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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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ABSTRACT

Objective: To investigate the pattern and trends of use of antipsychotics, antidepressants, hypnotics and anxiolytics in Alzheimer's disease and other dementias and in patients treated with antidementia medications.

Design: Cohort study with dementia patients formed in the UK 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 antipsychotics, antidepressants, hypnotics and anxiolytics up to 10 years before and 4 years after dementia diagnosis, and for up to 5 years before and 1 year after first use of AChEI or memantine.

Results: 50 349 patients with incident dementia diagnosis and 50 349 matched controls, 10 794 first-time users of AChEI and 669 of memantine. The mean prevalence of antipsychotic use from 1995 to 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 (10.7–26.3%) and a small increase in anxiolytic use. The matched cohort showed a lower use of antipsychotics and anxiolytics but a rise in antidepressants (5.9–13.4%). 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 while there was a steady increase in antidepressant use. There was a decline in antipsychotic use after the 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 (AD) and other dementias 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 patients with dementia overall and in patients treated with antidementia medications, that is, 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 (10.7–26.3%) 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% 1 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.

INTRODUCTION

Up to 90% of patients with Alzheimer's disease (AD) and other dementias will experience neuropsychiatric symptoms (NPS) such as, aggressive behaviour, agitation, repetitive vocalisations, wandering, depression, sleep

ARTICLE SUMMARY

Strengths and limitations of this study

- The CPRD is the largest primary care database in the world, containing the longitudinal records for up to 20 years of over three million patients.
- There may have been a trend towards diagnosing dementia at an earlier stage of the disease because of increasing awareness about AD and other dementia despite the fact that the mean age at the time of the first dementia diagnosis was stable over the entire study period.
- APs and antidementia drugs prescribed exclusively by hospital specialists are not completely recorded in CPRD.

problems and psychosis (delusions, paranoia and hallucinations) during the course of their disease.[1 2] These symptoms can be among the most distressing aspects of 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% vs 45%).[1]

Antipsychotic medications (APs) have frequently been prescribed as the first-line pharmacological treatment approach for NPS 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 dementia.[7–9]

Only the atypical antipsychotic risperidone has use in AD included in its licensed indications within the European Community. This license 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 AP 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 1800 deaths and 1620 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 antidementia agents—memantine and the acetylcholinesterase inhibitors (AChEIs) have beneficial effects on NPS 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 stabilised the proportion of AP users.[20] In the USA, a study using national Veterans Affairs data has examined changes in typical and atypical antipsychotic use in outpatients with dementia from 1999 through 2007.[21] Use of atypical antipsychotics began to decline significantly in 2003, and after the FDA 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 (ie, 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 1 April 2012 known as the General Practice Research Database. Participating general practitioners (GPs) currently contribute data on more than five 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 3-year history in the CPRD before a first diagnosis of dementia between 1 January 1995 and 30 June 2011. Dementia was defined by Read medical codes for AD, 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 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 1 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 1995–2011.

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 1 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 prevalence of psychotropic drug use was described using binomial regression and the method of generalised estimating equations for AChEI and memantine use separately[24] and 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 per cent of AD patients taking the respective psychotropic medication during prefirst and postfirst recording of AChEI and memantine. All analyses were performed with STATA MP V.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 years with 34.6% men. There was an increasing trend over time for patients with dementia to be seen by a specialist, that is, 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 1995–2011, 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 (10.7–26.3%), a small increase in anxiolytic use (2.7–4%), and a decrease in hypnotic use (13–7.9%). 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 (5.9–13.4%, figure 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 1 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

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	1995–2011	1995	2011	1995–2011	2003–2011	2003–2011	2003–2011
Total	50 439	879	3108	50 439	669	10 794	379
Males	17 432 (34.6)	304 (34.6)	1170 (37.6)	17 432 (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							
60–64	896 (1.8)	9 (1.0)	48 (1.5)	896 (1.8)	25 (3.7)	324 (3.0)	16 (4.2)
65–69	2058 (4.1)	50 (5.7)	118 (3.8)	2058 (4.1)	43 (6.4)	670 (6.2)	52 (13.7)
70–74	4798 (9.5)	89 (10.1)	287 (9.2)	4798 (9.5)	77 (11.5)	1502 (13.9)	73 (19.3)
75–80	9610 (19.1)	161 (18.3)	510 (16.4)	9610 (19.1)	150 (22.4)	2608 (24.2)	111 (29.3)
80–84	13 383 (26.5)	243 (27.6)	812 (26.1)	13 383 (26.5)	194 (29.0)	3112 (28.8)	76 (20.1)
85–90	12 414 (24.6)	206 (23.4)	817 (26.3)	12 414 (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 antidementia drug (%)					38 (5.7)	948 (8.8)	14 (3.7)
Duration of dementia at time of first use of antidementia drug (mean years±SD					1.4±1.7	0.7±1.1	2.7±2.0
Referral to specialist* in previous 6 months	25 205 (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)
Use of antipsychotics at or before index day							
Index day	6289 (12.5)	175 (19.9)	231 (7.4)	1322 (2.6)	175 (26.2)	1143 (10.6)	89 (23.5)
1–182 days	7394 (14.7)	197 (22.4)	300 (9.7)	2439 (4.8)	182 (27.2)	1325 (12.3)	108 (28.5)
183–365 days	4950 (9.8)	135 (15.4)	225 (7.2)	2403 (4.8)	128 (19.1)	906 (8.4)	80 (21.1)
1–2 years	5329 (10.6)	123 (14.0)	256 (8.2)	3218 (6.4)	122 (18.2)	930 (8.6)	67 (17.7)
2–3 years	4792 (9.5)	105 (11.9)	246 (7.9)	3157 (6.3)	89 (13.7)	783 (7.5)	43 (11.5)
3–4 years	4353 (8.6)	99 (11.3)	234 (7.5)	2937 (5.8)	78 (12.6)	677 (6.8)	32 (8.7)
4–5 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)
Use of antidepressants at or before index day							
Index day	11 164 (22.1)	94 (10.7)	817 (26.3)	4981 (9.9)	228 (34.1)	2843 (26.3)	134 (35.4)
1–182 days	13 165 (26.1)	129 (14.7)	922 (29.7)	6189 (12.3)	239 (35.7)	3130 (29.0)	142 (37.5)
183–365 days	11 204 (22.2)	107 (12.2)	801 (25.8)	5807 (11.5)	201 (30.0)	2832 (26.2)	127 (33.5)
1–2 years	11 284 (22.4)	115 (13.1)	782 (25.2)	6417 (12.7)	209 (31.2)	2716 (25.2)	129 (34.0)
2–3 years	10 014 (19.9)	107 (12.2)	667 (21.5)	5970 (11.8)	177 (27.2)	2234 (21.4)	109 (29.1)
3–4 years	8912 (17.7)	87 (9.9)	618 (19.9)	5535 (11.0)	142 (22.9)	1897 (19.0)	94 (25.6)
4–5 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)

Continued

Table 1 Continued

	Complete dementia cohort	Dementia cohort	Dementia cohort	Matched control cohort	Memantine subcohort	AChEI subcohort	Memantine plus AChEI subcohort
Use of anxiolytics at or before index day							
Index day	2265 (4.5)	24 (2.7)	123 (4.0)	1327 (2.6)	88 (13.2)	444 (4.1)	51 (13.5)
1–182 days	3304 (6.6)	36 (4.1)	188 (6.0)	2075 (4.1)	116 (17.3)	668 (6.2)	67 (17.7)
183–365 days	2506 (5.0)	24 (2.7)	132 (4.2)	1988 (3.9)	87 (13.0)	593 (5.5)	42 (11.1)
1–2 years	2901 (5.8)	41 (4.7)	159 (5.1)	2354 (4.7)	89 (13.3)	646 (6.0)	46 (12.1)
2–3 years	2778 (5.5)	52 (5.9)	159 (5.1)	2356 (4.7)	75 (11.5)	541 (5.2)	46 (12.3)
3–4 years	2698 (5.4)	49 (5.6)	146 (4.7)	2295 (4.6)	65 (10.5)	509 (5.1)	40 (10.9)
4–5 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)
1–182 days	6287 (12.5)	137 (15.6)	317 (10.2)	4559 (9.0)	145 (21.7)	1066 (9.9)	87 (23.0)
183–365 days	5267 (10.4)	115 (13.1)	275 (8.8)	4437 (8.8)	131 (19.6)	916 (8.5)	68 (17.9)
1–2 years	5690 (11.3)	129 (14.7)	322 (10.4)	4913 (9.7)	128 (19.1)	980 (9.1)	64 (16.9)
2–3 years	5472 (10.8)	127 (14.4)	288 (9.3)	4872 (9.7)	97 (14.9)	901 (8.6)	53 (14.1)
3–4 years	5266 (10.4)	128 (14.6)	293 (9.4)	4732 (9.4)	84 (13.6)	859 (8.6)	47 (12.8)
4–5 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).

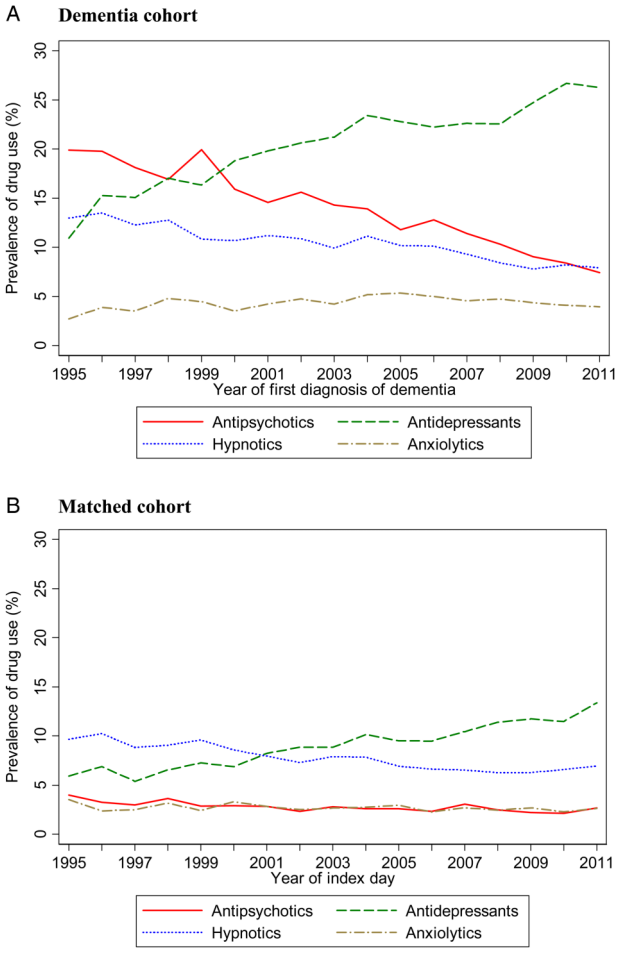

Figure 1 (A and B) Prevalence of psychotropic drug use in dementia and matched control cohort by year at the time of first dementia diagnosis or index day, 1995–2011.

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% 1 year before the dementia diagnosis, to 24.7% on the date of the diagnosis and to 31.6% 4 years after the dementia diagnosis, compared with 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 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 men. Memantine users were more likely to have a record of a referral to a psychiatrist/geriatrician in the 182 days before the first

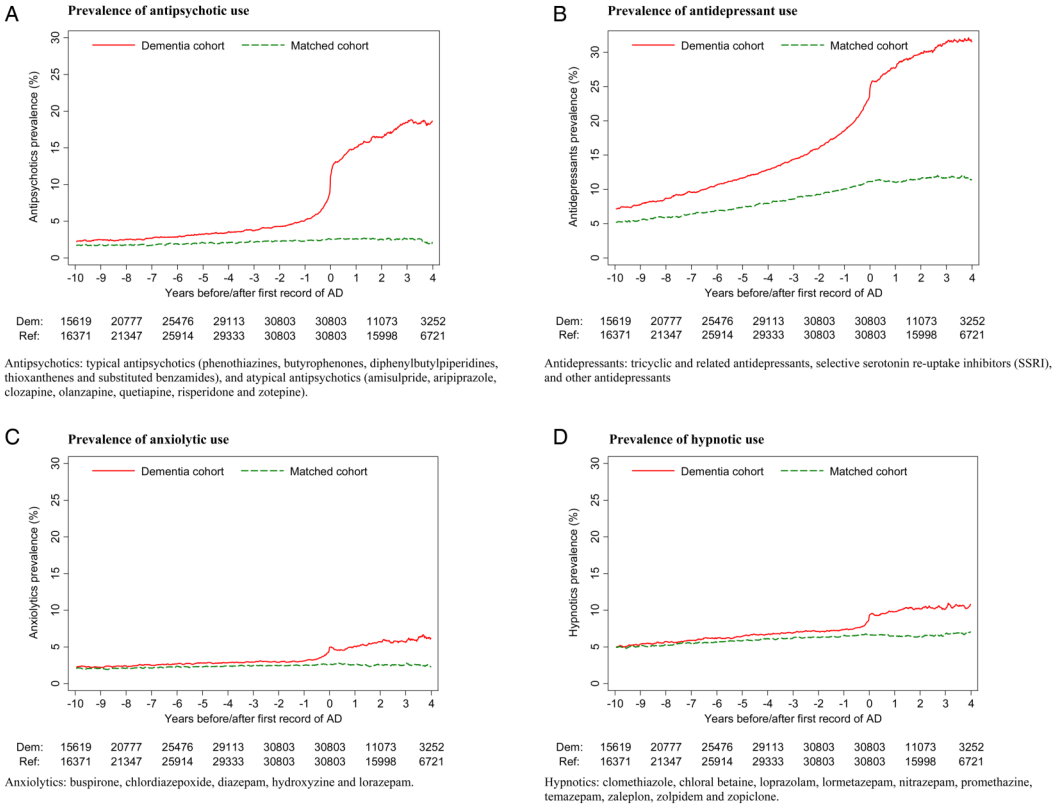

Figure 2 (A–D) Prevalence of psychotropic use in dementia cohort and in matched control cohort before and after the first dementia diagnosis for 2005–2011 cohort.

prescription compared with 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 four classes of psychotropic drugs was more frequently prescribed in the memantine group compared to the AChEI group, table 1 and figure 3A,B. 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, that is, 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

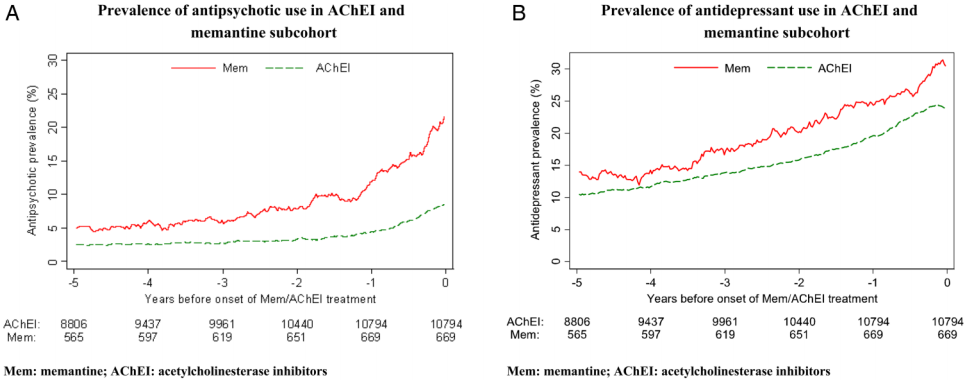

Figure 3 (A and B) Prevalence of psychotropic drug use in AChEI and memantine (Mem) subcohorts in the 5 years preceding the first prescription (index day), excluding patients without a previous prescription for the other compound, AChEI or memantine, 2003–2011.

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, 2005–2011

	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)
Antipsychotics	0.69	−0.22	0.91 (0.73 to 1.09)	0.36	0.13	0.23 (0.20 to 0.26)
Atypical antipsychotics	0.60	−0.19	0.79 (0.62 to 0.96)	0.30	0.10	0.20 (0.18 to 0.23)
Typical antipsychotics	0.12	−0.09	0.21 (0.12 to 0.30)	0.06	0.03	0.04 (0.02 to 0.05)
Antidepressants	0.56	−0.02	0.58 (0.38 to 0.79)	0.47	0.27	0.19 (0.14 to 0.24)
Tricyclic antidepressants	0.05	−0.17	0.22 (0.13 to 0.31)	0.00	0.03	−0.04 (−0.06 to −0.01)
SSRI	0.33	0.01	0.33 (0.15 to 0.50)	0.34	0.15	0.20 (0.16 to 0.24)
Other antidepressants	0.22	0.06	0.16 (0.04 to 0.28)	0.17	0.10	0.07 (0.05 to 0.09)
Anxiolytics	0.22	−0.12	0.34 (0.21 to 0.48)	0.06	0.01	0.04 (0.02 to 0.06)
Hypnotics	0.16	−0.26	0.42 (0.26 to 0.59)	0.11	0.00	0.11 (0.08 to 0.14)

AChEI, acetylcholinesterase inhibitors.

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, that is, 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 AP (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 with 0.06 and 0.01 before and after AChEI use. Hypnotic use showed a similar pattern, table 2. 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 overprescription 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 (10.7–26.3%) 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 (5.9–13.4%). 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% 1 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 with non-dementia there was also an excess use of antidepressants increasing from 7.2% to 18.6% among people with dementia.

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 NPS in people with Mild

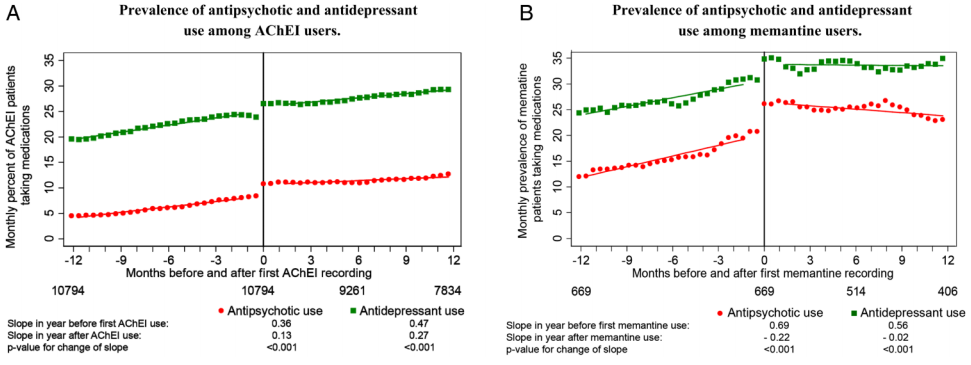

Figure 4 (A and B) Prevalence of antipsychotic and antidepressant use in the year before and after first use of AChEI and memantine, excluding patients without a previous prescription for the other compound, AChEI or memantine).

Cognitive Impairment (MCI) were apathy, depression, agitation, delusions, hallucinations and sleep impairment.[25] In MCI patients, NPS 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 actual diagnosis of dementia.

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] 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 contrary, 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 with 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 1995–2011. 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 National Institute for Health and Clinical Excellence (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 GPs 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 antidementia 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 AP at the start of memantine therapy compared with AChEI therapy; patients with more advanced disease would be expected to display more NPS.

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, while 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 antidementia 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 NPS of dementia 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 carehomes 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 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 AP.

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 AP 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 dementia because of the increasing awareness about AD and related conditions 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 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 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 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 AD 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 standardised 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 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 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 antidementia 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 NPS 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 AP.

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Contributors CM and RJ contributed equally. CM and SR conceived of and designed the study and 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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Competing interests All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: CM has received research support from Bayer Pharma AG, CSL Behring and Merz Pharmaceuticals, and consultancy from CSL Behring and Boehringer-Ingelheim. RWJ has served as a member of advisory boards for Elan Pharmaceuticals, Eli Lilly, Lundbeck, Merz Pharmaceuticals, Pfizer, a member of a data safety monitoring board for Roche pharmaceuticals, a consultant for Janssen Alzheimer Immunotherapy, Merz Pharmaceuticals and Nutricia, and has been on the speakers' bureau for Eisai, Elan, Lundbeck, Merz Pharmaceuticals, Novartis, Nutricia and Pfizer; his institution has received grants for clinical research from Abbott, Eli Lilly and Servier. SR has no conflict of interest to declare.

Ethics approval The Clinical Practice Research Datalink group obtained ethical approval from a multicentre research ethics committee. The Clinical Practice Research Datalink group obtained ethical approval from a multicentre research ethics committee for purely observational research using data from the database, such as ours.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

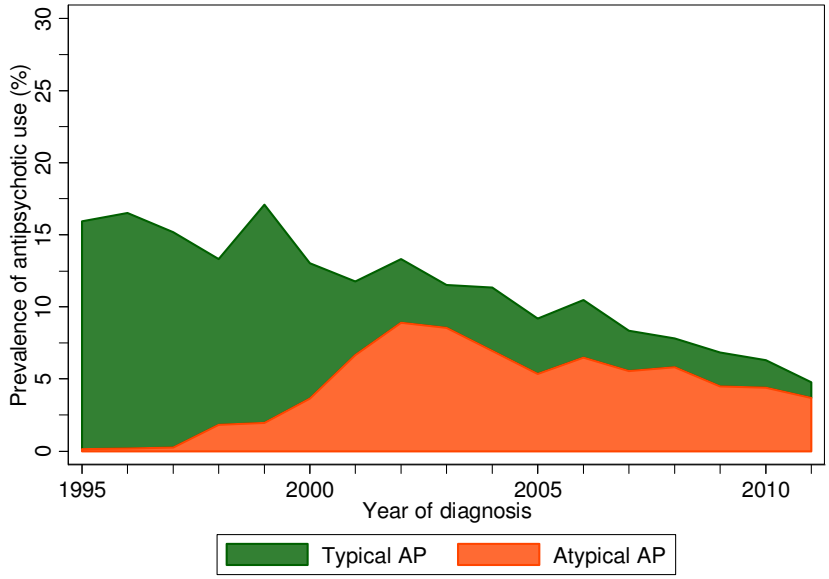
REFERENCES

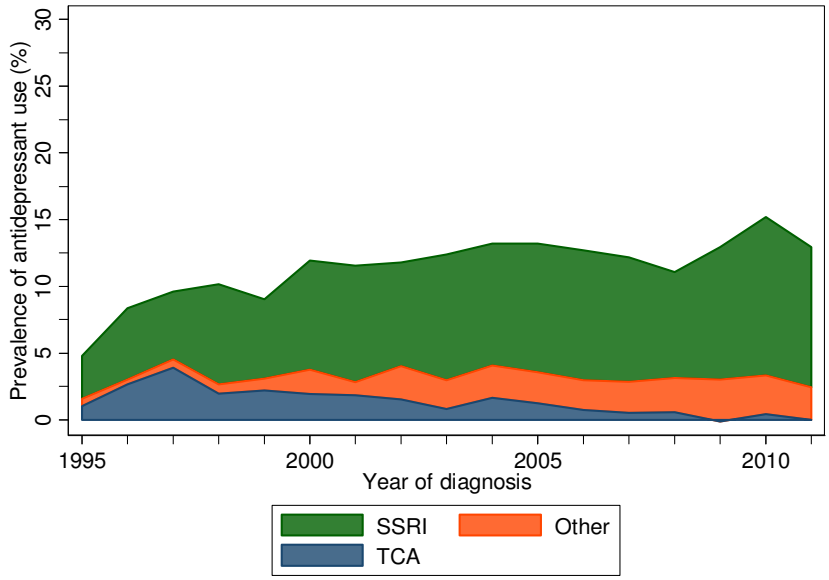
1. Georges J, Jansen S, Jackson J, *et al*. Alzheimer's disease in real life—the dementia carer's survey. *Int J Geriatr Psychiatry* 2008;23:546–51.
2. Steinberg M, Shao H, Zandi P, *et al*. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *Int J Geriatr Psychiatry* 2008;23:170–7.
3. Steele C, Rovner B, Chase GA, *et al*. Psychiatric symptoms and nursing home placement of patients with Alzheimer's disease. *Am J Psychiatry* 1990;147:1049–51.
4. Yaffe K, Fox P, Newcomer R, *et al*. Patient and caregiver characteristics and nursing home placement in patients with dementia. *JAMA* 2002;287:2090–7.
5. Schneider LS, Tariot PN, Dagerman KS, *et al*. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med* 2006;355:1525–38.
6. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. *Am J Geriatr Psychiatry* 2006;14:191–210.
7. Ballard C, Hanney ML, Theodoulou M, *et al*. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. *Lancet Neurol* 2009;8:151–7.
8. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 2005;294:1934–43.
9. Wang PS, Schneeweiss S, Avorn J, *et al*. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med* 2005;353:2335–41.
10. MHRA. Antipsychotics: use in elderly people with dementia. *Drug Saf* Update 2009;1:5.
11. U.S. Food and Drug Administration. Public Health Advisory. Deaths with antipsychotics in elderly patients with behavioural disturbances (Internet). 11 April 2005. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/UCM053171 (accessed 2 Aug 2012).
12. Banerjee S. The use of antipsychotic medication for people with dementia: time for action. An independent report commissioned and funded by the UK Department of Health. 2009. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_108302.pdf (accessed 9 Aug 2012).
13. Desplanques-Leperre A, Riolacci N, Blin, *et al*. Understanding and improving the prescription of psychotropic drugs in the elderly in France. Presented at the International Forum on Quality and Safety in Health Care (IFQSHC) (Internet). Presented 19 March 2009. http://www.has-sante.fr/portail/upload/docs/application/pdf/2009-03/abstract_has_ifqshc_march2009.pdf (accessed 2 Jul 2012).
14. Ballard CG, Gauthier S, Cummings JL, *et al*. Management of agitation and aggression associated with Alzheimer disease. *Nat Rev Neurol* 2009;5:245–55.
15. Wilcock GK, Ballard CG, Cooper JA, *et al*. Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: a pooled analysis of 3 studies. *J Clin Psychiatry* 2008;69:341–8.
16. Gauthier S, Loft H, Cummings J. Improvement in behavioural symptoms in patients with moderate to severe Alzheimer's disease by memantine: a pooled data analysis. *Int J Geriatr Psychiatry* 2008;23:537–45.
17. Trinh NH, Hoblyn J, Mohanty S, *et al*. Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a meta-analysis. *JAMA* 2003;289:210–16.
18. Holmes C, Wilkinson D, Dean C, *et al*. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. *Neurology* 2004;63:214–19.
19. Howard RJ, Juszczak E, Ballard CG, *et al*. Donepezil for the treatment of agitation in Alzheimer's disease. *N Engl J Med* 2007;357:1387–92.
20. Vidal JS, Lacombe JM, Dartigues JF, *et al*. Evaluation of the impact of memantine treatment initiation on psychotropics use: a study from the French national health care database. *Neuroepidemiology* 2008;31:193–200.
21. Kales HC, Zivin K, Kim HM, *et al*. Trends in antipsychotic use in dementia 1999–2007. *Arch Gen Psychiatry* 2011;68:190–7. Erratum in: *Arch Gen Psychiatry*. 2011 May;**68**:466. Ignacio, Rosalindo (corrected to Ignacio, Rosalinda V). PubMed PMID: 21300946.
22. Wood L, Martinez C. The general practice research database: role in pharmacovigilance. *Drug Saf* 2004;27:871–81.
23. Read Codes—NHS Connecting for Health. http://www.connectingforhealth.nhs.uk/systemsandservices/data/uktc/readcodes (accessed 2 Nov 2012).
24. Wagner AK, Soumerai SB, Zhang F, *et al*. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* 2002;27:299–309.
25. Lyketsos CG, Lopez O, Jones B, *et al*. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment. *JAMA* 2002;288:1475–83.
26. Modrego PJ, Ferrández J. Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: a prospective cohort study. *Arch Neurol* 2004;61:1290–3.
27. National Dementia and Antipsychotic Prescribing Audit 2012. Health and Social Care Information Centre. http://www.ic.nhs.uk/webfiles/Services/NCASP/audits%20and%20reports/National_Dementia_and_Antipsychotic_Prescribing_Audit_National_Report_V1.0_17_07_12_Interactive.pdf (accessed 8 Nov 2012).
28. Coupland C, Dhiman P, Morriss R, *et al*. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ* 2011;343:d4551.
29. Citalopram and escitalopram: QT interval prolongation—new maximum daily dose restrictions (including in elderly patients), contraindications, and warnings. *Drug Saf* Update 2011;5:A1.
30. Seitz DP, Adunuri N, Gill SS, *et al*. Antidepressants for agitation and psychosis in dementia. *Cochrane Database Syst Rev* 2011;(2):CD008191.
31. Passmore AP, Craig DA. The future of memory clinics. *Psychiatrist* 2004;28:375–7.
32. NHS Workforce Review Team 2008. Workforce summary—old age psychiatry. http://www.cfwi.org.uk/intelligence/previous-projects/workforce-summaries/old-age-psychiatry (accessed 2 Nov 2012).
33. NICE technology appraisal guidance 111. Donepezil, galantamine, rivastigmine (review) and memantine for the

treatment of Alzheimer's disease. November 2006 (amended September 2007, August 2009) (amended). This guidance has been replaced by TA217 and is no longer available. http://publications.nice.org.uk/donepezil-galantamine-rivastigmine-review-and-memantine-for-the-treatment-of-alzheimers-ta111 (accessed 2 Nov 2012).
34. NICE technology appraisal guidance 217 Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease. Review of NICE technology appraisal guidance 111. Issued March 2011. http://www.nice.org.uk/nicemedia/live/13419/53619/53619.pdf (accessed 8 Jun 2011).
35. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. *Cochrane Database Syst Rev* 2006;(2):CD003154.
36. Fox C, Crugel M, Maidment I, *et al*. Efficacy of memantine for agitation in Alzheimer's disease: a randomised double-blind placebo controlled trial. *PLoS One* 2012;7:e35185.
37. Howard R, McShane R, Lindesay J, *et al*. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med* 2012;366:893–903.
38. Craig D, Mirakhur A, Hart DJ, *et al*. A cross-sectional study of neuropsychiatric symptoms in 435 patients with Alzheimer's disease. *Am J Geriatr Psychiatry* 2005;13:460–8.

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 prescription rate of antidementia drugs per 100 dementia patients since 1995