MCI has also been reported to double the risk of dementia.

[27] The increasing prescription of psychotropic medication in the years before the diagnosis of dementia may therefore be reflecting the symptomatology that often precedes the development and diagnosis of dementia; it may also reflect a tendency to switch from prescribing an antipsychotic drug to an antidepressant.

Although still lower than might have been expected, referral to specialists was noted to increase over the period 1995 to 2011. This may partly reflect the way information is collected in the CPRD but probably mainly reflects the lack of licensed drug treatments in 1995 (donepezil being the first to become available in 1997) and the large increase since then in the number of memory clinics and old age psychiatrists. Memantine users were more likely to have a record of referral to a psychiatrist or geriatrician in the 182 days before the first prescription than AChEI users. The NICE guidance on the use of these drugs in the treatment of AD, first issued in 2001, has always recommended that treatment should be initiated by a specialist and prescribing taken over by general practitioners as part of a shared care protocol. [25]. It is likely therefore that drug treatment may have been initiated a few months before the first date that it was noted on the GPRD when the initial prescription has been provided by the specialist. Some GPs may have initiated treatment but it is less likely that they would have initiated treatment with memantine during this time given the initial recommendation of NICE in 2006 about the compound. Practice also varies across the UK such that in some areas GPs are advised that they should not prescribe these compounds at all, in which case prescribing remains with the specialist and would not be noted on the CPRD.

For the subcohorts treated with antidementia drugs, there were far greater numbers who received an AChEI in comparison with either memantine alone or in combination with an

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3 AChEI, reflecting the somewhat restricted use of memantine during this time as a result of  
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5 not being recommended by NICE in 2006 (subsequently altered in the revised guidance of  
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7 2011), [25]. The mean duration of dementia at first prescription was less for an AChEI (0.7  
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9 years) than either memantine (1.4 years) or the combination of an AChEI with memantine  
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11 (2.6 years). The AChEIs are usually the first drugs to be used and are approved for use in  
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13 mild to moderate AD whereas memantine is approved for moderate to severe AD so it would  
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15 be predicted that memantine would be used later in the course of the illness. This would also  
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17 explain the sharper rise in the use of antidepressants and antipsychotic medication at the  
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19 commencement of memantine therapy compared with AChEI therapy; patients with more  
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21 advanced disease would be expected to display more behavioural and psychological  
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23 symptoms.  
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28 The four classes of psychotropic drugs were more frequently prescribed in the memantine  
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30 group than in the AChEI group not only on the index day but also in the 5 years prior to  
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32 prescribing. In addition, whilst the slopes for monthly use of antipsychotics and  
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34 antidepressants were positive in the year leading up to either AChEI or memantine use, the  
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36 slope was steeper in the memantine cohort. There was also an acute increase in antipsychotic  
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38 and antidepressant medication at the start of antidementia drug therapy but again this was  
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40 more prominent for the patients initiated on memantine. More memantine patients were  
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42 taking anxiolytics and hypnotics on the index date than AChEI patients, which may reflect an  
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44 increase in behavioural problems such as anxiety and sleep disturbance in patients who are  
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46 then started on memantine. This suggests that there may be differences in the type of patient  
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48 selected to receive memantine. Memantine has been shown to have a beneficial effect on the  
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50 behavioural and psychological symptoms of dementia (BPSD) in clinical trials [15, 16] and a  
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52 Cochrane Review meta-analysis showed that AD patients taking memantine were less likely  
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54 to develop agitation. [28] Thus, patients may be selected to receive memantine partly because  
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of behavioural issues that are reflected in the higher levels of prescribing of psychotropic drugs at the time the memantine is initiated.

There are also differences after the initiation of either AChEIs or memantine. For AChEI users the slopes for antipsychotic and antidepressant use continued to increase but at a reduced rate whereas for memantine users there was a stabilisation in antidepressant use and a decline in the use of atypical and typical antipsychotic medication. This supports the idea that memantine may reduce behavioural problems such as agitation and reduce or delay the need to prescribe antipsychotic medication.

The data for antidepressant and antipsychotic use after initiation of memantine are similar to the results from the French National Health Care Database where the onset of memantine therapy was associated with a stabilisation of psychotropic drug use. [20]

**Strengths and limitations**

This study has used the extensive data provided within the CPRD to examine the use of psychotropic drugs, and particularly antipsychotic medication in people with dementia including those receiving treatment with antidementia drugs (AChEIs and/or memantine).

Although the numbers receiving memantine are considerably lower than those receiving AChEIs, this reflects the prescribing pattern over the period studied and also that the NICE Guidance on drug treatment for AD did not formally recommend memantine until its most recent review. [25]

It is plausible that patients were diagnosed at an earlier stage of the AD because of the increasing awareness about dementia and from 1997 onwards the availability of drug treatments for people with mild to moderate AD. As behaviours such as agitation and aggression become more common as the disease becomes more severe [29] and the use of antipsychotics tends to increase, the apparent decrease in use of AP in our study could have

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3 resulted from the earlier diagnosis of AD. In this case, we would have overestimated the  
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5 reduction of AP use. However, the fact that the mean age at the time of the first AD diagnosis  
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7 was stable over the entire study period does not support this alternative explanation.  
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11 The evaluation of the duration of AD treatment and of the use of psychotropic drugs in this  
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13 analysis is based on drugs prescribed or recorded by GPs. The use of AD medications and of  
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15 psychotropic drugs is assumed to start on the date of the recording of the respective  
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17 medication but we may have missed initial prescriptions where this was provided to the  
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19 patient directly by a specialist and not recorded by the GP although subsequent prescriptions  
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21 may be issued and recorded by the GP. Antidementia drugs prescribed exclusively by  
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23 hospital specialists will not be fully captured by the GP and there are areas in the UK where  
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25 all prescriptions for anti-dementia drugs are still only issued by specialists.  
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## 28 29 30 **Conclusions**

31  
32 Over the period 1995-2011, there has been a marked reduction in the prevalence of  
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34 antipsychotic drug use on the day that a diagnosis of dementia was first noted by GPs. In  
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36 contrast there was a steady increase in antidepressant use, a small increase in anxiolytic use  
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38 and a decrease in hypnotic use. Antipsychotic use did increase over the 10 years prior to the  
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40 dementia diagnosis with a more marked increase in the year before the dementia diagnosis on  
41  
42 the CPRD. Antidepressant use increased exponentially over the 10 years prior to the dementia  
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44 diagnosis. Psychotropic drugs were more frequently prescribed in the memantine treated  
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46 subgroup than in the AChEI subgroup not only on the index day but also in the 5 years prior  
47  
48 to prescribing. The slopes for use of antipsychotics and antidepressants were positive in the  
49  
50 year leading up to either AChEI or memantine use; the slope was steeper in the cohort  
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52 eventually started on memantine with an immediate increase at the start of antidementia drug  
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54 therapy that was again more prominent for patients initiated on memantine suggesting that  
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this cohort was experiencing more behavioural and psychological symptoms and likely to have more advanced dementia.

There were also differences between the subcohorts after the initiation of antidementia drugs. For AChEI users the slopes for antipsychotic and antidepressant use continued to increase but at a reduced rate whereas for memantine users there was a stabilisation in antidepressant use and a decline in the use of atypical and typical antipsychotic medication.

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**Contributorship:**

CM and RJ conceived of and designed the study. SR and CM performed the statistical analyses. CM, SR and RJ interpreted the results. CM and RJ drafted the manuscript. All authors revised the manuscript for intellectual content, and read and approved the final manuscript.

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**Conflict of interest:**

Yes, I will upload an ICMJE conflicts of interest form for each author of this manuscript.

**Data sharing:**

No additional data are available.

**Table 1: Characteristics of patients in dementia cohort and subset treated with memantine, AChEI and the combination of memantine and AChEI**

	Complete dementia cohort	Dementia cohort	Dementia cohort	Matched control cohort	Memantine subcohort	AChEI subcohort	Memantine plus AChEI subcohort
Study period	1995 to 2011	1995	2011	1995 to 2011	2003 to 2011	2003 to 2011	2003 to 2011
Total	50439	879	3108	50439	669	10794	379
Males	17432 (34.6)	304 (34.6)	1170 (37.6)	17432 (34.6)	243 (36.3)	3855 (35.7)	156 (41.2)
Age mean ± SD	82.0±7.3	81.7±7.3	82.5±7.4	82.0±7.3	79.9±7.5	79.4±7.0	76.4±7.1
Median age	83	82	83	83	80	80	77
Age 60 to 64	896 (1.8)	9 (1.0)	48 (1.5)	896 (1.8)	25 (3.7)	324 (3.0)	16 (4.2)
65 to 69	2058 (4.1)	50 (5.7)	118 (3.8)	2058 (4.1)	43 (6.4)	670 (6.2)	52 (13.7)
70 to 74	4798 (9.5)	89 (10.1)	287 (9.2)	4798 (9.5)	77 (11.5)	1502 (13.9)	73 (19.3)
75 to 80	9610 (19.1)	161 (18.3)	510 (16.4)	9610 (19.1)	150 (22.4)	2608 (24.2)	111 (29.3)
80 to 84	13383 (26.5)	243 (27.6)	812 (26.1)	13383 (26.5)	194 (29.0)	3112 (28.8)	76 (20.1)
85 to 90	12414 (24.6)	206 (23.4)	817 (26.3)	12414 (24.6)	118 (17.6)	1978 (18.3)	41 (10.8)
≥90	7280 (14.4)	121 (13.8)	516 (16.6)	7280 (14.4)	62 (9.3)	600 (5.6)	10 (2.6)
First recording of dementia after index prescription of antdementia drug (%)					38 (5.7)	948 (8.8)	14 (3.7)
Duration of dementia at time of first use of antdementia drug (mean years ± SD					1.4±1.7	0.7±1.1	2.7±2.0
Referral to specialist* in previous 6 months	25205 (50.0)	224 (25.5)	2010 (64.7)	1265 (2.5)	454 (67.9)	6549 (60.7)	173 (45.6)

Previous use of memantine					0 (0.0)	9 (0.1)	35 (9.2)
Previous use of AChEI					119 (17.8)	0 (0.0)	342 (90.2)
<b>Use of antipsychotics at or before index day</b>							
Index day	6289 (12.5)	175 (19.9)	231 (7.4)	1322 (2.6)	175 (26.2)	1143 (10.6)	89 (23.5)
1 to 182 days	7394 (14.7)	197 (22.4)	300 (9.7)	2439 (4.8)	182 (27.2)	1325 (12.3)	108 (28.5)
183 to 365 days	4950 (9.8)	135 (15.4)	225 (7.2)	2403 (4.8)	128 (19.1)	906 (8.4)	80 (21.1)
1 to 2 years	5329 (10.6)	123 (14.0)	256 (8.2)	3218 (6.4)	122 (18.2)	930 (8.6)	67 (17.7)
2 to 3 years	4792 (9.5)	105 (11.9)	246 (7.9)	3157 (6.3)	89 (13.7)	783 (7.5)	43 (11.5)
3 to 4 years	4353 (8.6)	99 (11.3)	234 (7.5)	2937 (5.8)	78 (12.6)	677 (6.8)	32 (8.7)
4 to 5 years	3685 (8.0)	63 (8.3)	225 (7.6)	2583 (5.6)	58 (9.7)	611 (6.5)	25 (7.1)
≥5 years	7298 (17.3)	43 (7.6)	603 (21.0)	5983 (14.2)	111 (19.6)	1440 (16.4)	65 (19.1)
<b>Use of antidepressants at or before index day</b>							
Index day	11164 (22.1)	94 (10.7)	817 (26.3)	4981 (9.9)	228 (34.1)	2843 (26.3)	134 (35.4)
1 to 182 days	13165 (26.1)	129 (14.7)	922 (29.7)	6189 (12.3)	239 (35.7)	3130 (29.0)	142 (37.5)
183 to 365 days	11204 (22.2)	107 (12.2)	801 (25.8)	5807 (11.5)	201 (30.0)	2832 (26.2)	127 (33.5)
1 to 2 years	11284 (22.4)	115 (13.1)	782 (25.2)	6417 (12.7)	209 (31.2)	2716 (25.2)	129 (34.0)
2 to 3 years	10014 (19.9)	107 (12.2)	667 (21.5)	5970 (11.8)	177 (27.2)	2234 (21.4)	109 (29.1)
3 to 4 years	8912 (17.7)	87 (9.9)	618 (19.9)	5535 (11.0)	142 (22.9)	1897 (19.0)	94 (25.6)
4 to 5 years	7420 (16.1)	70 (9.2)	524 (17.6)	4800 (10.4)	120 (20.1)	1534 (16.3)	73 (20.7)
≥5 years	9565 (22.7)	43 (7.6)	809 (28.2)	7164 (17.0)	158 (28.0)	2149 (24.4)	102 (29.9)
<b>Use of anxiolytics at or before index day</b>							
Index day	2265 (4.5)	24 (2.7)	123 (4.0)	1327 (2.6)	88 (13.2)	444 (4.1)	51 (13.5)
1 to 182 days	3304 (6.6)	36 (4.1)	188 (6.0)	2075 (4.1)	116 (17.3)	668 (6.2)	67 (17.7)

183 to 365 days	2506 (5.0)	24 (2.7)	132 (4.2)	1988 (3.9)	87 (13.0)	593 (5.5)	42 (11.1)
1 to 2 years	2901 (5.8)	41 (4.7)	159 (5.1)	2354 (4.7)	89 (13.3)	646 (6.0)	46 (12.1)
2 to 3 years	2778 (5.5)	52 (5.9)	159 (5.1)	2356 (4.7)	75 (11.5)	541 (5.2)	46 (12.3)
3 to 4 years	2698 (5.4)	49 (5.6)	146 (4.7)	2295 (4.6)	65 (10.5)	509 (5.1)	40 (10.9)
4 to 5 years	2448 (5.3)	44 (5.8)	146 (4.9)	2014 (4.4)	60 (10.1)	461 (4.9)	29 (8.2)
≥5 years	4624 (11.0)	26 (4.6)	387 (13.5)	3904 (9.3)	108 (19.1)	1024 (11.6)	60 (17.6)
Use of hypnotics at or before index day							
Index day	4935 (9.8)	114 (13.0)	246 (7.9)	3662 (7.3)	123 (18.4)	899 (8.3)	75 (19.8)
1 to 182 days	6287 (12.5)	137 (15.6)	317 (10.2)	4559 (9.0)	145 (21.7)	1066 (9.9)	87 (23.0)
183 to 365 days	5267 (10.4)	115 (13.1)	275 (8.8)	4437 (8.8)	131 (19.6)	916 (8.5)	68 (17.9)
1 to 2 years	5690 (11.3)	129 (14.7)	322 (10.4)	4913 (9.7)	128 (19.1)	980 (9.1)	64 (16.9)
2 to 3 years	5472 (10.8)	127 (14.4)	288 (9.3)	4872 (9.7)	97 (14.9)	901 (8.6)	53 (14.1)
3 to 4 years	5266 (10.4)	128 (14.6)	293 (9.4)	4732 (9.4)	84 (13.6)	859 (8.6)	47 (12.8)
4 to 5 years	4669 (10.1)	106 (13.9)	271 (9.1)	4198 (9.1)	66 (11.1)	777 (8.2)	37 (10.5)
≥5 years	6611 (15.7)	71 (12.5)	489 (17.1)	5832 (13.9)	123 (21.8)	1296 (14.7)	70 (20.5)

\*Referrals to psychiatrist, geriatrician or neurologist; index day: day of first diagnosis of dementia in dementia cohort, respective day in the matched control cohort, or day of first use of memantine or an acetylcholinesterase inhibitor (AChEIs)

Table 2: Summary results: slope of the fitted regression line for the prevalence of concomitant psychotropic treatment in year before and after first use of memantine, 2005 to 2011

	Memantine			AChEI		
	Slope 12 months before	Slope 12 months after	Slope difference (95% CI)	Slope 12 months before	Slope 12 months after	Slope difference (95% CI)
<b>Antipsychotics</b>	<b>0.69</b>	<b>-0.22</b>	<b>0.91 (0.73, 1.09)</b>	<b>0.36</b>	<b>0.13</b>	<b>0.23 (0.20, 0.26)</b>
Atypical antipsychotics	0.6	-0.19	0.79 (0.62, 0.96)	0.3	0.1	0.20 (0.18, 0.23)
Typical antipsychotics	0.12	-0.09	0.21 (0.12, 0.30)	0.06	0.03	0.04 (0.02, 0.05)
<b>Antidepressants</b>	<b>0.56</b>	<b>-0.02</b>	<b>0.58 (0.38, 0.79)</b>	<b>0.47</b>	<b>0.27</b>	<b>0.19 (0.14, 0.24)</b>
Tricyclic antidepressants	0.05	-0.17	0.22 (0.13, 0.31)	0	0.03	-0.04 (-0.06, -0.01)
SSRI	0.33	0.01	0.33 (0.15, 0.50)	0.34	0.15	0.20 (0.16, 0.24)
Other antidepressants	0.22	0.06	0.16 (0.04, 0.28)	0.17	0.1	0.07 (0.05, 0.09)
<b>Anxiolytics</b>	<b>0.22</b>	<b>-0.12</b>	<b>0.34 (0.21, 0.48)</b>	<b>0.06</b>	<b>0.01</b>	<b>0.04 (0.02, 0.06)</b>
<b>Hypnotics</b>	<b>0.16</b>	<b>-0.26</b>	<b>0.42 (0.26, 0.59)</b>	<b>0.11</b>	<b>0</b>	<b>0.11 (0.08, 0.14)</b>

Figure 1a-b: Prevalence of psychotropic drug use in dementia and matched control cohort by year at the time of first dementia diagnosis or index day, 1995 to 2011

Figure 1a: Dementia cohort

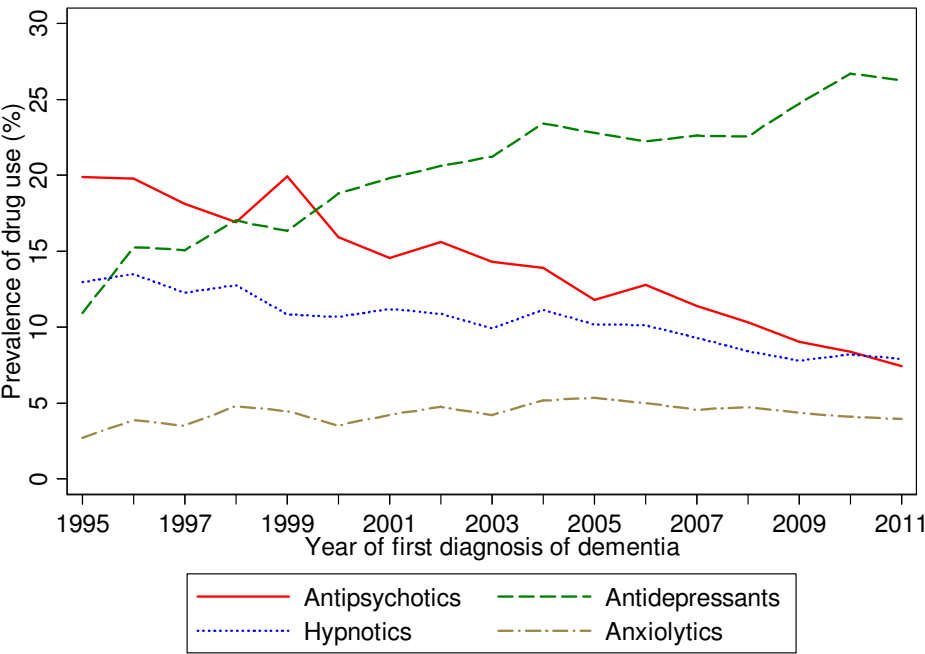




Figure 1b: Control cohort

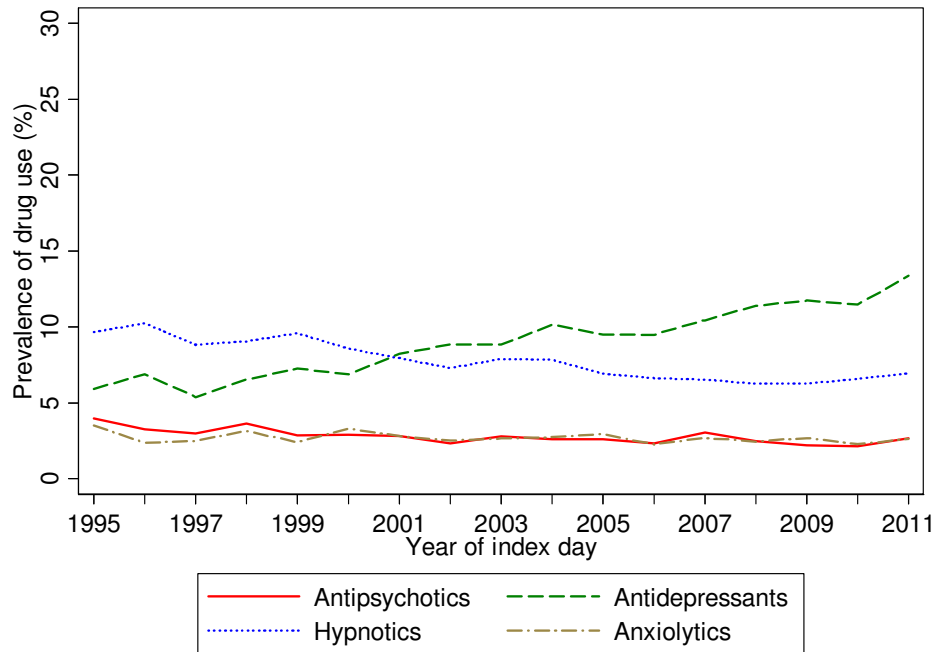
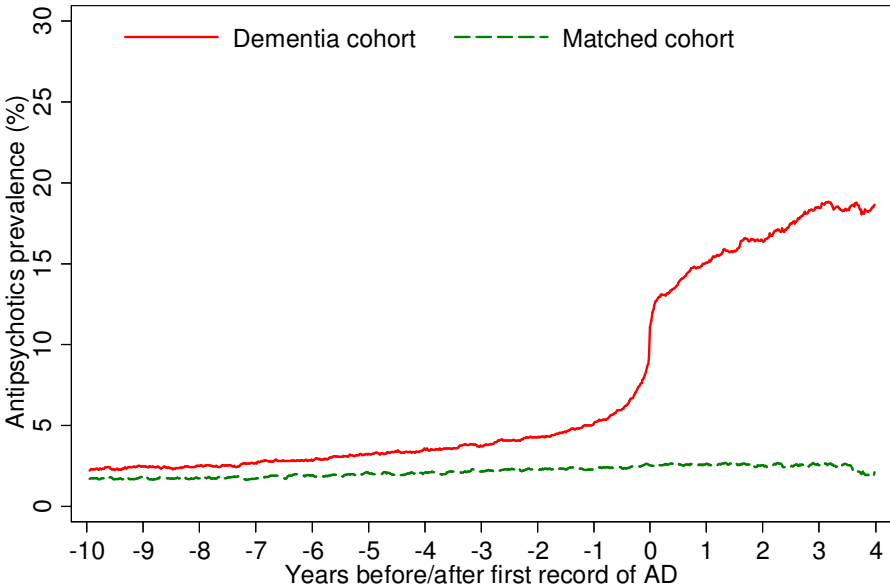


Figure 2a-d: Prevalence of psychotropic use in dementia cohort and in matched control cohort before and after the first dementia diagnosis for 2005 to 2011 cohort

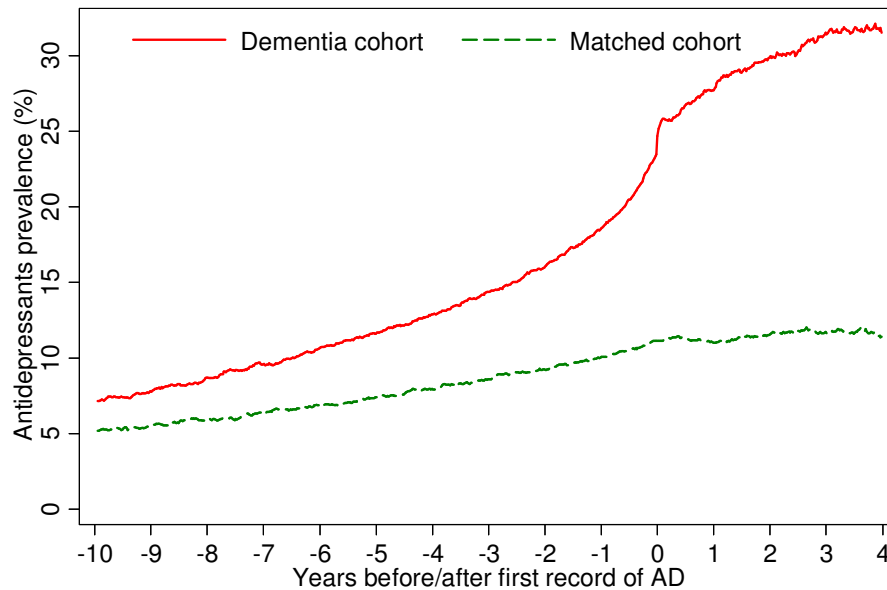
Figure 2a: Prevalence of antipsychotic use



Dem:	15619	20777	25476	29113	30803	30803	11073	3252
Ref:	16371	21347	25914	29333	30803	30803	15998	6721

Antipsychotics: typical antipsychotics (phenothiazines, butyrophenones, diphenylbutylpiperidines, thioxanthenes and substituted benzamides), and atypical antipsychotics (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone and zotepine).

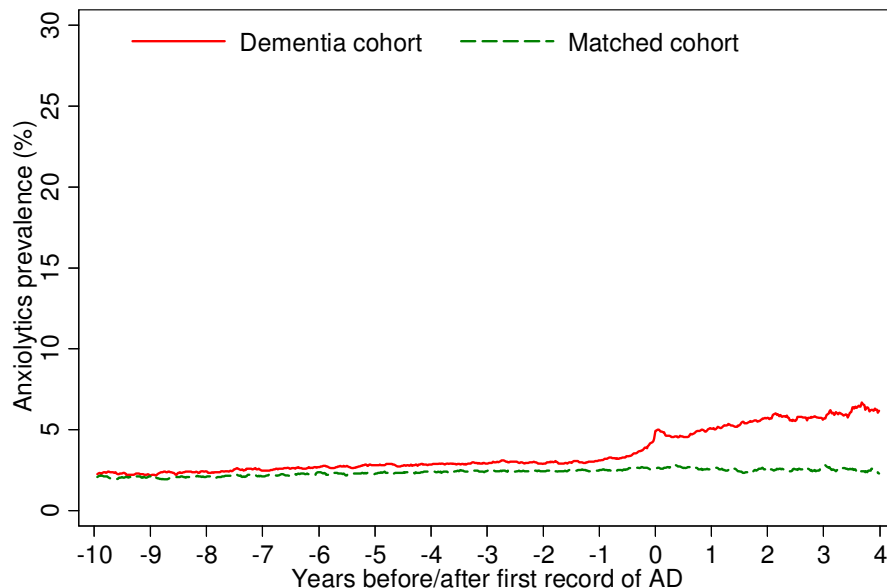
**Figure 2b: Prevalence of antidepressant use**



Dem:	15619	20777	25476	29113	30803	30803	11073	3252
Ref:	16371	21347	25914	29333	30803	30803	15998	6721

Antidepressants: tricyclic and related antidepressants, selective serotonin re-uptake inhibitors (SSRI) and other antidepressants.

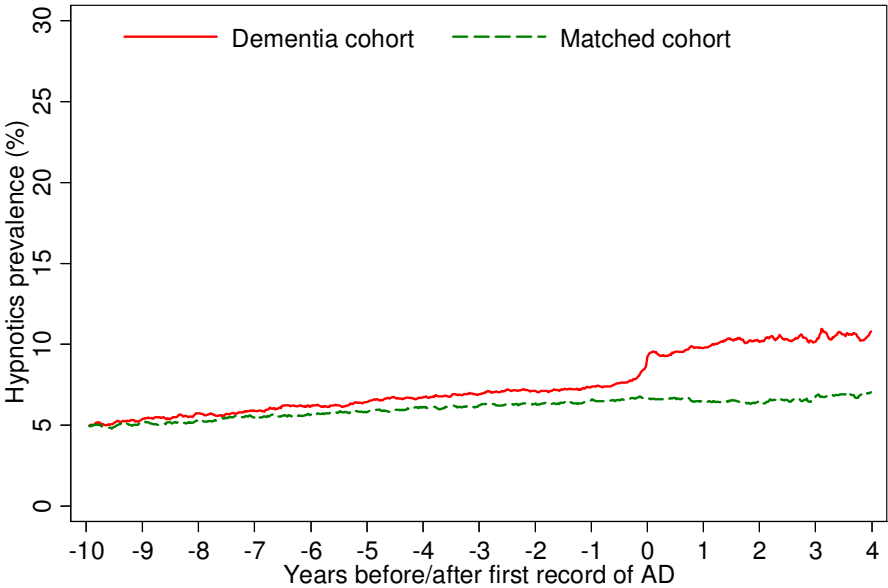
**Figure 2c: Prevalence of anxiolytic use**



Dem:	15619	20777	25476	29113	30803	30803	11073	3252
Ref:	16371	21347	25914	29333	30803	30803	15998	6721

Anxiolytics: buspirone, chlordiazepoxide, diazepam, hydroxyzine and lorazepam.

Figure 2d: Prevalence of hypnotic use



Dem:	15619	20777	25476	29113	30803	30803	11073	3252
Ref:	16371	21347	25914	29333	30803	30803	15998	6721

Hypnotics: clomethiazole, chloral betaine, loperazolam, lormetazepam, nitrazepam, promethazine, temazepam, zaleplon, zolpidem and zopiclone.

**Figure 3a-d: Prevalence of psychotropic drug use in AChEI and memantine (Mem) subcohort in the 5 years preceding the first prescription (index day), excluding patients without a previous prescription for the other compound, AChEI or memantine, 2003 to 2011.**

**Figure 3a: Prevalence of antipsychotic use in AChEI and memantine subcohort**

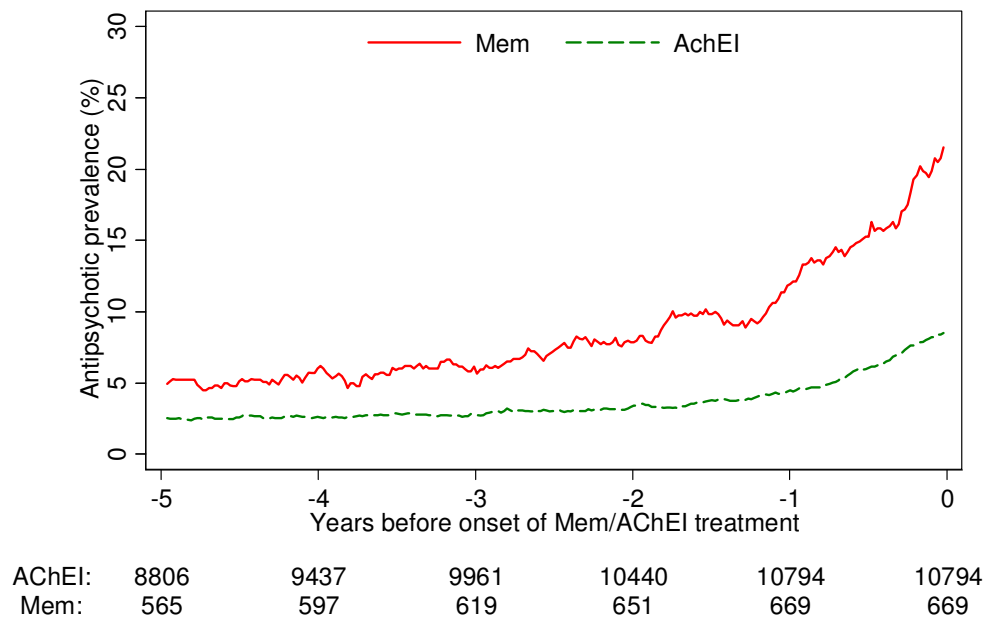


Figure 3b: Prevalence of antidepressant use in AChEI and memantine subcohort

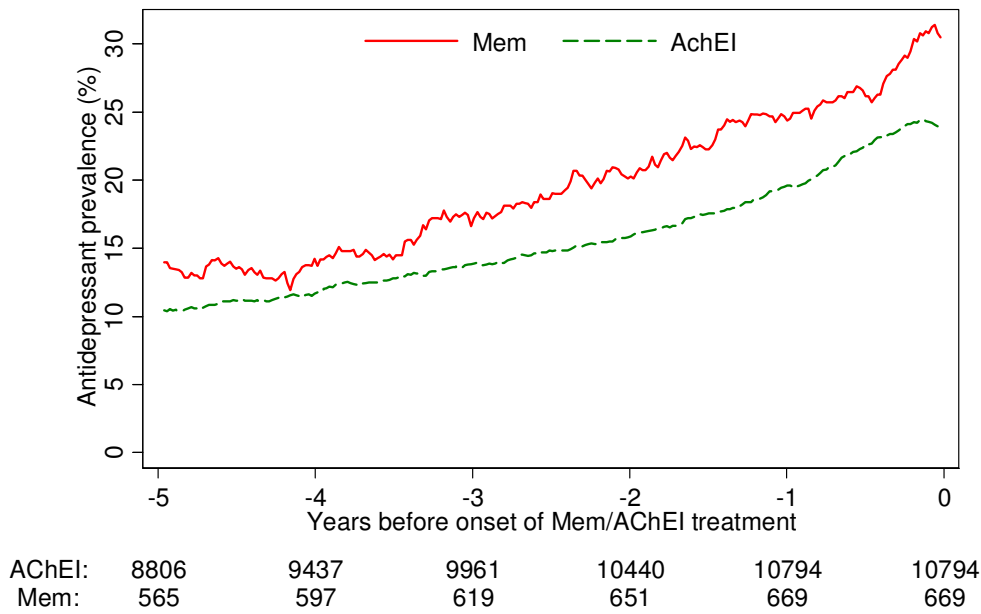
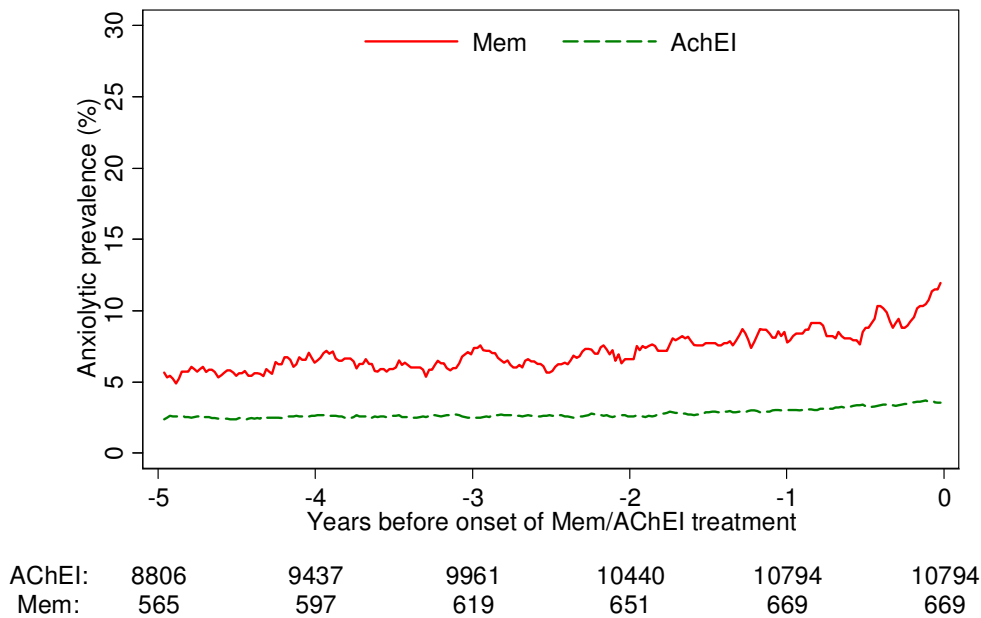
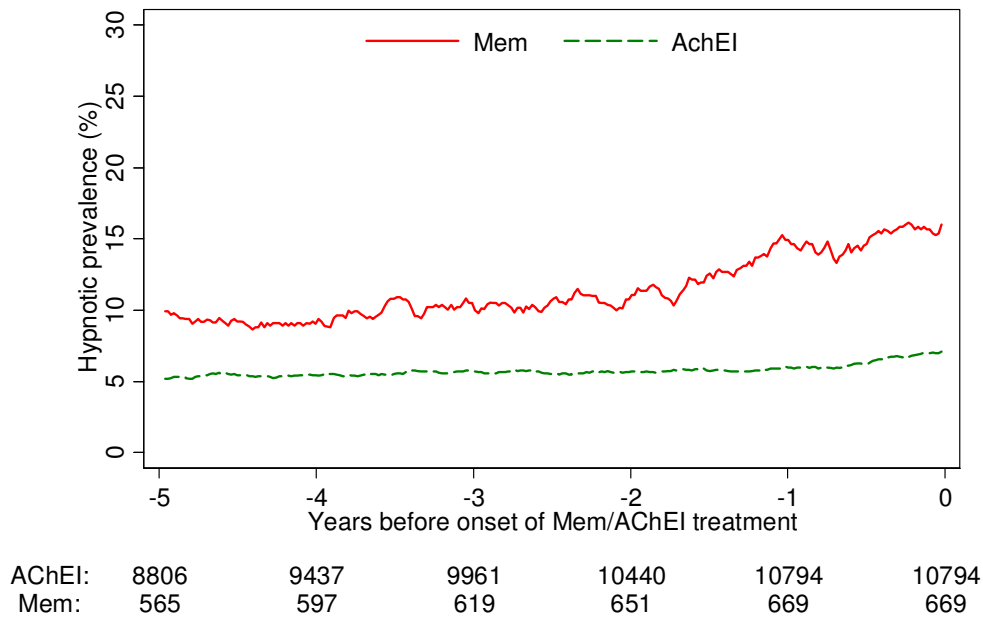


Figure 3c: Prevalence of anxiolytic use in AChEI and memantine subcohort



**Figure 3d: Prevalence of hypnotic use in AChEI and memantine subcohort**



review only

Figure 4a-d: Prevalence of antipsychotic and antidepressant use in the year before and after first use of AChEI and memantine, excluding patients without a previous prescription for the other compound, AChEI or memantine).

Figure 4a: Prevalence of antipsychotic and antidepressant use among AChEI users.

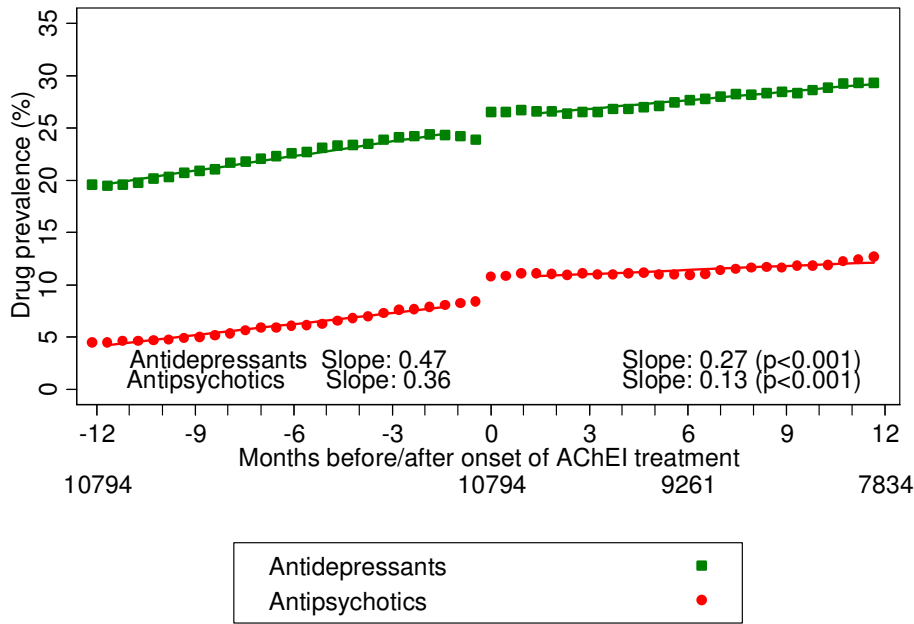




Figure 4b: Prevalence of antipsychotic and antidepressant use among memantine users.

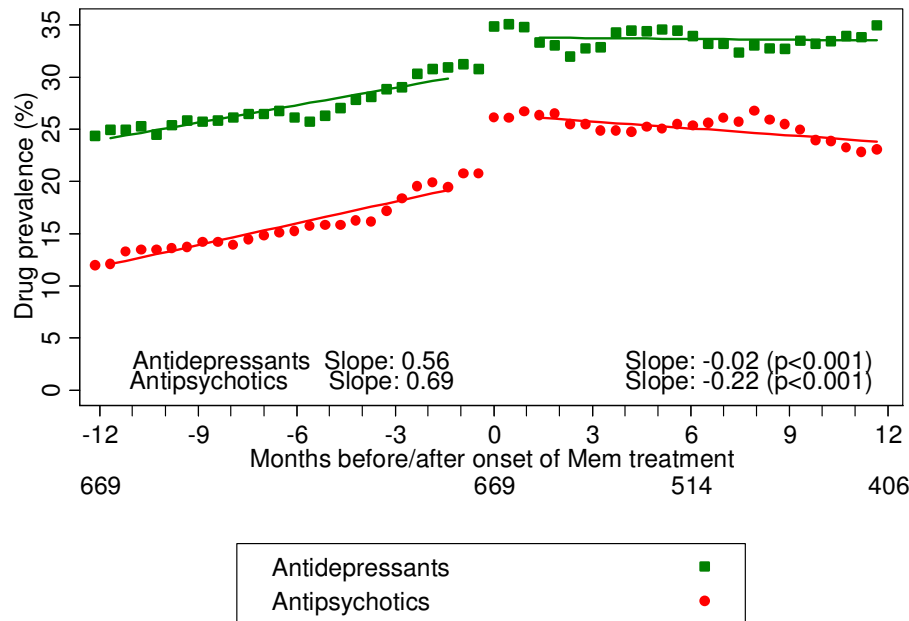


Figure 4c: Prevalence of anxiolytic and hypnotic use among AChEI users.

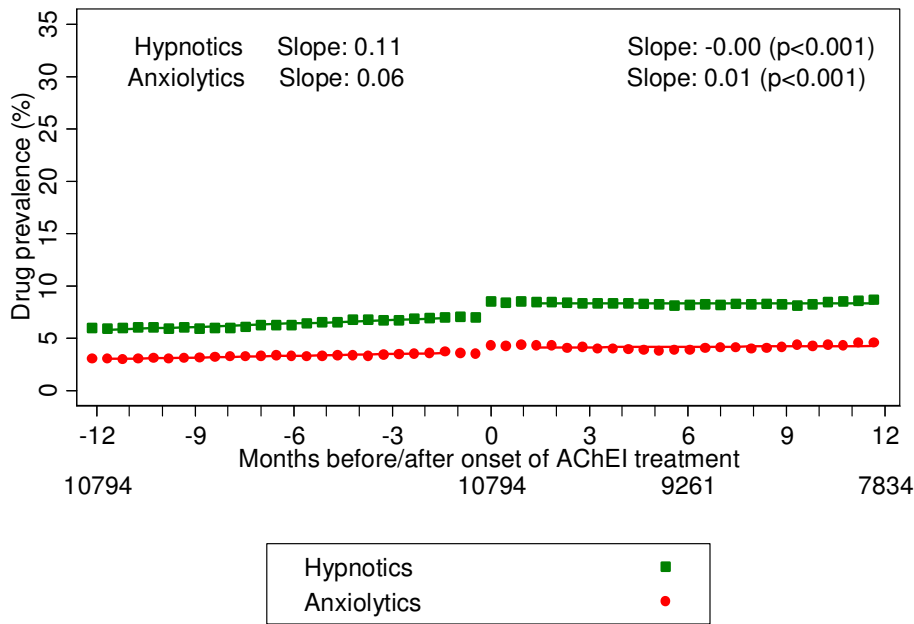
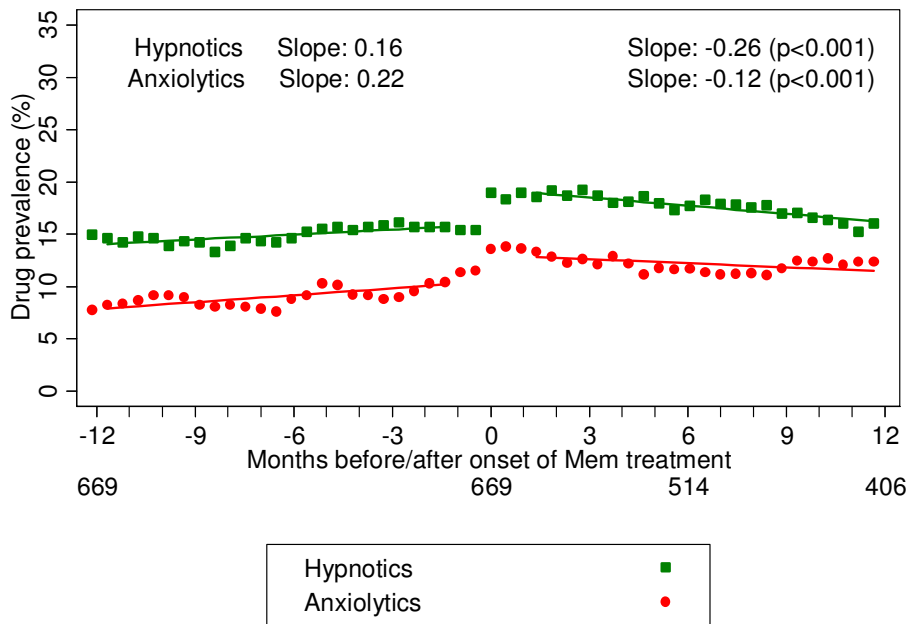


Figure 4d: Prevalence of anxiolytic and hypnotic use among memantine users.



## Article summary

### Article focus

- Antipsychotic medications (APs) have frequently been prescribed as the first-line pharmacological treatment approach for neuropsychiatric symptoms in Alzheimer's disease (AD) and other dementias (~~AD~~) but their use has been associated with several risk concerns
- To describe the pattern and trends of use of AP, antidepressants, hypnotics and anxiolytics in ~~AD and in~~ patients with dementia overall and in patients treated with antidementia medications, i.e. acetylcholinesterase inhibitors (AChEIs) and memantine in primary care in the UK.

### Key messages

- The mean prevalence of AP use on the first recording of a dementia was 12.5%, decreasing markedly from 19.9% in 1995 to 7.4% in 2011. In contrast, there was a steady increase in the use of antidepressants (10.7% to 26.3%) and a small increase in the use of anxiolytics.
- AP use in patients with a first dementia diagnosis between 2005 and 2011 increased from 2.2% 10 years prior to the dementia diagnosis to 5.1% one year preceding the dementia diagnosis and 11.1% at the time of entering the dementia diagnosis on the Clinical Practice Research Datalink (CPRD).
- The monthly use of AP increased in the year leading up to the first AChEI or memantine use; after treatment initiation the monthly use for those prescribed AChEIs continued to increase but at a reduced rate whereas antipsychotic use declined for those prescribed memantine.

### Strengths and limitations of this study

- The Clinical Practice Research Datalink (CPRD) is the largest primary care database in the world, containing the longitudinal records for up to 20 years of over 3 million patients
- There may have been a trend towards diagnosing dementia-AD at an earlier stage of the disease AD because of ~~the~~ increasing awareness about AD and other

~~dementia-related conditions~~ despite the fact that the mean age at the time of the first ~~dementia AD~~ diagnosis was stable over the entire study period.

- APs and antidementia drugs prescribed exclusively by hospital specialists are not completely recorded in CPRD

**Introduction**

~~Functional deficits and neuropsychiatric/behavioural symptoms contribute significantly to the disabilities associated with Alzheimer's disease (AD).~~ Up to 90% of patients with Alzheimer's disease (AD) and other dementias will experience neuropsychiatric symptoms (NPS) such as ~~hallucinations, delusions~~, aggressive behaviour, agitation, repetitive vocalizations, wandering, depression, sleep problems and psychosis (delusions, paranoia and hallucinations) ~~affective disturbances~~ during the course of their disease. [1,2] These symptoms can be amongst the most distressing aspects of ~~AD dementia~~, increasing caregiver burden, contributing to poor patient quality of life, and often triggering the transfer to institutional care. [1,3,4] In a survey of carers by Alzheimer Europe, behavioural symptoms including agitation, aggression, and irritability were cited more often than cognitive symptoms as the most problematic symptoms of AD (50% versus 45%). [1]

Antipsychotic medications (APs) have frequently been prescribed as the first-line pharmacological treatment approach for neuropsychiatric symptoms in ~~AD dementia~~ and other dementias but their use has been associated with several serious concerns. Treatment with APs has been shown to raise the risk of adverse events including cerebrovascular events, somnolence, and extrapyramidal symptoms as well as accelerated cognitive decline. [5-7] Furthermore, APs are associated with an increased mortality risk in elderly patients with and without ~~AD dementia~~. [7-9]

Only the atypical antipsychotic risperidone has use in AD included in its licensed indications within the European Community. This licence followed a review in 2008 and is restricted to

“the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer’s dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others”. [10] In the UK risperidone is included within the Black Triangle Scheme that identifies medicines whose safety profiles are monitored intensively; healthcare professionals are asked to report via the Yellow Card Scheme all suspected side-effects that occur in the treatment of elderly people with dementia.

The US Food and Drug Administration (FDA) has issued warnings against the use of typical and atypical APs in patients with dementia [11] and, in 2008, the UK Department of Health commissioned an independent report on the use of antipsychotic medication in people with dementia. [12] This report concluded that APs appear to have only a limited positive effect but can cause significant harm to people with dementia – including an additional 1,800 deaths and 1,620 cerebrovascular adverse events in the UK per year. [12] Although APs may offer benefit to some patients, the report generally recommended “reducing the use of antipsychotic drugs for people with dementia.” [12] The French High Authority for Health (HAS) raised similar concerns, criticising the excessive prescribing of APs to patients with AD. [13]

There is some evidence that the currently available anti-dementia agents – memantine and the acetylcholinesterase inhibitors (AChEIs) have beneficial effects on NPS behavioural disturbances in AD, and they are generally well tolerated [14-18] although the 12-week CALM-AD trial was unable to show that the AChEI donepezil was more effective than placebo in treating agitation in patients with AD. [19] Furthermore, a retrospective study in France has shown that there was an apparent increasing trend of AP use before the initiation of memantine therapy and that memantine stabilized the proportion of AP users. [20] In the United States, a study using national Veterans Affairs data has examined changes in atypical and atypical conventional antipsychotic use in outpatients with dementia from 1999 through

2007. [21] Use of atypical antipsychotics began to decline significantly in 2003, and after the Food and Drug Administration advisory warning in 2005 a further significant decline was evident.

The aim of the current study was to investigate the pattern and trends of use of psychotropic drugs (i.e., antipsychotics, antidepressants, hypnotics and anxiolytics) in people with dementia and their association with use of AChEIs (donepezil, galantamine, or rivastigmine) and memantine to better understand their use in primary care in the UK.

**Methods**

An observational cohort study was carried out using data from the UK Clinical Practice Research Datalink (CPRD), until 1st April 2012 known as the General Practice Research Database. Participating general practitioners (GPs) currently contribute data on more than 5 million patients and are broadly representative of the UK population in terms of age, gender and region. [22] The CPRD comprises data on patient demographics, medical diagnoses, all GP prescriptions (electronic issue), referrals to secondary care, and hospital discharge reports.

Patient findings and procedures are coded with Read medical codes, a coded thesaurus of clinical terms recommended particularly for use in primary care. [23] Prescription information includes date of prescription, drug substance, daily dose, daily quantity and number of packs/pack size. Dispensing information is not available. GP practices are required to meet defined quality standards before they can contribute to the CPRD.

**Study population and study design**

The study population consisted of patients in the CPRD at least 60 years of age and with at least three years history in the CPRD before a first diagnosis of dementia between 1 January 1995 and 30 June 2011. Dementia was defined by a-Read medical codes for Alzheimer’s

disease, vascular dementia or other dementia. A control cohort was generated by randomly selecting for each dementia patient, one control, matched on gender and year of birth but without a recording of dementia during the entire observational period. The date of the first diagnosis of dementia was defined as the index day in the dementia cohort, and the same date was taken as the index day for the matched control. Matched controls were also required to have a minimum of 3 years in the CPRD prior to the index day.

Two subcohorts were created by the first-time use of AChEI or memantine from 2003 to 2011 (with the index day based on first drug use rather than on first diagnosis of dementia) to assess the use of psychotropic medications in association with antidementia medication.

Almost all of the patients in these subcohorts will be receiving treatment for AD, either alone or as part of a mixed dementia, but the Read coding system does not necessarily provide an exact diagnosis of AD nor how the diagnosis was made. The date of the first prescription for an AChEI or memantine was defined as the index day for the subcohort analyses. Patients with both AChEI and memantine prescriptions were not analysed further. As some patients were given antidementia medications before the first recording of a dementia diagnosis, patients on AChEI and memantine were required to have a minimum of one year in the CPRD prior to the first use of an antidementia medication.

The study endpoint was the use of psychotropic medications (APs, antidepressants, anxiolytics and hypnotics). Use of any psychotropic medication was identified from recordings by the GP.

First, the prevalence of psychotropic drug use was assessed by its exposure status on the date of the first recording of a dementia diagnosis or index day of the respective matched controls for the complete study period of 1995 to 2011.

To investigate the temporal relationship between the use of psychotropic drugs in association with the first dementia diagnosis the study cohort was restricted to those with a first dementia diagnosis between 2005 and 2011 to estimate the prevalence of psychotropic use up to 10 years before and up to 4 years after the index day.

Psychotropic use in the AChEI and memantine subcohorts was assessed for up to 5 years before and up to one year after first use of AChEI or memantine.

**Data analysis**

For each prescription of a psychotropic drug, a prescription-specific duration was calculated from the number of tablets prescribed combined with the dosing instructions and adding a grace period of 30 days. The 30-day grace period was used to allow for any residual effect of the drug or any remaining medication due to a lack of compliance. The prescription-specific duration was used to calculate the exposure prevalence of each psychotropic drug class per week of the observational period.

The prevalence of AP and antidepressant use attributable to dementia was estimated by subtracting the prevalence of APs and antidepressants in the matched cohort from the respective prevalence of the dementia cohort.

For each month up to the year before and after initiation of treatment with AChEI or memantine, the proportion of patients using psychotropic medications (APs, antidepressants, anxiolytics and hypnotics) was estimated. The weekly ~~or monthly~~ prevalence of psychotropic drug use was described using binomial regression and the method of generalized estimating equations for AChEI and memantine use separately [24] and ~~for the antedementia drug use~~ shown as the slope of the fitted regression line for the year before and separately for the year after first use of AChEI and memantine respectively. Trends of psychotropic drug use before and after initiation of AChEI and memantine respectively were tested for statistical



significance using the Wald's test whereby the slope describes the monthly percent of AD patients taking the respective psychotropic medication during pre- and post first recording of AChEI and memantine. All analyses were performed with STATA MP ~~Intercooled~~ Version 12.1 (StataCorp LP). The study protocol was approved by the Independent Scientific Advisory Committee for GPRD research.

## Results

### Dementia cohort

A total of 50,349 patients with a first-time diagnosis of dementia were identified in the CPRD between 1995 and June 2011. The mean age of dementia patients was 82.0 years with 34.6% males. There was an increasing trend over time for patients with dementia to be seen by a specialist, i.e. psychiatrists, geriatricians or neurologists, from 25.5% in 1995 to 64.7% in 2011.

At the time of the first dementia diagnosis between 1995 and 2011, 12.5% were given antipsychotics, 22.1% antidepressants, 4.5% anxiolytics and 9.8% hypnotics. The age at first dementia diagnosis increased from 81.7 to 82.5 years and the proportion of men from 34.6% to 37.6% from 1995 to 2011, Table 1. Over the years 1995 to 2011, the prevalence of AP use on the day of the first dementia diagnosis decreased from 19.9% to 7.4%. There was a steady increase in antidepressant use (10.7% to 26.3%), a small increase in anxiolytic use (2.7% to 4.0%), and a decrease in hypnotic use (13.0% to 7.9%). The matched cohort without dementia showed a nearly constant use of antipsychotics and anxiolytics during the entire study period, a small decrease in the use of hypnotics, but also an increase in the use of antidepressants (5.9% to 13.4%), Figures 1a-b.

In patients with a first dementia diagnosis between 2005 and 2011 and with up to 10 years of medical history, antipsychotic use was 2.2% 10 years prior to the dementia diagnosis and increased linearly up until one year preceding the dementia diagnosis to 5.1%; on the date of the dementia diagnosis it was 11.1% and then it increased to 18.7% after a further 4 years. In the matched cohort and during the same period antipsychotic use was nearly constant ranging between 1.7% and 2.6%, Figure 2a. A similar pattern was observed in the use of antidepressants. For patients with a dementia diagnosis, antidepressant use increased from 7.2% 10 years before and 18.6% one year before the dementia diagnosis, to 24.7% on the date of the diagnosis, and to 31.6% four years after the dementia diagnosis, compared to 10.1%, and 11.4% for the matched cohort for the same time period, Figure 2b. Anxiolytics and hypnotic use only started to increase noticeably in the year before the dementia diagnosis, Figure 2c-d.

**AChEI and/or memantine subcohort**

Within the dementia cohort, 10,794 patients were treated with an AChEI, 669 with memantine and 379 with both an AChEI and memantine. The mean ~~duration of dementia at first prescription~~time since dementia diagnosis was 0.7 years in the AChEI group, 1.4 years in the memantine group and 2.6 years in the AChEI and memantine group. Age and gender were comparable in the AChEI and memantine subgroups, but patients on both AChEI and memantine were younger and more often males. Memantine users were more likely to have a record of a referral to a psychiatrist/geriatrician in the 182 days before the first prescription compared to AChEI users (67.9% vs. 60.7%). A total of 17.8% of first-time users of memantine were recorded as having been given AChEI previously, Table 1.

During the 5-year period prior to the index prescribing of memantine or AChEI each of the 4 classes of psychotropic drugs was more frequently prescribed in the memantine group

compared to the AChEI group, Table 1 and Figure 3a-bd. On the index day, 26.2% of memantine and 10.6% of AChEI patients were prescribed antipsychotics, 34.1% and 26.3% respectively were prescribed antidepressants, 13.2% and 4.1% anxiolytics and 18.4% and 8.3% hypnotics, Table 1.

The slope for all classes of antipsychotics and antidepressants were positive in the 12 months leading up to memantine and AChEI use but steeper in the memantine cohort, i.e. antipsychotics: memantine 0.69 versus AChEIs 0.36; antidepressants: memantine 0.56 versus AChEIs 0.47, Table 2. There was an acute increase of antipsychotic and antidepressant medication at the start of memantine and AChEI use respectively. The sharp increase was more prominent among memantine users, Figure 4a-b, suggesting that they had more behavioural issues at this point. Following use of AChEI the slopes for use of all classes of antipsychotics and antidepressants continued to increase over the next year but at a reduced rate, i.e. 0.13 for antipsychotics, 0.27 for antidepressants. In contrast, in the year following first memantine use, there was a stabilisation in antidepressant use (slope -0.02) and a declining use of both atypical and typical antipsychotic medication (slope -0.22), Table 2. However, levels of antipsychotic and antidepressant use did not return to the levels before either memantine or AChEI use, Figure 4a-b. Although the prevalence of anxiolytic and hypnotic drug use was higher in the memantine cohort, the slopes for anxiolytics were 0.22 and -0.12 in the year before and after memantine use compared to 0.06 and 0.01 before and after AChEI use. Hypnotic use showed a similar pattern, Table 2 and Figure 4c-d. The slope for use of all psychotropic drugs showed a statistically significant change in the year before and after use of AChEI and memantine, respectively.

## Discussion

The mean prevalence of AP use over the period 1995-2011 on the day the first recording of a dementia diagnosis was noted was 12.5%, decreasing markedly from 19.9% in 1995 to 7.4% in 2011. This reduction is to be welcomed given the concerns about the over-prescription of APs and probably reflects on the increased publicity about the excessive prescribing [12] and the risks of their use versus their limited benefits.

In contrast there was a steady increase in the use of antidepressants (10.7% to 26.3%) and a small increase in the use of anxiolytics. The matched non-dementia cohort showed a lower but nearly constant use of antipsychotics and anxiolytics but also showed a rise in antidepressant use (5.9% to 13.4%). Both groups showed a decrease in the use of hypnotics.

Antipsychotic use in patients with a first dementia diagnosis between 2005 and 2011 increased from 2.2% 10 years prior to the dementia diagnosis to 5.1% one year preceding the dementia diagnosis and 11.1% at the time of entering the dementia diagnosis on the CPRD. In the same period and compared to non-dementia there was also an excess use of antidepressants increasing from 7.2% to 18.6% among people with dementia.

~~Neuropsychiatric symptoms~~NPS are common in dementia but increasing attention is being paid to their occurrence in the prodromal stages leading up to dementia. In a population-based study, the most common ~~NPSneuropsychiatric symptoms~~ in people with Mild Cognitive Impairment (MCI) were apathy, depression, agitation, delusions, hallucinations and sleep impairment. [25] In MCI patients, ~~NPS neuropsychiatric symptoms~~ were associated with a higher risk of dementia onset. Depression in MCI has also been reported to double the risk of dementia. [26] The increasing prescription of psychotropic medication in the years before the diagnosis of dementia may therefore be reflecting the symptomatology that often precedes the ~~development and actual~~ diagnosis of dementia; ~~it may also reflect a tendency to switch from prescribing an antipsychotic drug to an antidepressant.~~

The recent UK National Dementia and Antipsychotic Prescribing Audit 2012 also showed a decrease in the prescribing of antipsychotics and hypnotics in people with dementia by GPs in England. In contrast to the present study, there was a similar reduction in the use of antidepressants. The 2012 Audit was voluntary and included about half of GP Practices whereas our data are taken from all practices contributing to the CPRD so the populations sampled are different.-[27]

If there has been a switch from prescribing antipsychotic drugs to antidepressant medication then this is not without risks, especially for older patients. A recent observational study found significant associations between the use of antidepressant drugs and several severe adverse outcomes in people aged 65 and over with depression. [28] More recently the recommended maximum doses of citalopram and escitalopram in older patients has been reduced following concerns about their association with increased electrical abnormalities of the heart. [29] On the other hand, a Cochrane review of antidepressants for agitation and psychosis in dementia [30] does suggest that from the limited data available that SSRIs and trazodone appeared to be well tolerated when compared to placebo or either atypical or typical antipsychotics.

Although still lower than might have been expected, referral to specialists was noted to increase over the period 1995 to 2011. This may partly reflect the way information is collected in the CPRD but probably mainly reflects the lack of licensed drug treatments in 1995 (donepezil being the first to become available in 1997) and the large increase since then in the number of memory clinics and old age psychiatrists. [31,32] Memantine users were more likely to have a record of referral to a psychiatrist or geriatrician in the 182 days before the first prescription than AChEI users. The NICE guidance on the use of these drugs in the treatment of AD, first issued in 2001, has always recommended that treatment should be initiated by a specialist and prescribing taken over by general practitioners as part of a shared care protocol. [33] It is likely therefore that drug treatment may have been initiated a few

months before the first date that it was noted on the GPRD when the initial prescription has been provided by the specialist. Some GPs may have initiated treatment but it is less likely that they would have initiated treatment with memantine during this time given the initial recommendation of NICE in 2006 about the compound. Practice also varies across the UK such that in some areas GPs are advised that they should not prescribe these compounds at all, in which case prescribing remains with the specialist and would not be noted on the CPRD.

For the subcohorts treated with antideementia drugs, there were far greater numbers who received an AChEI in comparison with either memantine alone or in combination with an AChEI, reflecting the somewhat restricted use of memantine during this time as a result of not being recommended by NICE in 2006 (subsequently altered in the revised guidance of 2011). [34] The mean duration of dementia at first prescription was less for an AChEI (0.7 years) than either memantine (1.4 years) or the combination of an AChEI with memantine (2.6 years). The AChEIs are usually the first drugs to be used and are approved for use in mild to moderate AD whereas memantine is approved for moderate to severe AD so it would be predicted that memantine would be used later in the course of the illness. This would also potentially explain the sharper rise in the use of antidepressants and antipsychotic medication at the commencement of memantine therapy compared with AChEI therapy; patients with more advanced disease would be expected to display more NPSbehavioural and psychological symptoms.

The four classes of psychotropic drugs were more frequently prescribed in the memantine group than in the AChEI group not only on the index day but also in the 5 years prior to prescribing. In addition, whilst the slopes for monthly use of antipsychotics and antidepressants were positive in the year leading up to either AChEI or memantine use, the slope was steeper in the memantine cohort. There was also an acute increase in antipsychotic

and antidepressant medication at the start of antimentia drug therapy but again this was more prominent for the patients initiated on memantine. More memantine patients were taking anxiolytics and hypnotics on the index date than AChEI patients, which may reflect an increase in behavioural problems such as anxiety and sleep disturbance in patients who are then started on memantine. This suggests that there may be differences in the type of patient selected to receive memantine. Memantine has been shown to have a beneficial effect on the ~~NPSneuropsychiatric symptoms~~ behavioural and psychological symptoms of dementia (BPSD) in clinical trials [15, 16] and a Cochrane Review meta-analysis showed that AD patients taking memantine were slightly less likely to develop agitation, although the review concluded that there was no evidence either way about whether memantine has an effect on agitation which is already present. [35] In a study of clinically significant agitation in subjects from care-homes or hospitals, memantine had no effect on the Cohen-Mansfield Agitation Inventory at either 6 or 12 weeks; the authors commented that it still remains to be determined whether memantine has a role in milder agitation in AD. [36] In the recent UK Donepezil and Memantine for moderate to severe Alzheimer's disease (DOMINO) study, memantine treatment was associated with a significantly smaller worsening of the Neuro Psychiatric Inventory Score, with a benefit that was equivalent to 83% of the 12-month deterioration (4.8 NPI points) seen in the group discontinuing donepezil and receiving placebo memantine, whereas the difference between those who continued donepezil and those who discontinued donepezil was not significant. [37] Thus, patients may be selected to receive memantine partly because of concern about behavioural issues and these may be that ~~are~~ reflected in the higher levels of prescribing of psychotropic drugs at the time the memantine is initiated.

There are also differences after the initiation of either AChEIs or memantine. For AChEI users the slopes for antipsychotic and antidepressant use continued to increase but at a



reduced rate whereas for memantine users there was a stabilisation in antidepressant use and a decline in the use of atypical and typical antipsychotic medication. ~~This supports the idea that memantine may reduce behavioural problems such as agitation and reduce or delay the need to prescribe antipsychotic medication.~~

The data for antidepressant and antipsychotic use after initiation of memantine are similar to the results from the French National Health Care Database where the onset of memantine therapy was associated with a stabilisation of psychotropic drug use. [20]

**Strengths and limitations**

This study has used the extensive data provided within the CPRD to examine the use of psychotropic drugs, and particularly antipsychotic medication in people with dementia including those receiving treatment with antidementia drugs (AChEIs and/or memantine). Although the numbers receiving memantine are considerably lower than those receiving AChEIs, this reflects the prescribing pattern over the period studied and also that the NICE Guidance on drug treatment for AD did not formally recommend memantine until its most recent review. [34]

It is plausible that patients were diagnosed at an earlier stage of their ~~ir dementia~~ AD because of the increasing awareness about ~~AD and related conditions~~ dementia and from 1997 onwards the availability of drug treatments for people with mild to moderate AD. As behaviours such as agitation and aggression become more common as the ~~disease-dementia~~ becomes more severe [38] and the use of antipsychotics tends to increase, the apparent decrease in use of AP in our study could have resulted from the earlier diagnosis of ~~AD~~ dementia. In this case, we would have overestimated the reduction of AP use. However, the fact that the mean age at the time of the first ~~AD~~ dementia diagnosis was stable over the entire study period does not support this alternative explanation.



The largest limitation of observational studies is selection bias, as to enter into the study cohort, an individual must have been diagnosed with Alzheimer's disease or another dementia, and for the subset treated with antidementia drugs to have a prescription of either memantine or of AChEIs. A selection bias would have occurred if patients with dementia were not representative of those in the general population regarding their pattern of psychotropic drug use. However, our data were drawn from all GP practices contributing to the CPRD which are deemed representative and a selection bias of GP practices is unlikely. Another potential limitation of observational data is that clinical information on NPS and on severity of dementia is incomplete and not recorded in a standardized structure in CPRD. Therefore, the association between psychotropic drug use in those treated with AChEI and memantine could have been confounded by severity of dementia. Severity of dementia would certainly have resulted in a preference for treatment with AChEIs or memantine.

The evaluation of the duration of ~~AD-antidementia~~ treatment and of the use of psychotropic drugs in this analysis is based on drugs prescribed or recorded by GPs. The use of ~~antidementia AD~~ medications and of psychotropic drugs is assumed to start on the date of the recording of the respective medication but we may have missed initial prescriptions where this was provided to the patient directly by a specialist and not recorded by the GP although subsequent prescriptions may be issued and recorded by the GP. Antidementia drugs prescribed exclusively by hospital specialists will not be fully captured by the GP and there are areas in the UK where all prescriptions for anti-dementia drugs are still only issued by specialists.

## Conclusions

Over the period 1995-2011, there has been a marked reduction in the prevalence of antipsychotic drug use on the day that a diagnosis of dementia was first noted by GPs. In

contrast there was a steady increase in antidepressant use, a small increase in anxiolytic use and a decrease in hypnotic use. Antipsychotic use did increase over the 10 years prior to the dementia diagnosis with a more marked increase in the year before the dementia diagnosis on the CPRD. Antidepressant use increased exponentially over the 10 years prior to the dementia diagnosis. Psychotropic drugs were more frequently prescribed in the memantine treated subgroup than in the AChEI subgroup not only on the index day but also in the 5 years prior to prescribing. The slopes for use of antipsychotics and antidepressants were positive in the year leading up to either AChEI or memantine use; the slope was steeper in the cohort eventually started on memantine with an immediate increase at the start of antidementia drug therapy that was again more prominent for patients initiated on memantine suggesting that this cohort was experiencing more behavioural and psychological symptoms and likely to have more advanced dementia.

There were also differences between the subcohorts after the initiation of antidementia drugs. For AChEI users the slopes for antipsychotic and antidepressant use continued to increase but at a reduced rate whereas for memantine users there was a stabilisation in antidepressant use and a decline in the use of atypical and typical antipsychotic medication.

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**Table 1: Characteristics of patients in dementia cohort and subset treated with memantine, AChEI and the combination of memantine and AChEI**

	Complete dementia cohort	Dementia cohort	Dementia cohort	Matched control cohort	Memantine subcohort	AChEI subcohort	Memantine plus AChEI subcohort
Study period	1995 to 2011	1995	2011	1995 to 2011	2003 to 2011	2003 to 2011	2003 to 2011
Total	50439	879	3108	50439	669	10794	379
Males	17432 (34.6)	304 (34.6)	1170 (37.6)	17432 (34.6)	243 (36.3)	3855 (35.7)	156 (41.2)
Age mean $\pm$ SD	82.0 $\pm$ 7.3	81.7 $\pm$ 7.3	82.5 $\pm$ 7.4	82.0 $\pm$ 7.3	79.9 $\pm$ 7.5	79.4 $\pm$ 7.0	76.4 $\pm$ 7.1
Median age	83	82	83	83	80	80	77
Age 60 to 64	896 (1.8)	9 (1.0)	48 (1.5)	896 (1.8)	25 (3.7)	324 (3.0)	16 (4.2)
65 to 69	2058 (4.1)	50 (5.7)	118 (3.8)	2058 (4.1)	43 (6.4)	670 (6.2)	52 (13.7)
70 to 74	4798 (9.5)	89 (10.1)	287 (9.2)	4798 (9.5)	77 (11.5)	1502 (13.9)	73 (19.3)
75 to 80	9610 (19.1)	161 (18.3)	510 (16.4)	9610 (19.1)	150 (22.4)	2608 (24.2)	111 (29.3)
80 to 84	13383 (26.5)	243 (27.6)	812 (26.1)	13383 (26.5)	194 (29.0)	3112 (28.8)	76 (20.1)
85 to 90	12414 (24.6)	206 (23.4)	817 (26.3)	12414 (24.6)	118 (17.6)	1978 (18.3)	41 (10.8)
$\geq 90$	7280 (14.4)	121 (13.8)	516 (16.6)	7280 (14.4)	62 (9.3)	600 (5.6)	10 (2.6)
First recording of dementia after index prescription of antdementia drug (%)					38 (5.7)	948 (8.8)	14 (3.7)
Duration of dementia at time of first use of antdementia drug (mean years $\pm$ SD)					1.4 $\pm$ 1.7	0.7 $\pm$ 1.1	2.7 $\pm$ 2.0
Referral to specialist* in previous 6 months	25205 (50.0)	224 (25.5)	2010 (64.7)	1265 (2.5)	454 (67.9)	6549 (60.7)	173 (45.6)

Previous use of memantine					0 (0.0)	9 (0.1)	35 (9.2)
Previous use of AChEI					119 (17.8)	0 (0.0)	342 (90.2)
<b>Use of antipsychotics at or before index day</b>							
Index day	6289 (12.5)	175 (19.9)	231 (7.4)	1322 (2.6)	175 (26.2)	1143 (10.6)	89 (23.5)
1 to 182 days	7394 (14.7)	197 (22.4)	300 (9.7)	2439 (4.8)	182 (27.2)	1325 (12.3)	108 (28.5)
183 to 365 days	4950 (9.8)	135 (15.4)	225 (7.2)	2403 (4.8)	128 (19.1)	906 (8.4)	80 (21.1)
1 to 2 years	5329 (10.6)	123 (14.0)	256 (8.2)	3218 (6.4)	122 (18.2)	930 (8.6)	67 (17.7)
2 to 3 years	4792 (9.5)	105 (11.9)	246 (7.9)	3157 (6.3)	89 (13.7)	783 (7.5)	43 (11.5)
3 to 4 years	4353 (8.6)	99 (11.3)	234 (7.5)	2937 (5.8)	78 (12.6)	677 (6.8)	32 (8.7)
4 to 5 years	3685 (8.0)	63 (8.3)	225 (7.6)	2583 (5.6)	58 (9.7)	611 (6.5)	25 (7.1)
≥5 years	7298 (17.3)	43 (7.6)	603 (21.0)	5983 (14.2)	111 (19.6)	1440 (16.4)	65 (19.1)
<b>Use of antidepressants at or before index day</b>							
Index day	11164 (22.1)	94 (10.7)	817 (26.3)	4981 (9.9)	228 (34.1)	2843 (26.3)	134 (35.4)
1 to 182 days	13165 (26.1)	129 (14.7)	922 (29.7)	6189 (12.3)	239 (35.7)	3130 (29.0)	142 (37.5)
183 to 365 days	11204 (22.2)	107 (12.2)	801 (25.8)	5807 (11.5)	201 (30.0)	2832 (26.2)	127 (33.5)
1 to 2 years	11284 (22.4)	115 (13.1)	782 (25.2)	6417 (12.7)	209 (31.2)	2716 (25.2)	129 (34.0)
2 to 3 years	10014 (19.9)	107 (12.2)	667 (21.5)	5970 (11.8)	177 (27.2)	2234 (21.4)	109 (29.1)
3 to 4 years	8912 (17.7)	87 (9.9)	618 (19.9)	5535 (11.0)	142 (22.9)	1897 (19.0)	94 (25.6)
4 to 5 years	7420 (16.1)	70 (9.2)	524 (17.6)	4800 (10.4)	120 (20.1)	1534 (16.3)	73 (20.7)
≥5 years	9565 (22.7)	43 (7.6)	809 (28.2)	7164 (17.0)	158 (28.0)	2149 (24.4)	102 (29.9)
<b>Use of anxiolytics at or before index day</b>							
Index day	2265 (4.5)	24 (2.7)	123 (4.0)	1327 (2.6)	88 (13.2)	444 (4.1)	51 (13.5)
1 to 182 days	3304 (6.6)	36 (4.1)	188 (6.0)	2075 (4.1)	116 (17.3)	668 (6.2)	67 (17.7)

183 to 365 days	2506 (5.0)	24 (2.7)	132 (4.2)	1988 (3.9)	87 (13.0)	593 (5.5)	42 (11.1)
1 to 2 years	2901 (5.8)	41 (4.7)	159 (5.1)	2354 (4.7)	89 (13.3)	646 (6.0)	46 (12.1)
2 to 3 years	2778 (5.5)	52 (5.9)	159 (5.1)	2356 (4.7)	75 (11.5)	541 (5.2)	46 (12.3)
3 to 4 years	2698 (5.4)	49 (5.6)	146 (4.7)	2295 (4.6)	65 (10.5)	509 (5.1)	40 (10.9)
4 to 5 years	2448 (5.3)	44 (5.8)	146 (4.9)	2014 (4.4)	60 (10.1)	461 (4.9)	29 (8.2)
≥5 years	4624 (11.0)	26 (4.6)	387 (13.5)	3904 (9.3)	108 (19.1)	1024 (11.6)	60 (17.6)
<b>Use of hypnotics at or before index day</b>							
Index day	4935 (9.8)	114 (13.0)	246 (7.9)	3662 (7.3)	123 (18.4)	899 (8.3)	75 (19.8)
1 to 182 days	6287 (12.5)	137 (15.6)	317 (10.2)	4559 (9.0)	145 (21.7)	1066 (9.9)	87 (23.0)
183 to 365 days	5267 (10.4)	115 (13.1)	275 (8.8)	4437 (8.8)	131 (19.6)	916 (8.5)	68 (17.9)
1 to 2 years	5690 (11.3)	129 (14.7)	322 (10.4)	4913 (9.7)	128 (19.1)	980 (9.1)	64 (16.9)
2 to 3 years	5472 (10.8)	127 (14.4)	288 (9.3)	4872 (9.7)	97 (14.9)	901 (8.6)	53 (14.1)
3 to 4 years	5266 (10.4)	128 (14.6)	293 (9.4)	4732 (9.4)	84 (13.6)	859 (8.6)	47 (12.8)
4 to 5 years	4669 (10.1)	106 (13.9)	271 (9.1)	4198 (9.1)	66 (11.1)	777 (8.2)	37 (10.5)
≥5 years	6611 (15.7)	71 (12.5)	489 (17.1)	5832 (13.9)	123 (21.8)	1296 (14.7)	70 (20.5)

\*Referrals to psychiatrist, geriatrician or neurologist; index day: day of first diagnosis of dementia in dementia cohort, respective day in the matched control cohort, or day of first use of memantine or an acetylcholinesterase inhibitor (AChEIs)

**Table 2: Summary results: slope of the fitted regression line for the prevalence of concomitant psychotropic treatment in year before and after first use of memantine, 2005 to 2011**

	Memantine cohort			AChEI cohort		
	Slope 12 months before	Slope 12 months after	Slope difference (95%CI)	Slope 12 months before	Slope 12 months after	Slope difference (95%CI)
<b>Antipsychotics</b>	<b>0.69</b>	<b>-0.22</b>	<b>0.91 (0.73, 1.09)</b>	<b>0.36</b>	<b>0.13</b>	<b>0.23 (0.20, 0.26)</b>
Atypical antipsychotics	0.6	-0.19	0.79 (0.62, 0.96)	0.3	0.1	0.20 (0.18, 0.23)
Typical antipsychotics	0.12	-0.09	0.21 (0.12, 0.30)	0.06	0.03	0.04 (0.02, 0.05)
<b>Antidepressants</b>	<b>0.56</b>	<b>-0.02</b>	<b>0.58 (0.38, 0.79)</b>	<b>0.47</b>	<b>0.27</b>	<b>0.19 (0.14, 0.24)</b>
Tricyclic antidepressants	0.05	-0.17	0.22 (0.13, 0.31)	0	0.03	-0.04 (-0.06, -0.01)
SSRI	0.33	0.01	0.33 (0.15, 0.50)	0.34	0.15	0.20 (0.16, 0.24)
Other antidepressants	0.22	0.06	0.16 (0.04, 0.28)	0.17	0.1	0.07 (0.05, 0.09)
<b>Anxiolytics</b>	<b>0.22</b>	<b>-0.12</b>	<b>0.34 (0.21, 0.48)</b>	<b>0.06</b>	<b>0.01</b>	<b>0.04 (0.02, 0.06)</b>
<b>Hypnotics</b>	<b>0.16</b>	<b>-0.26</b>	<b>0.42 (0.26, 0.59)</b>	<b>0.11</b>	<b>0</b>	<b>0.11 (0.08, 0.14)</b>

AChEI: acetylcholinesterase inhibitors

**Figure 1a-b: Prevalence of psychotropic drug use in dementia and matched control cohort by year at the time of first dementia diagnosis or index day, 1995 to 2011**

**Figure 1a: Dementia cohort**

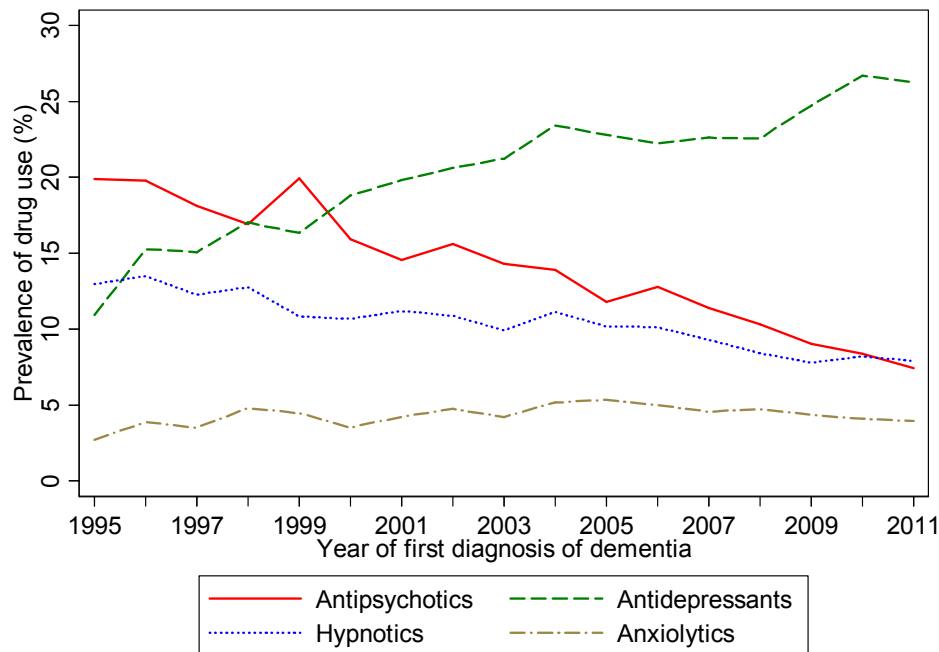
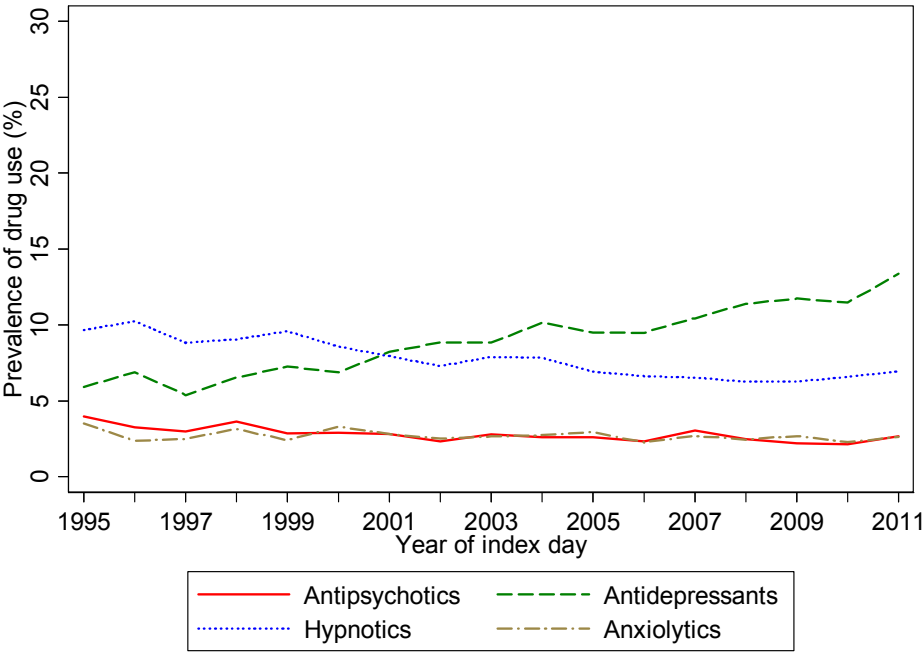
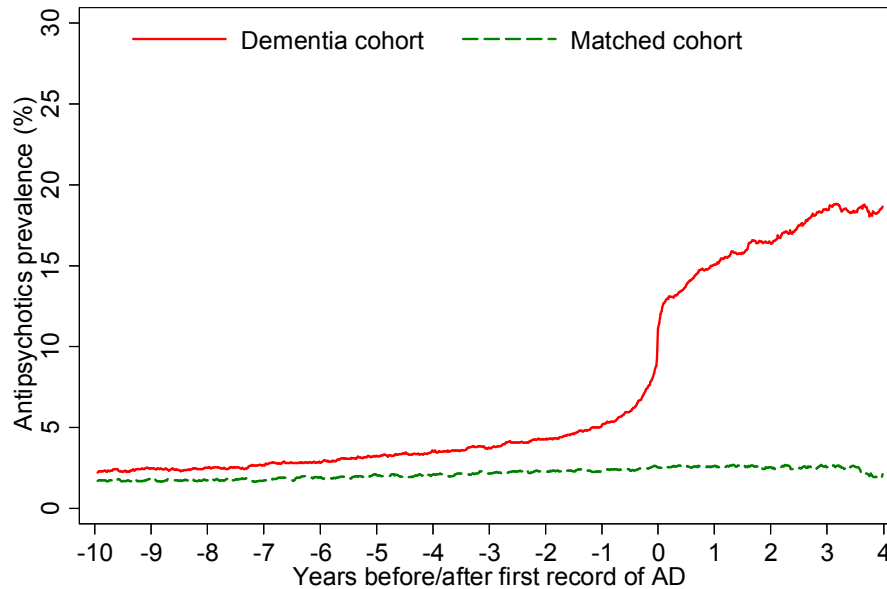


Figure 1b: Matched cohort



**Figure 2a-d: Prevalence of psychotropic use in dementia cohort and in matched control cohort before and after the first dementia diagnosis for 2005 to 2011 cohort**

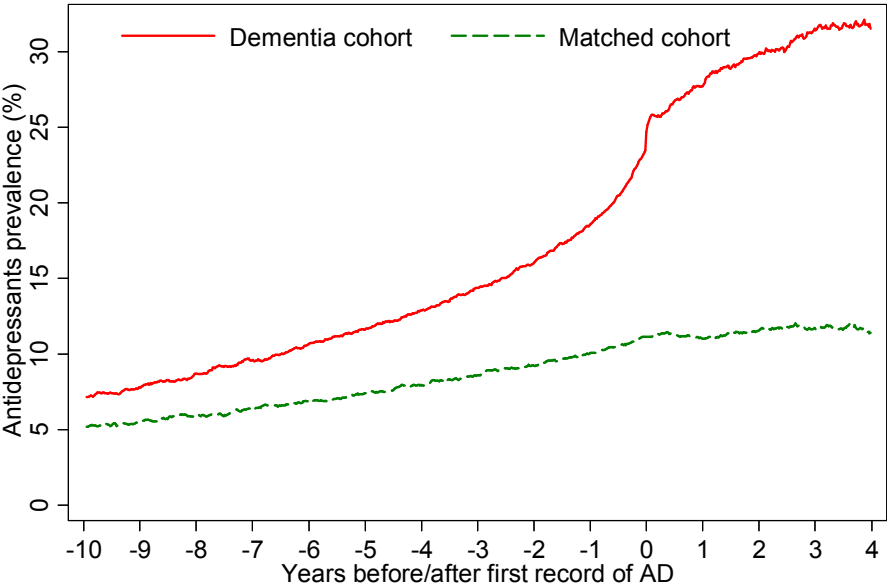
**Figure 2a: Prevalence of antipsychotic use**



Dem:	15619	20777	25476	29113	30803	30803	11073	3252
Ref:	16371	21347	25914	29333	30803	30803	15998	6721

Antipsychotics: typical antipsychotics (phenothiazines, butyrophenones, diphenylbutylpiperidines, thioxanthenes and substituted benzamides), and atypical antipsychotics (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone and zotepine).

Figure 2b: Prevalence of antidepressant use

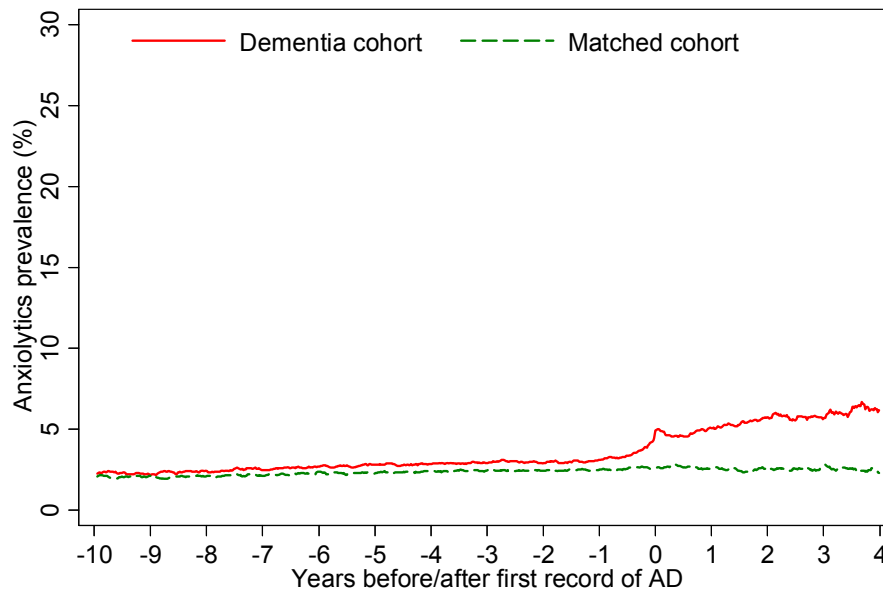


Dem:	15619	20777	25476	29113	30803	30803	11073	3252
Ref:	16371	21347	25914	29333	30803	30803	15998	6721

Antidepressants: tricyclic and related antidepressants (imipramine, nortriptyline, amitriptyline, desipramine, protriptyline, amitriptyline, amitriptyline /chlordiazepoxide, amoxapine, butriptyline, clomipramine, dosulepin, doxepin, fluphenazine /nortriptyline, iprindole, lofepramine, maprotiline, mianserin, trazodone, trimipramine and viloxazine), selective serotonin re-uptake inhibitors (SSRI) (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline), and other antidepressants (duloxetine, agomelatine, ascorbic acid/pyridoxine /tryptophan, flupentixol, mirtazapine, nefazodone, reboxetine, tryptophan, venlafaxine, iproniazid phosphate, isocarboxazid, moclobemide, phenelzine, tranilcypromine, amitriptyline /perphenazine)



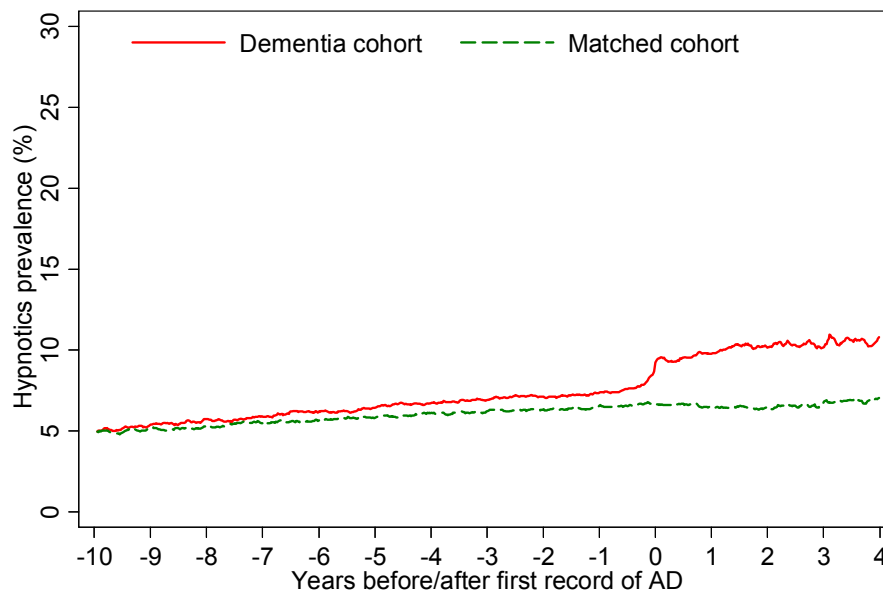
**Figure 2c: Prevalence of anxiolytic use**



Dem:	15619	20777	25476	29113	30803	30803	11073	3252
Ref:	16371	21347	25914	29333	30803	30803	15998	6721

Anxiolytics: buspirone, chlordiazepoxide, diazepam, hydroxyzine and lorazepam.

**Figure 2d: Prevalence of hypnotic use**

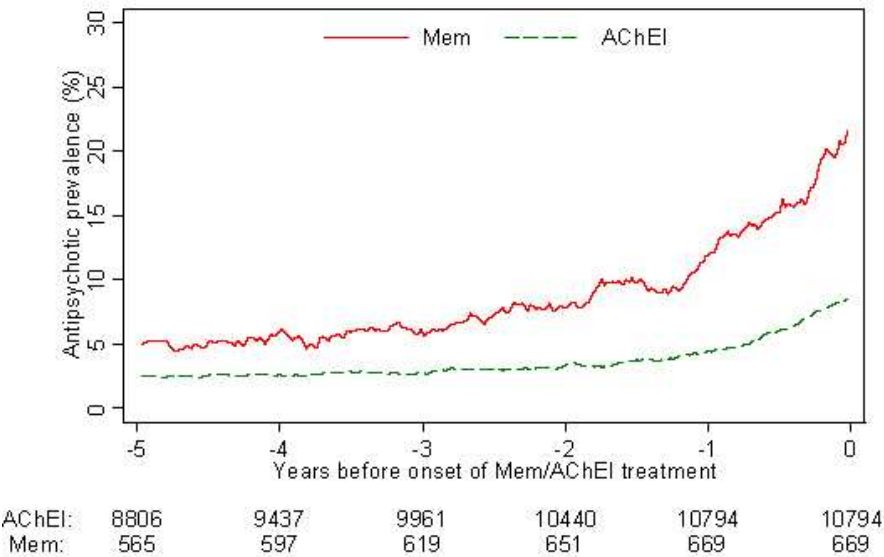


Dem:	15619	20777	25476	29113	30803	30803	11073	3252
Ref:	16371	21347	25914	29333	30803	30803	15998	6721

Hypnotics: clomethiazole, chloral betaine, loprazolam, lormetazepam, nitrazepam, promethazine, temazepam, zaleplon, zolpidem and zopiclone.

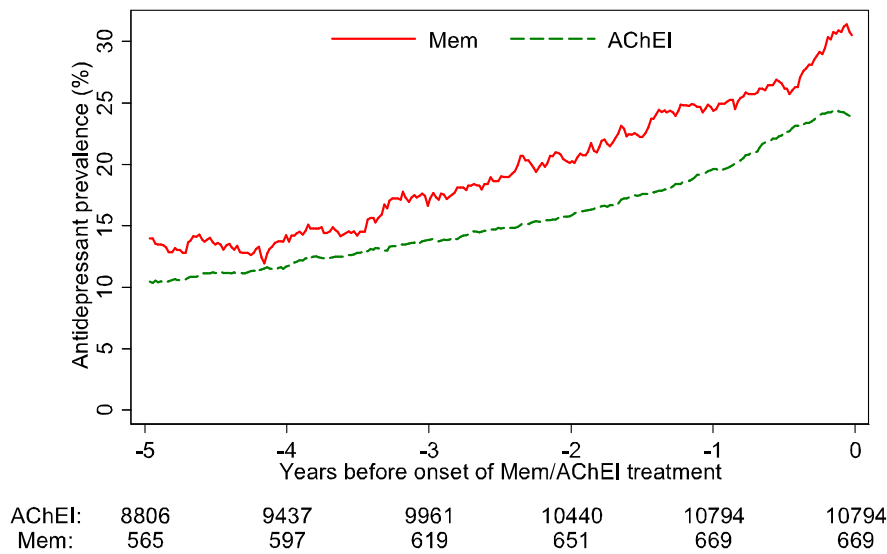
**Figure 3a-~~ab~~b:** Prevalence of psychotropic drug use in AChEI and memantine (Mem) subcohorts in the 5 years preceding the first prescription (index day), excluding patients without a previous prescription for the other compound, AChEI or memantine, 2003 to 2011.

**Figure 3a:** Prevalence of antipsychotic use in AChEI and memantine subcohort



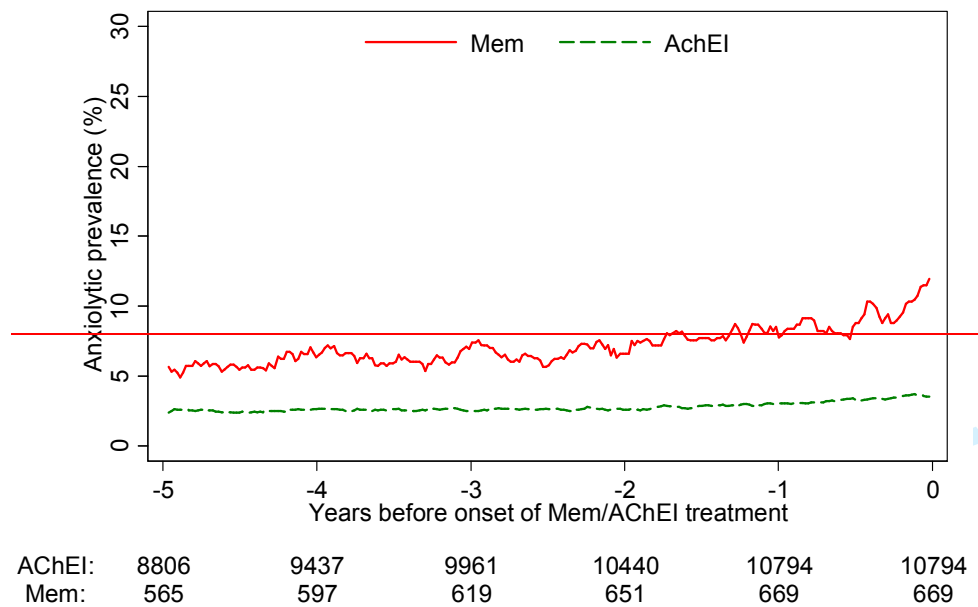
**Mem: memantine; AChEI: acetylcholinesterase inhibitors**

**Figure 3b: Prevalence of antidepressant use in AChEI and memantine subcohort**

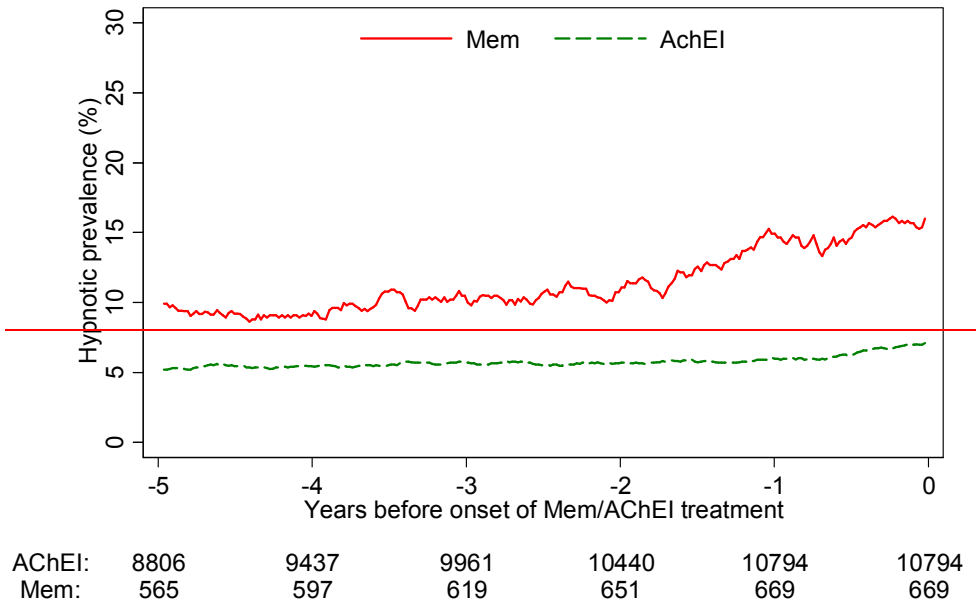


**Mem: memantine; AChEI: acetylcholinesterase inhibitors**

**Figure 3c: Prevalence of anxiolytic use in AChEI and memantine subcohort**



**Figure 3d: Prevalence of hypnotic use in AChEI and memantine subcohort**



**Figure 4a-bd:** Prevalence of antipsychotic and antidepressant use in the year before and after first use of AChEI and memantine, excluding patients without a previous prescription for the other compound, AChEI or memantine).

**Figure 4a:** Prevalence of antipsychotic and antidepressant use among AChEI users.

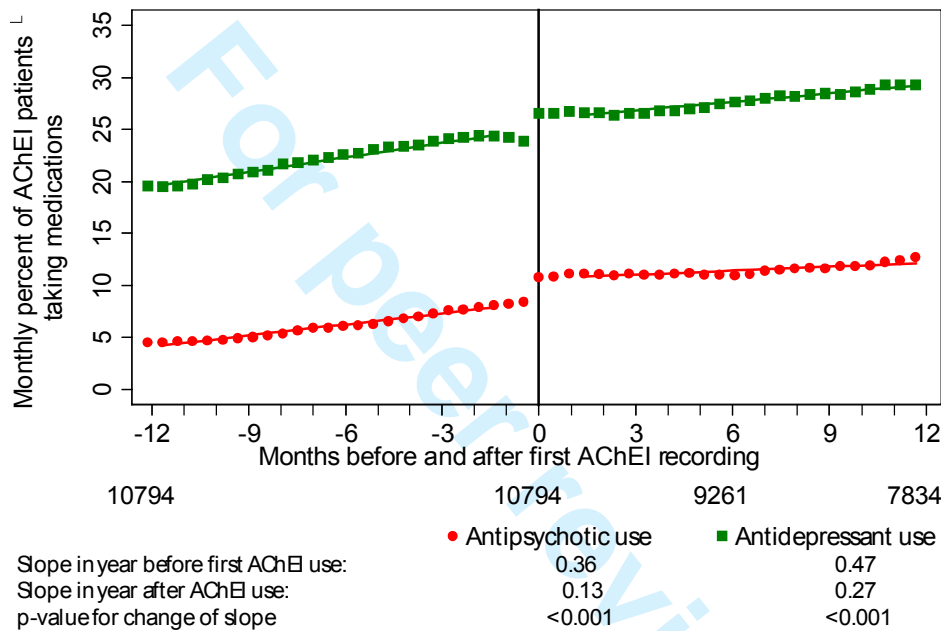


Figure 4b: Prevalence of antipsychotic and antidepressant use among memantine users.

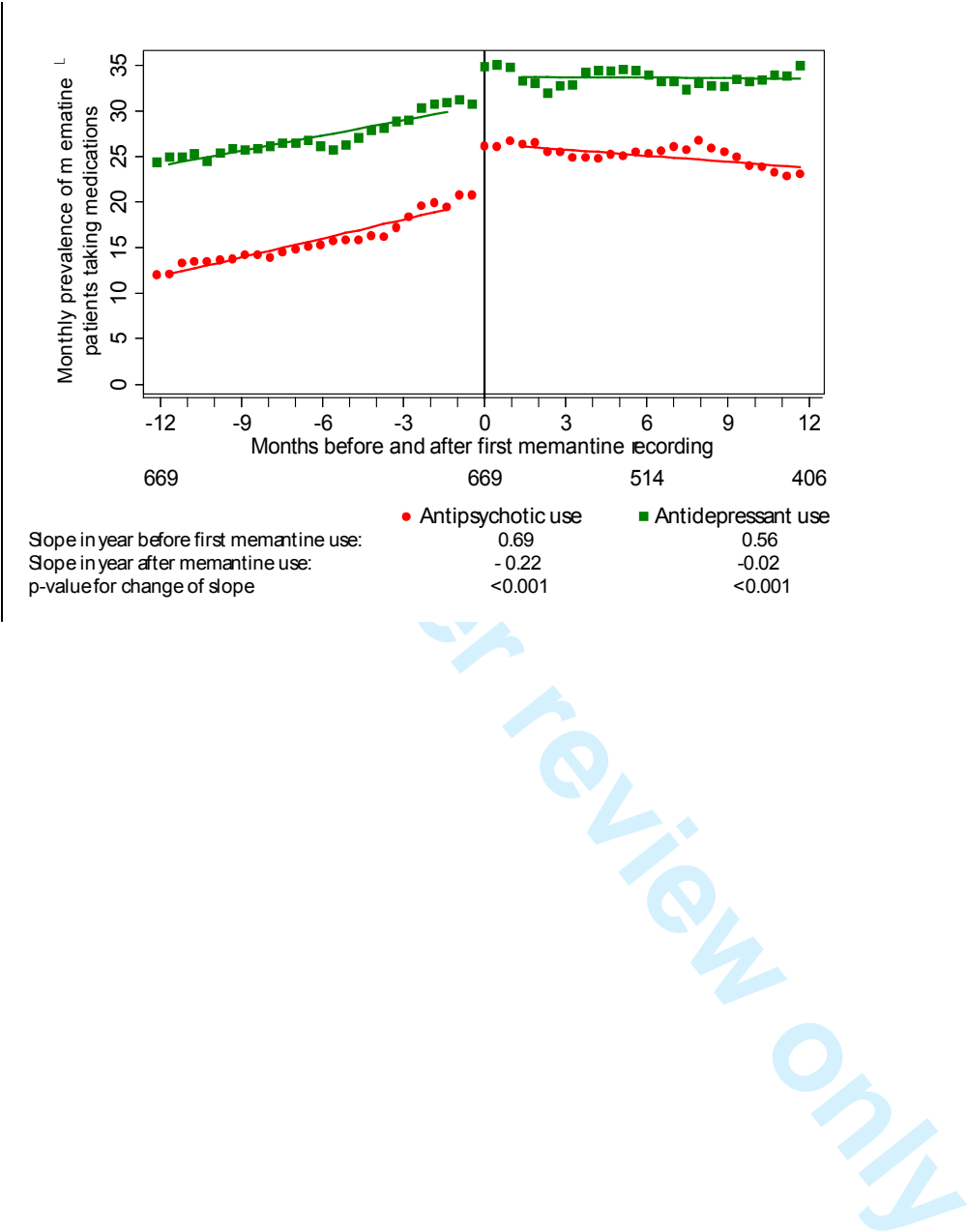


Figure 4c: Prevalence of anxiolytic and hypnotic use among AChEI users.

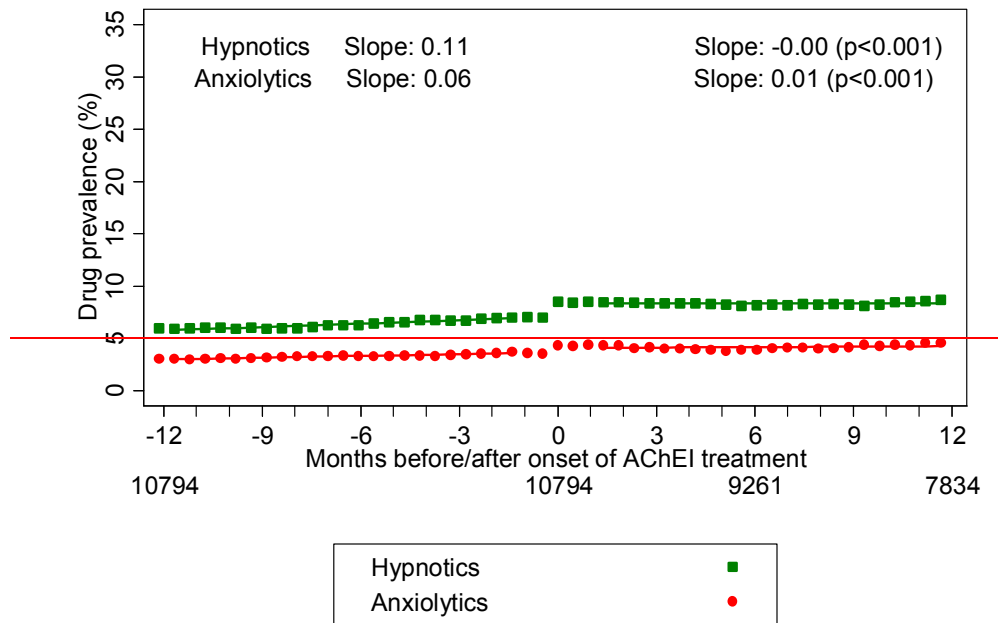
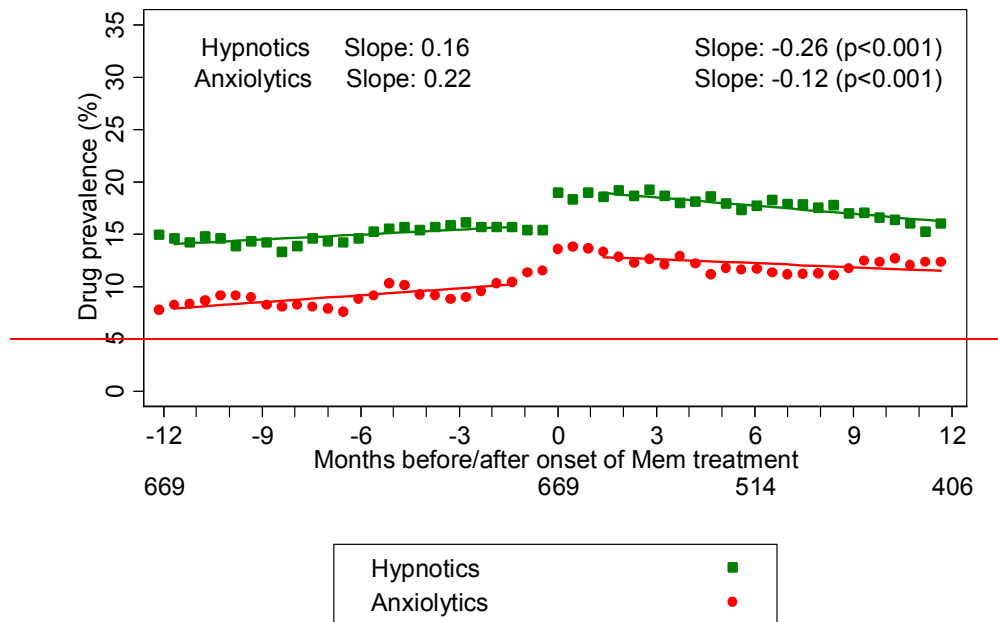


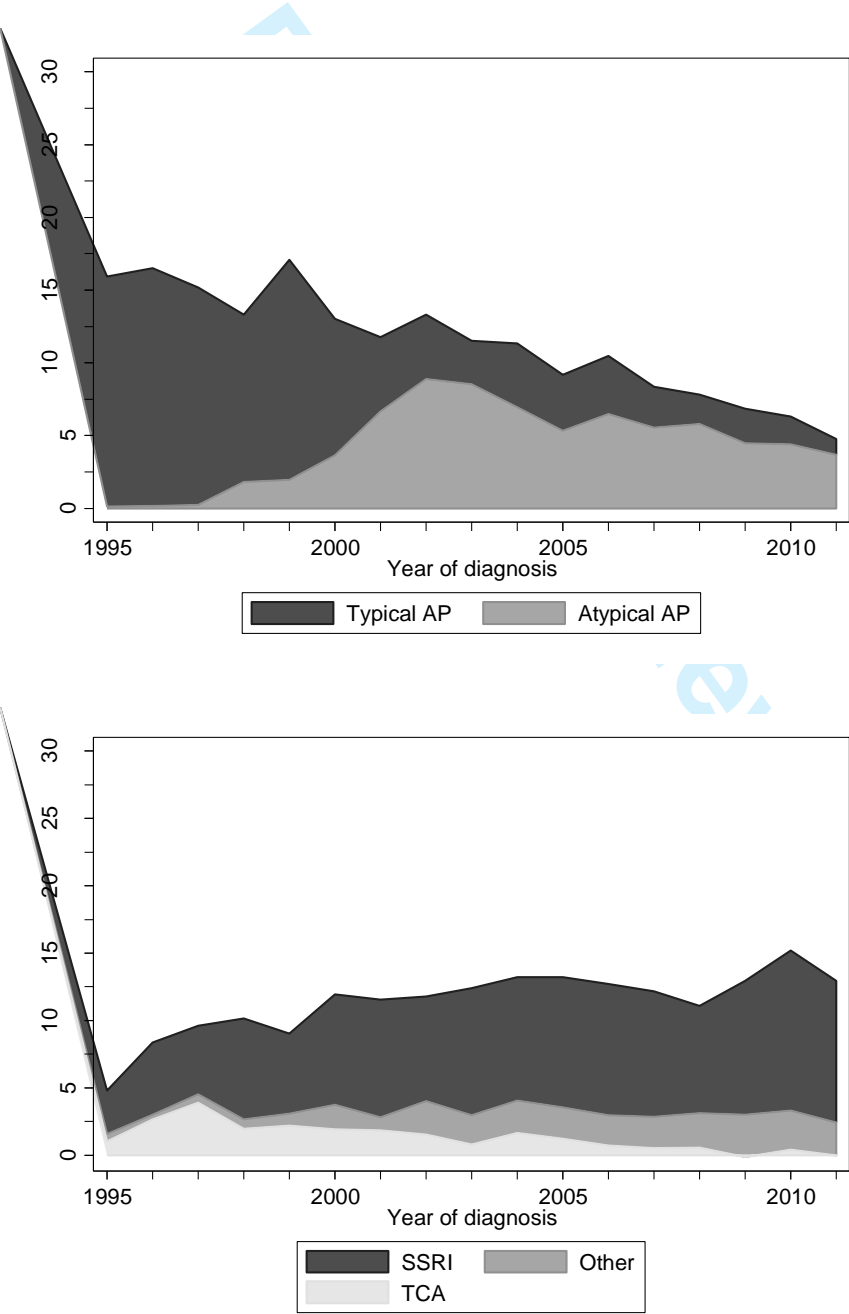
Figure 4d: Prevalence of anxiolytic and hypnotic use among memantine users.



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Supplementary data

Supplement Figure 1: Proportion of antipsychotics (above) and of antidepressants (below) attributable to dementia at the time of first diagnosis of dementia by type of antipsychotic, 1995 to 2011





**Supplement Figure 2: Monthly prevalence of use of antidementia drugs per 100 dementia patients since 1995**

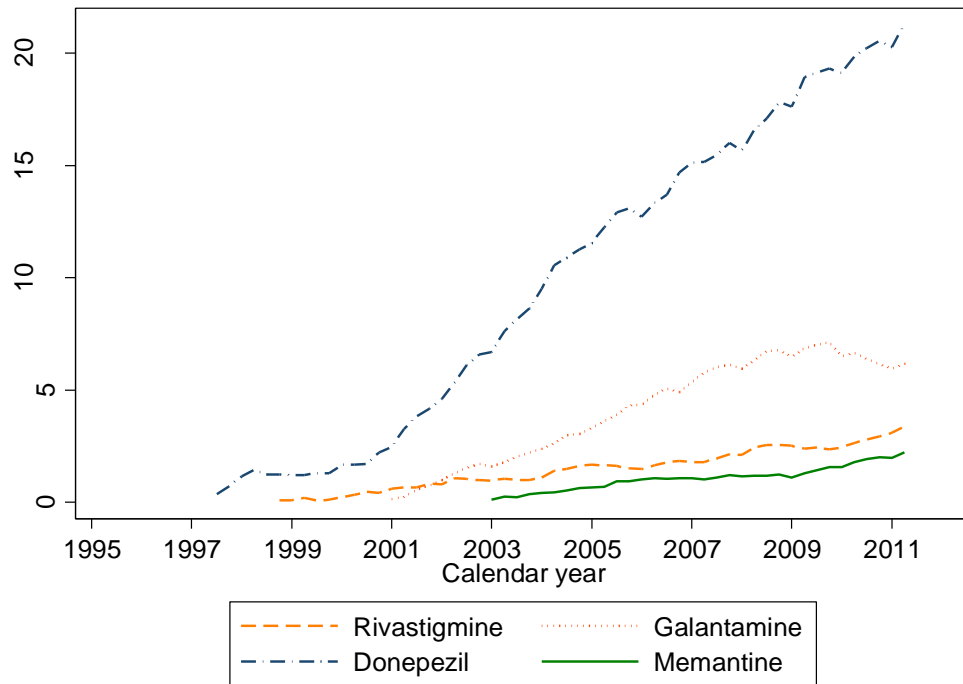
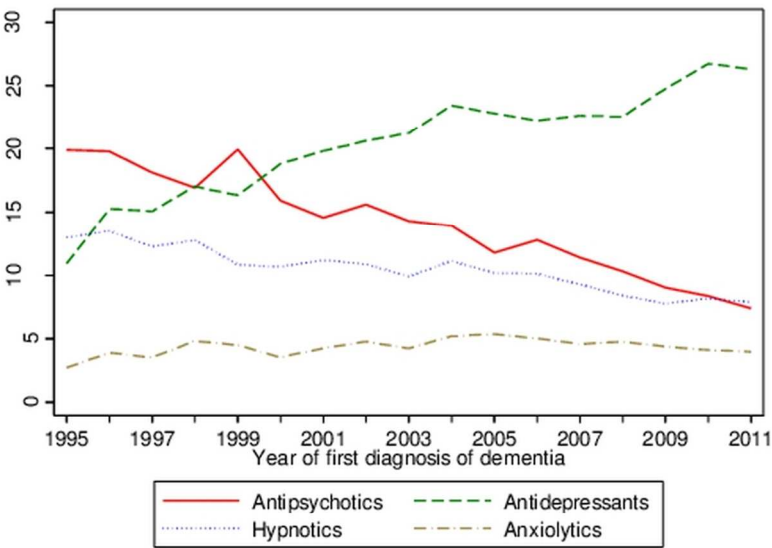
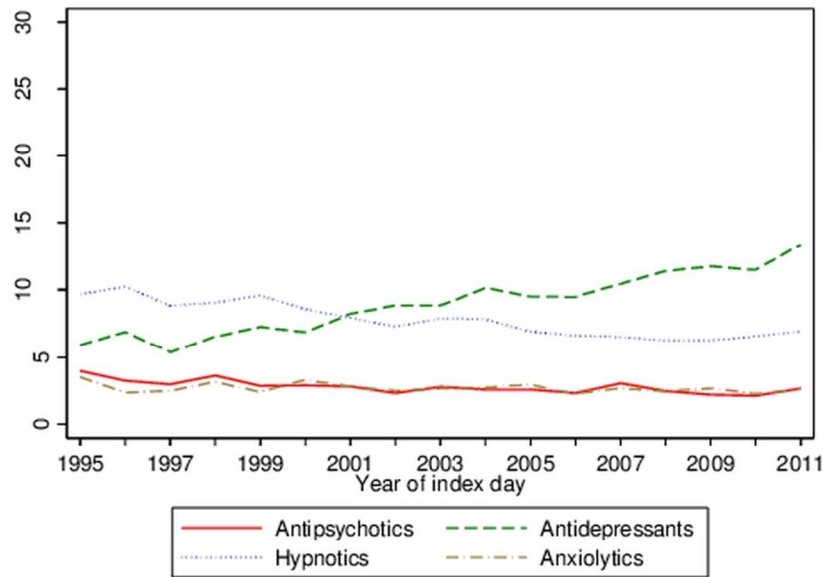


Figure 1a: Dementia cohort



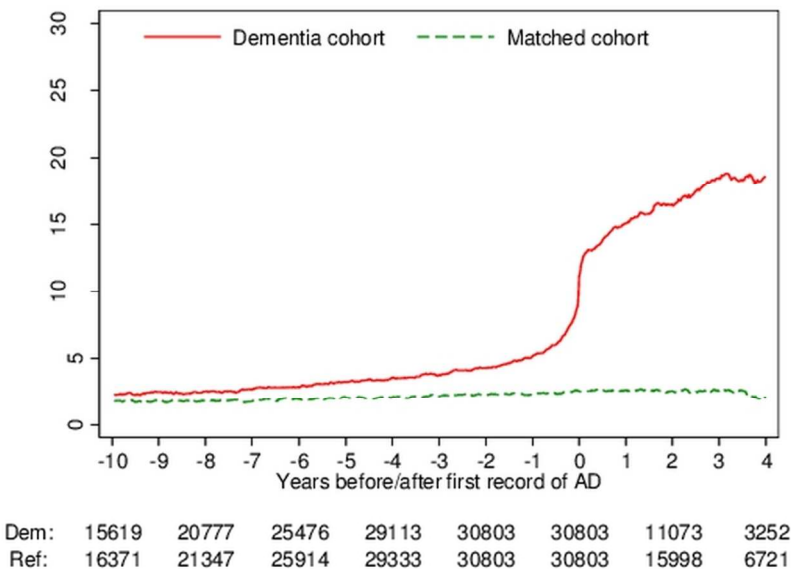
104x90mm (300 x 300 DPI)

Figure 1b: Control cohort



103x90mm (300 x 300 DPI)

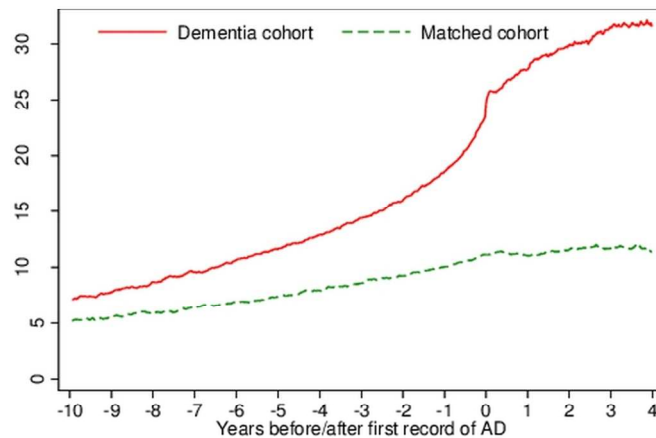
Figure 2a: Prevalence of antipsychotic use



Antipsychotics: typical antipsychotics (phenothiazines, butyrophenones, diphenylbutylpiperidines, thioxanthenes and substituted benzamides), and atypical antipsychotics (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone and zotepine).

93x90mm (300 x 300 DPI)

Figure 2b: Prevalence of antidepressant use

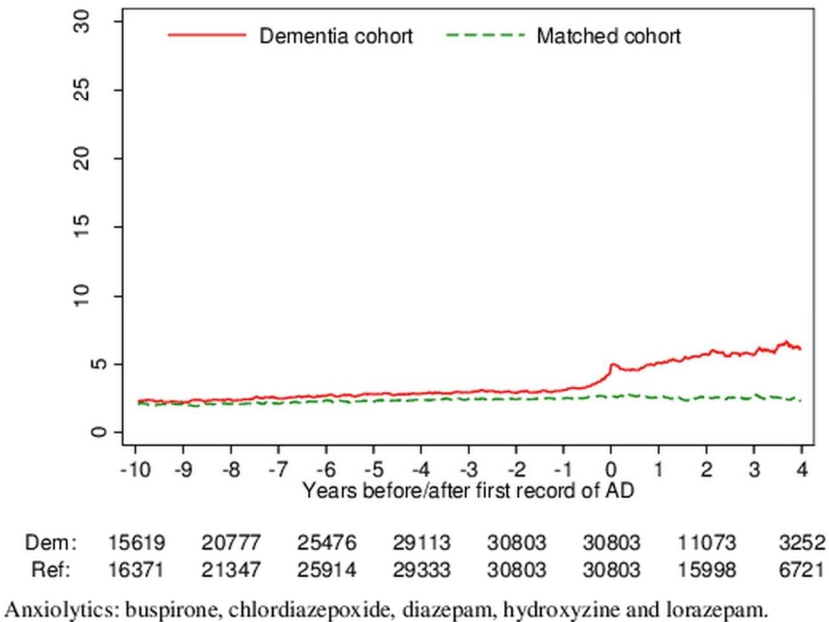


Dem:	15619	20777	25476	29113	30803	30803	11073	3252
Ref:	16371	21347	25914	29333	30803	30803	15998	6721

Antidepressants: tricyclic and related antidepressants, selective serotonin re-uptake inhibitors (SSRI) and other antidepressants.

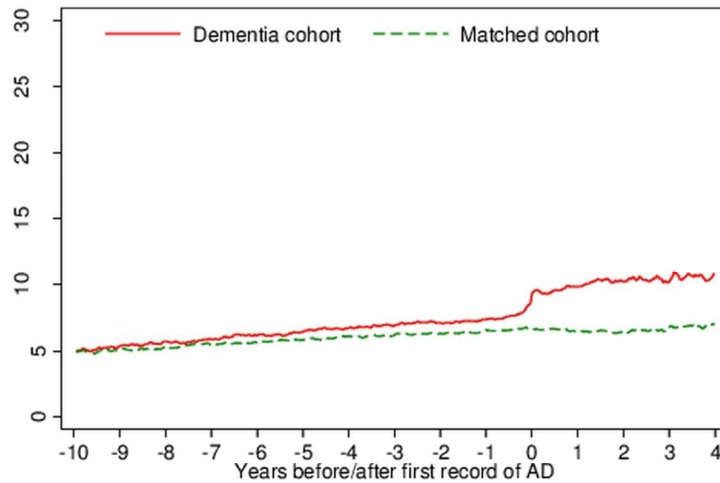
113x90mm (300 x 300 DPI)

Figure 2c: Prevalence of anxiolytic use



106x90mm (300 x 300 DPI)

Figure 2d: Prevalence of hypnotic use

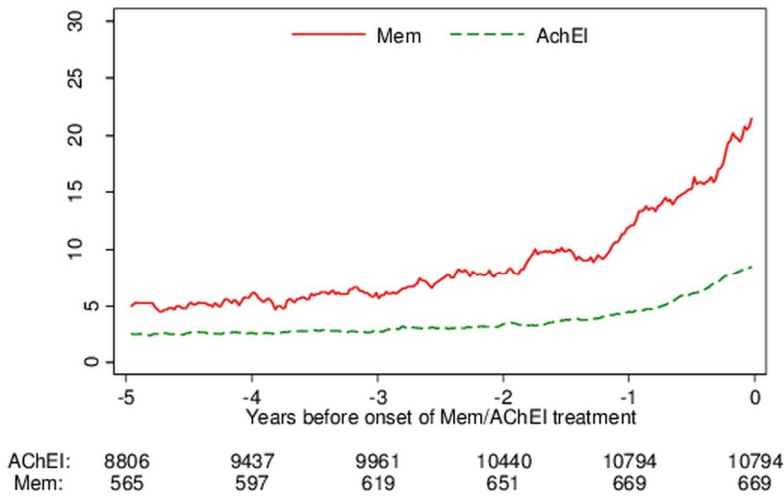


Dem:	15619	20777	25476	29113	30803	30803	11073	3252
Ref:	16371	21347	25914	29333	30803	30803	15998	6721

Hypnotics: clomethiazole, chloral betaine, loperazolam, lormetazepam, nitrazepam, promethazine, temazepam, zaleplon, zolpidem and zopiclone.

104x90mm (300 x 300 DPI)

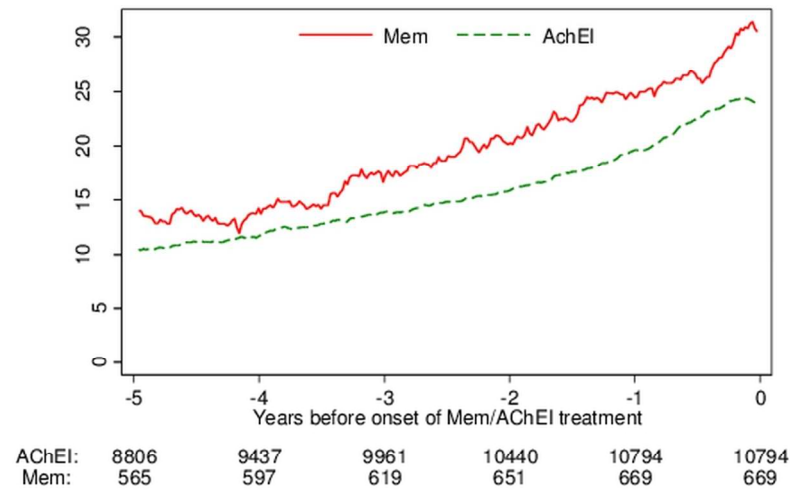
Figure 3a: Prevalence of antipsychotic use in AChEI and memantine subcohort



128x90mm (300 x 300 DPI)

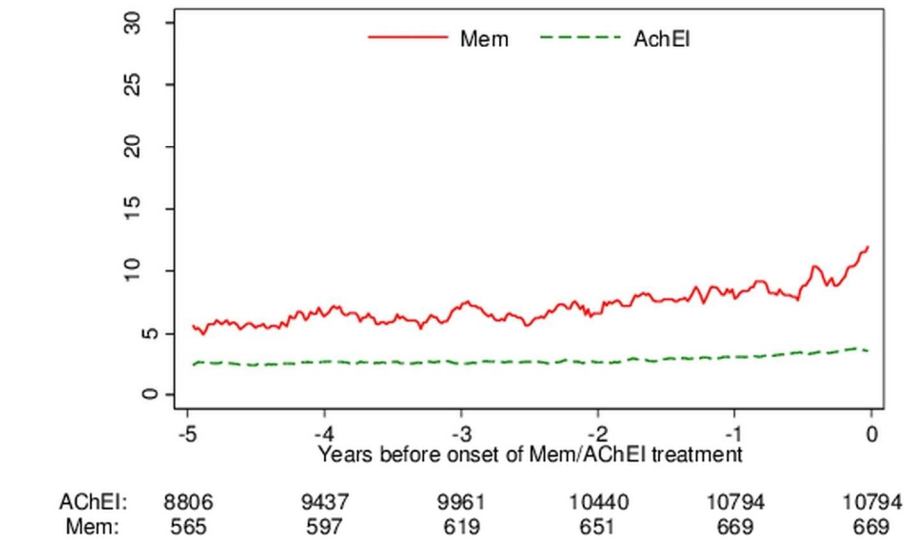


Figure 3b: Prevalence of antidepressant use in AChEI and memantine subcohort



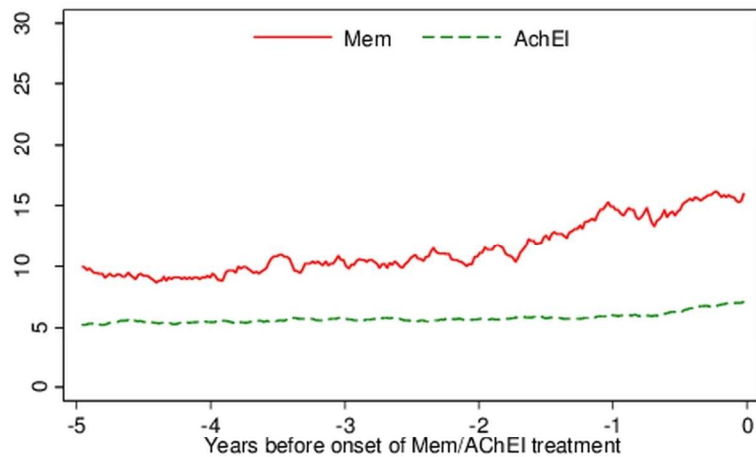
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Figure 3c: Prevalence of anxiolytic use in AChEI and memantine subcohort



113x90mm (300 x 300 DPI)

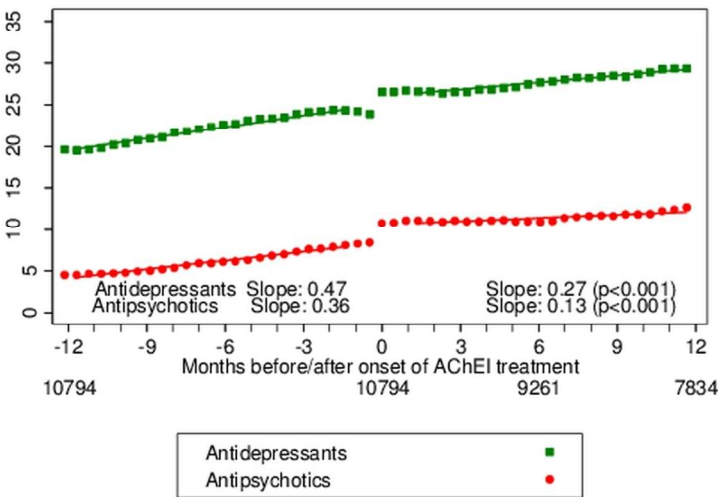
Figure 3d: Prevalence of hypnotic use in AChEI and memantine subcohort



AChEI:	8806	9437	9961	10440	10794	10794
Mem:	565	597	619	651	669	669

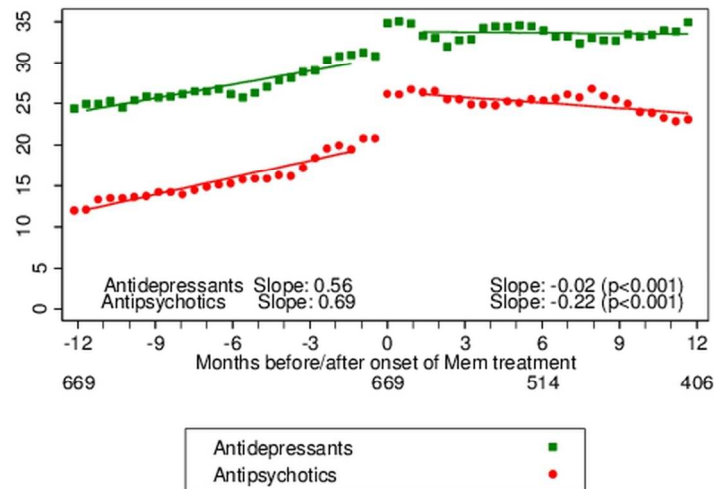
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Figure 4a: Prevalence of antipsychotic and antidepressant use among AChEI users.



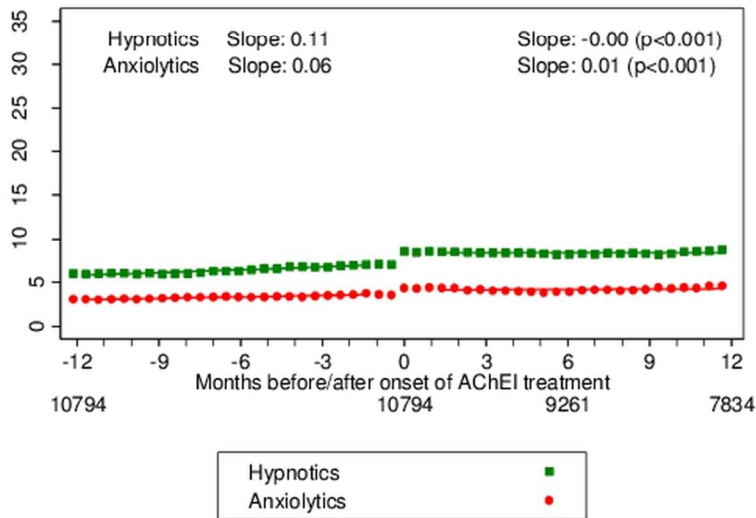
115x90mm (300 x 300 DPI)

Figure 4b: Prevalence of antipsychotic and antidepressant use among memantine users.



122x90mm (300 x 300 DPI)

Figure 4c: Prevalence of anxiolytic and hypnotic use among AChEI users.



110x90mm (300 x 300 DPI)

**Figure 4d: Prevalence of anxiolytic and hypnotic use among memantine users.**

