TITLE

What is the impact of regulatory guidance and expiry of drug patents on dementia drug prescriptions in England: a trend analysis in the Clinical Practice Research Datalink

CO-AUTHORS

Venexia M Walker (corresponding author)
Affiliations: Bristol Medical School, University of Bristol, Bristol, UK; MRC University of Bristol Integrative Epidemiology Unit, Bristol, UK
Address: Bristol Medical School, University of Bristol, Oakfield House, Oakfield Grove, Bristol, BS8 2BN
Email: venexia.walker@bristol.ac.uk

Neil M Davies
Affiliations: Bristol Medical School, University of Bristol, Bristol, UK; MRC University of Bristol Integrative Epidemiology Unit, Bristol, UK
Address: Bristol Medical School, University of Bristol, Oakfield House, Oakfield Grove, Bristol, BS8 2BN
Email: neil.davies@bristol.ac.uk

Patrick G Kehoe
Affiliations: Dementia Research Group, Bristol Medical School, University of Bristol, Bristol, UK
Address: Dementia Research Group, University of Bristol, Level 1, Learning & Research, Southmead Hospital, Bristol, BS10 5NB
Email: patrick.kehoe@bristol.ac.uk

Richard M Martin
Affiliations: Bristol Medical School, University of Bristol, Bristol, UK; MRC University of Bristol Integrative Epidemiology Unit, Bristol, UK
Address: Bristol Medical School, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS
Email: richard.martin@bristol.ac.uk

ABSTRACT

Background: Drugs for dementia have been available in England from 1997. Since their launch, there have been several changes to national guidelines and initiatives that may have influenced prescribing. These include changes in National Institute for health and Care Excellence (NICE) guidance; several government dementia strategies; the addition of dementia to the Quality and Outcomes Framework (QOF); and the expiry of drug patents. Despite this, there has been little research into the effect of these events on prescribing. This paper examines prescribing trends in England using data from the UK Clinical Practice Research Datalink since the launch of drugs for dementia up to 1st January 2016.

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Methods: We considered the monthly proportion of patients eligible for treatment, with a diagnosis of probable Alzheimer's disease, receiving their first prescription for each drug class – namely acetylcholinesterase (AChE) inhibitors (donepezil, rivastigmine, galantamine) and N-Methyl-D-aspartate (NMDA) receptor antagonists (memantine). Trend analysis using joinpoint models was then applied to identify up to two trend changes per treatment of interest.

Results: The overall trend was for increasing prescriptions in each drug class over the period they were studied. This was indicated by the average monthly percentage change, which was 6.0% (95% CI: -6.4 to 19.9; June 1997 to December 2015) for AChE inhibitors and 15.4% (95% CI: -77.1 to 480.9; January 2003 to December 2015) for NMDA receptor antagonists. Prescriptions of AChE inhibitors increased at the end of 2012, probably in response to the patent expiry of these drugs earlier that year. The Prime Minister's Dementia Challenge launched in May 2012 may also have contributed to the observed increase. However, neither this strategy nor patent expiry appeared to influence prescriptions of NMDA receptor antagonists. Instead trend changes in this drug class were driven by NICE guidance released in 2011 that allowed access to these drugs outside of clinical trials.

Conclusions: Dementia drug prescribing does not always respond to factors such as regulatory guidance, recommendations or patent expiry and, when it does, not necessarily in a predictable way. This suggests that improved communication with clinicians may be needed to improve the cost-effective use of drugs for dementia.

KEYWORDS

Alzheimer Disease, Dementia, Donepezil, Rivastigmine, Galantamine, Memantine, Clinical Practice Research Datalink, National Institute of health and Clinical Excellence, Quality and Outcomes Framework, England

BACKGROUND

There are currently four licensed treatments that provide symptomatic relief for patients with Alzheimer's disease in England - three acetylcholinesterase (AChE) inhibitors (donepezil, rivastigmine, galantamine) and one N-Methyl-D-aspartate (NMDA) receptor antagonist (memantine). [1] Since the first of these drugs became available in 1997, there have been several changes in national guidelines for the treatment of Alzheimer's disease, as well as several initiatives to encourage better diagnosis and treatment of the disease. Despite this, there has been little research into whether such changes to guidelines and initiatives have directly influenced clinical practice. We examined how prescription rates in England have changed since the launch of these drugs up to 1st January 2016, using data from the UK Clinical Practice Research Datalink (CPRD). We investigated how prescribing was affected by changes in National Institute of health and Care Excellence (NICE) guidance (including the 2006 guidance that was subject to legal challenges); the addition of dementia to the Quality and Outcomes Framework (QOF); the introduction of ambitious government dementia strategies and the expiry of drug patents. The timings of each of these changes, which may have influenced aspects of drug prescribing and clinical practice, are discussed further below and summarized in Table 1.

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Table 1: Events prior to 1st January 2016 that potentially effected prescription rates.

Event Date	Event
May 1997	Donepezil first recorded in CPRD
September 1998	Rivastigmine first recorded in CPRD
January 2001	Galantamine first recorded in CPRD and first NICE guidance released
December 2002	Memantine first recorded in CPRD
May 2006	NICE recommend restricting drug access
September 2007	QOF revised to include dementia
February 2009	First National Dementia Strategy launched
May 2011	NICE remove recommendation restricting drug access
January 2012	Galantamine patent expired
February 2012	Donepezil patent expired
May 2012	Prime Minister's Dementia Challenge launched
July 2012	Rivastigmine patent expired
April 2014	Memantine patent expired
February 2015	Prime Minister's Challenge on Dementia 2020 launched

CPRD: Clinical Practice Research Datalink; NICE: National Institute for health and Care Excellence; QOF: Quality and Outcomes Framework.

NICE guidance on the prescribing of drugs for dementia

In the past NICE guidance has used scores from the mini mental state examination (MMSE), in combination with other measures, to guide whether a patient should be prescribed a drug for dementia. The test, proposed in 1975 by Folstein et al, scores a patient's cognition out of 30, where normal cognition is considered as a score of 24 or more. [2] The original NICE guidance, issued in 2001, on the use of drugs to treat Alzheimer's disease recommended that the three AChE inhibitors should be used for all patients scoring 12 or above on the MMSE until the drugs were deemed no longer effective. [3,4] In June 2006, NICE revised their guidance so that the use of AChE inhibitors was restricted to patients with moderate Alzheimer's disease – this was defined as patients scoring between 10 and 20 points on the MMSE. The 2006 guidance was also the first to consider the use of the NMDA receptor antagonist, memantine, which was recommended for use only in clinical trials for patients with moderate to severe disease. [5] This revision of the guidance was controversial due to the way in which it assessed cost effectiveness, which was expected to restrict access to these drugs, and was ultimately the subject of a high court challenge by the Alzheimer's society and two drug manufacturers: Eisai and Pfizer. [6–8] This led to a further revision being made to the NICE guidance at the end of May 2011, which recommended AChE inhibitors for patients with mild to moderate Alzheimer's disease and memantine for patients with moderate to severe Alzheimer's disease, or who could not tolerate AChE inhibitors. [9] The most recent NICE guidance was issued in 2016, however this guidance did not change any of the recommendations relating to specific drugs. In all iterations of the NICE guidance up to 2016, i.e. for the duration of our study, treatment had to be initiated by a specialist. As of September 2016, this has changed to include GPs and other healthcare professionals who have specific training. [10] Treatment has, and continues to be, deemed effective as long as there has been "an improvement or no

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deterioration in MMSE score, together with evidence of global improvement on the basis of behavioral and/or functional assessment." [4]

Inclusion of dementia on the QOF

QOF is a voluntary incentive program, introduced in 2004, to improve services in primary care. [11] Dementia first appeared in QOF as an 'indicator' in September 2007. [12] There are currently three indicators for dementia included in the framework. The first requires that the practice establish and maintain a register of patients diagnosed with dementia and the further two indicators refer to the ongoing management of the disease. [13] The inclusion of dementia on the QOF could therefore have encouraged more of a focus on the diagnosis and pharmacological management of the disease in participating practices.

Government dementia strategies

The first National Dementia Strategy was launched by the Department of Health in February 2009. The aim of that strategy was "to ensure that significant improvements are made to dementia services across three key areas: improved awareness, earlier diagnosis and intervention, and a higher quality of care". [14] This strategy was followed in 2012 by the Prime Minister's Dementia Challenge, which looked to improve care and research by 2015, and more recently the Prime Minister's Challenge on Dementia 2020. [15,16] The most recent strategy aims to build on the work of its predecessors to make England the best place for both dementia care and research. In general such strategies may help to increase the awareness of dementia for both the public and health services. [17,18]

Drug patents

The charity King's fund found that the prescription of generic drugs over their patented alternatives has "saved the NHS around £7.1 billion and allowed more than 490 million more items to be prescribed to patients" between 1976 and 2013. [19] AChE inhibitors for the treatment of Alzheimer's disease became available generically from 2012, while NMDA receptor antagonists became available generically from 2014 (Table 2). [20] Therefore, in recent years the cost of drugs for dementia has reduced significantly from previous years. This serves as a potential factor in rates of prescribing, particularly in publically funded health care services such as the NHS in England.

Table 2: Patent information for the drugs for dementia. [20]

Generic name	Patent name	Drug class	Patent expiry
Donepezil	Aricept	AChE inhibitor	January 2012
Rivastigmine	Exelon	AChE inhibitor	February 2012
Galantamine	Reminyl	AChE inhibitor	July 2012
Memantine	Ebixa	NMDA receptor antagonist	April 2014

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METHODS

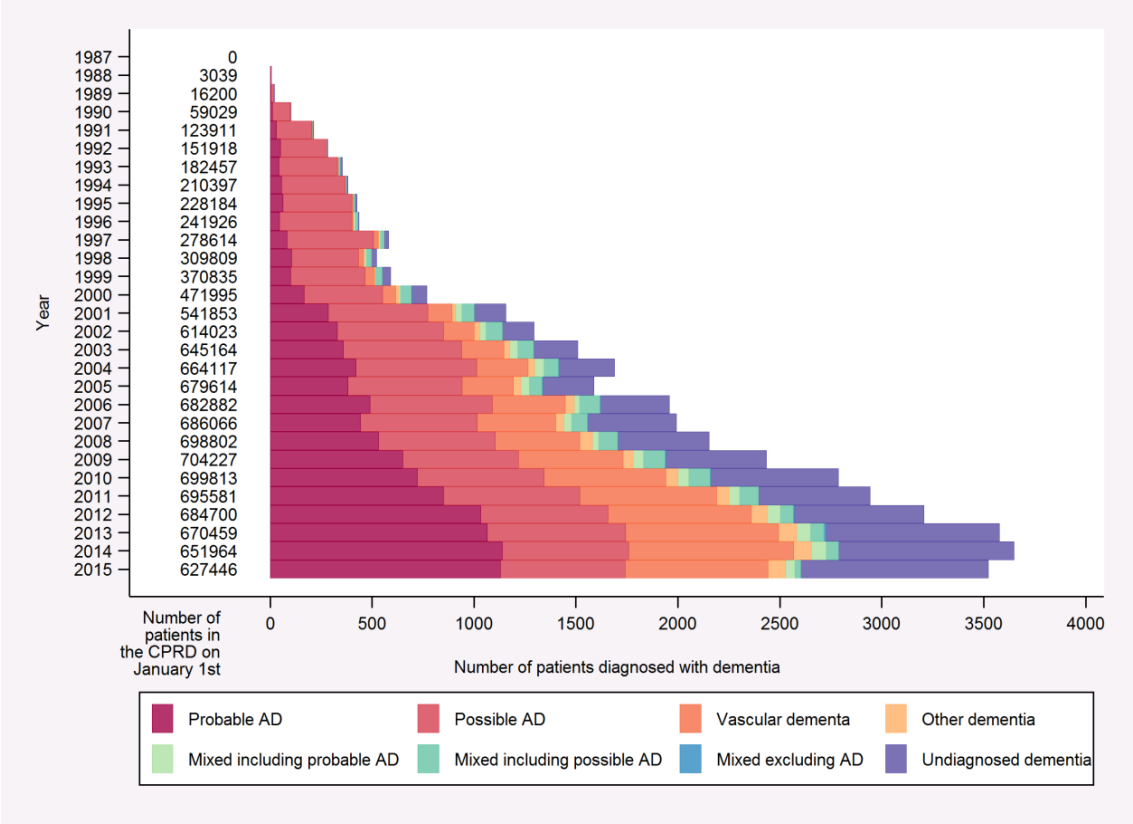
Aim

The aim of the study was to examine prescribing trends in England from the launch of the drugs for dementia up to 1st January 2016, using data from the CPRD. [Approved by the CPRD's Independent Scientific Advisory Committee, ISAC Protocol ID 15_246R.]

Design

This study was a joinpoint analysis of the proportion of patients, who were eligible for treatment and had a diagnosis of 'probable Alzheimer's disease', that received their first prescription for the treatment of interest in each month. We defined patients as eligible for their first prescription if they had the diagnosis of interest with no previous prescription for the treatment of interest. The time period was measured in units of one month as this was the smallest clinically meaningful measure we could realistically define. We investigated treatment rates as a proportion of eligible patients, because the underlying rate of diagnosis of dementia has changed over time in the CPRD, as illustrated in Figure 1.

Figure 1: Bar graph illustrating the number of patients diagnosed with dementia, by diagnosis type.



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The data presented here is restricted to patients who received a diagnosis prior to 1st January 2016 and are from an English practice with a last data collection date in 2016 to reflect the main analysis. Definitions for each of the diagnoses are presented in Table 3.

The four treatments for dementia were separated according to drug class, i.e. AChE inhibitors (donepezil, rivastigmine and galantamine) and NMDA receptor antagonists (memantine), in the main analysis. Exposure date was taken to be the date on which the first prescription requesting the drug(s) being considered was recorded. This allowed patients who had previously been prescribed AChE inhibitors to be included in the NMDA receptor antagonist analysis. This is necessary as NMDA receptor antagonists may be prescribed alongside AChE inhibitors and are often given to patients later in the course of their disease, potentially following exposure to AChE inhibitors.

Setting

This study used data from the CPRD, an ongoing UK-based primary care database, established in 1987, which includes data on "over 11.3 million patients from 674 practices in the UK" to date. The CPRD is "broadly representative of the UK general population" and was generally comparable to the last census in 2011 for age, sex, and ethnicity. Young people and smaller practices tend to be slightly underrepresented in the database. [21,22] The data used in this study were obtained as part of a larger project investigating whether commonly prescribed drugs can be repurposed for the prevention or treatment of Alzheimer's and other neurodegenerative diseases. [23] For this project, we sampled patients older than 40 years with at least 12 consecutive months of records classified as 'acceptable' by the CPRD from an 'up to standard' practice. The data were taken from the March 2016 CPRD GOLD database snapshot, which covered the period from January 1st 1987 to February 29th 2016 inclusive.

Sample

For this study, we considered the data available from January 1st 1987 to December 31st 2015 inclusive, from practices with a last data collection date in 2016 - this ensured all data were complete for the timeframe being considered. We also restricted the data to English practices. This is because guidelines and initiatives can differ by nation in the UK – for example, all nations are subject to patent expiry but the National Dementia Strategy is only applicable to England, with other nations having their own strategies. Additional file 1 presents a sensitivity analysis investigating the effect of limiting the study to practices in England. The analysis concludes that as the majority of the CPRD data is obtained from English practices and the proportion of people included in the study is similar for England and the CPRD as whole, the representativeness of the CPRD is likely to have been preserved in our study. To be included in the study, a patient had to have a diagnosis of dementia as determined by a Read or product code (see Additional files 2 and 3 for code lists). Read and product codes uniquely identify clinical terms and prescriptions respectively in the CPRD and are recorded by the GP at the time of the consultation with the date. [24] The diagnoses and their definitions are provided in Table 3. The diagnosis was defined based on the combination of codes from the following Read code lists - probable Alzheimer's disease, possible Alzheimer's disease, other dementia, vascular dementia - as well as the following product code lists: donepezil, rivastigmine, galantamine, memantine. We used treatment to define diagnosis under the assumption that

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treatment implies diagnosis. Diagnosis date was taken to be the first date on which a code from any of the lists was recorded. We performed a sensitivity analysis to test the diagnosis definitions, which is presented in full in Additional file 4 with the necessary code lists provided in Additional file 5. For this, we considered the sensitivity and specificity of both the code lists (possible Alzheimer's disease, probable Alzheimer's disease, non-specific dementia, other dementia, and vascular dementia) and the diagnoses (Table 3) in the CPRD dataset. Linked data from the Office of National Statistics (ONS) death registry and the Hospital Episode Statistics (HES) inpatient dataset were used as the comparators.

Table 3: Diagnosis definitions used in the study, presented with the number of patients.

Diagnosis	Definition	Patients
Probable AD	One or more codes on the list 'probable AD'. Patients who also have codes on the list 'possible AD' are included.	10651
Possible AD	One or more codes on the list 'possible AD' only.	12167
Vascular dementia	One or more codes on the list 'vascular dementia' only.	7058
Other dementia	One or more codes on the list 'other dementia' only.	827
Mixed including probable AD	One or more codes on the list 'probable AD', with one or more codes from either 'vascular dementia', 'other dementia' or both. Patients who also have codes on the list 'possible AD' are included.	697
Mixed including possible AD	One or more codes on the list 'possible AD', with one or more codes from either 'vascular dementia', 'other dementia' or both.	1347
Mixed excluding AD	One or more codes on the list 'vascular dementia' and one or more codes on the list 'other dementia'.	39
Undiagnosed dementia	One or more codes on the list 'non-specific dementia' and/or one or more codes on any of the following lists: 'donepezil', 'rivastigmine', 'galantamine' and 'memantine'. No codes on the lists 'probable AD', 'possible AD', 'other dementia' or 'vascular dementia'.	7416
Total	**One or more codes on any of the following lists: 'probable AD', 'possible AD', 'other dementia', 'vascular dementia', 'donepezil', 'rivastigmine', 'galantamine' and 'memantine'.**	**40202**

AD: Alzheimer's disease; CPRD: Clinical Practice Research Datalink. The data presented here is restricted to patients who received a diagnosis prior to 1st January 2016 and are from an English practice with a last data collection date in 2016 to reflect the main analysis.

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Analysis

The analysis of each treatment of interest started on the first day of the month following the first recorded prescription for that treatment. For example, the first prescription for memantine occurred on 16th December 2002 and so the analysis of this drug started on 1st January 2003. Table 4 details the timescale for the main analyses. For each patient, we used the month and year of their diagnosis (as defined in Table 3) and, if applicable, their first prescription. For each month, we calculated: (A) the number of patients receiving their first prescription in that month; and (B) the number of patients with a diagnosis who had not received treatment before the first of the month. Dividing A by B provided the proportion of patients with diagnoses who received their first prescription for the treatment of interest each month. We also calculated the standard error of this proportion. Trend analysis using joinpoint models was then conducted. The optimum number of joinpoints, as determined by the software and up to a maximum number of two, was used to select the model. We refer to the period between two joinpoints as a 'segment' and number them chronologically. Our model assumes that the rate of prescription "changes at a constant percentage of the rate of the previous year" and so is determined by the following equation: $\ln y = xb$. This allows us to consider the monthly percent change. The trend over the entire study period is summarized using the average monthly percent change. This is calculated as the average of the monthly percent changes, weighted by segment length. [25] All analysis was conducted using Joinpoint Regression Program (version 4.3.1.0; National Cancer Institute, USA) and Stata (version 14.1; StataCorp, USA). [26,27] The model specifications for the joinpoint analyses are provided in Additional file 6. The Stata code used in this analysis is available online from GitHub. [28]

Table 4: Patient numbers and dates for the main analyses.

Analysis	First record in CPRD	Analysis start date	Treated patients	Eligible patients
AChE inhibitors	30/05/1997	01/06/1997	5019	10456
NMDA receptor antagonists	16/12/2002	01/01/2003	1052	9964

Donepezil, rivastigmine and galantamine are acetylcholinesterase (AChE) inhibitors and memantine is an N-Methyl-D-aspartate (NMDA) receptor antagonist. The end date of the study is 31st December 2015.

RESULTS

Trend analysis for AChE inhibitors

The proportion of patients with probable Alzheimer's disease receiving their first prescription for an AChE inhibitor increased throughout the study period (Figure 2). This is reflected in the average monthly percent change, which was 6.0 (95% CI: -6.4 to 19.9) for the period from June 1997 to December 2015. For much of the study period, the trend was for an increasing proportion of patients to receive their first prescription for an AChE inhibitor with a monthly percent change of 5.4 (95% CI: 4.2 to 6.7). In October 2012 (95% CI: September 2011 to April 2013, p-value=0.816), the prescription rate surged with a monthly percent change of 67.2 (95% CI: -96.6 to 8179.8). Less than a year later, in May 2013 (95% CI: November 2012 to April 2014,

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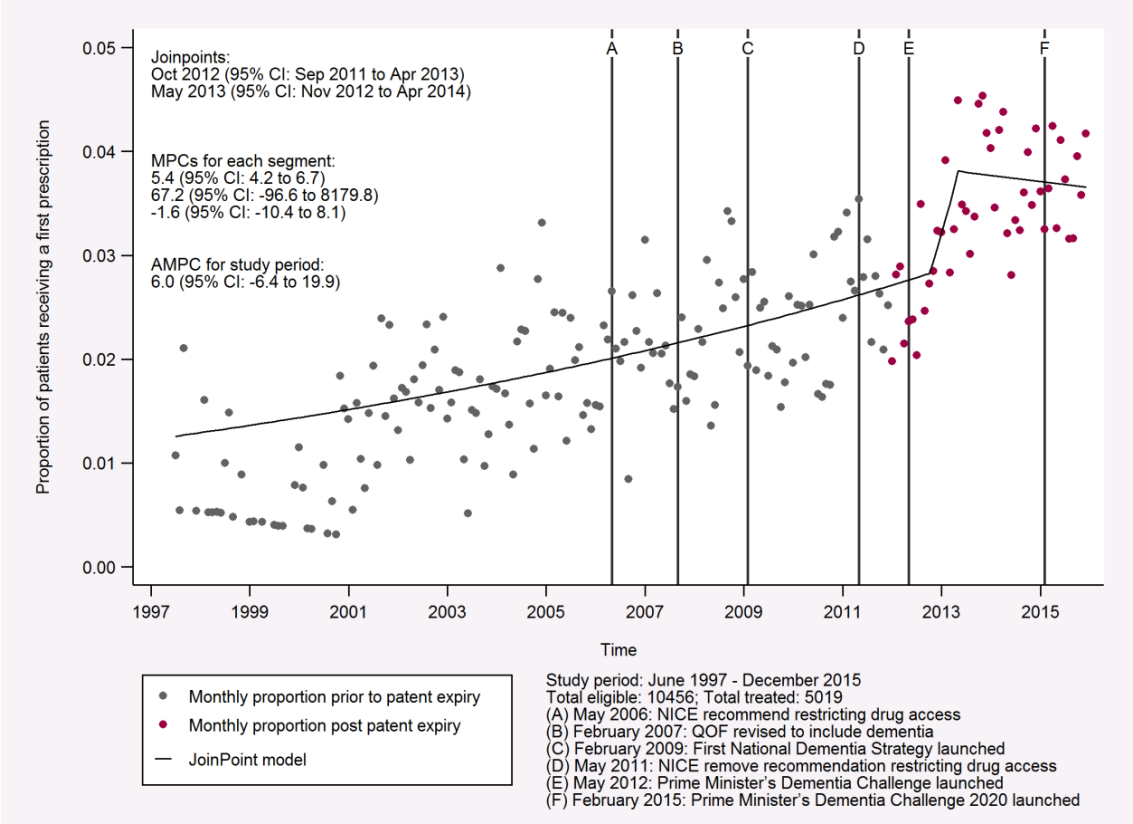
p-value=0.789), the trend reversed so that prescription rates were falling. In the months that followed, the monthly percent change had a value of -1.6 (95% CI: -10.4 to 8.1), falling below zero for the first time since the launch of these drugs.

Figure 2: Indicative graph of AChE inhibitor prescriptions in patients with probable Alzheimer's disease.



This graph shows the proportion of patients with probable Alzheimer's disease receiving their first prescription for an AChE inhibitor (donepezil, rivastigmine, or galantamine) each month from June 1997 to December 2015. The fixed lines indicate events with the potential to effect prescription rates during the study period. The joinpoints, monthly percent change (MPC) for each segment and the average monthly percent change (AMPC) for the entire study period are also presented.

Trend analysis for NMDA receptor antagonists

Figure 3 presents the equivalent analysis for the NMDA receptor antagonist, memantine, which was released after the AChE inhibitors. The analysis of this drug therefore started in January 2003, instead of June 1997. Memantine was also prescribed much less than the other drugs with a total of 1052 patients treated in this analysis compared with 5019 in the corresponding AChE inhibitor analysis, despite similar numbers of eligible patients. This is partly related to the indication of these drugs. Memantine is generally recommended for more advanced disease than the AChE inhibitors and is often added to a prescription of AChE inhibitors following progression of the disease. Despite this, as observed for the AChE inhibitors, the proportion of

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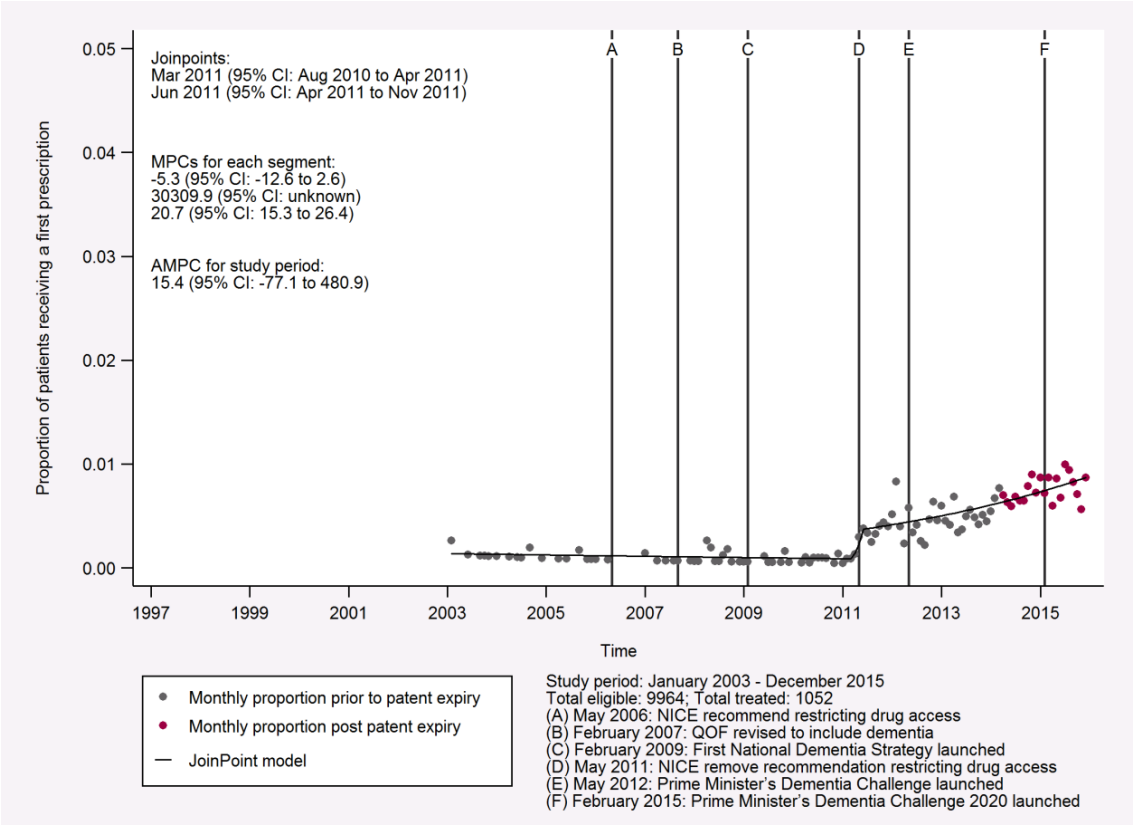
patients with probable Alzheimer's disease receiving their first prescription for an NMDA receptor antagonist increased on average throughout the study period. The average monthly percent change for the period from January 2003 to December 2015 was 15.4 (95% CI: -77.1 to 480.9), though the 95% CI around this estimate is large. The initial trend for prescribing of this drug showed a reduced number of prescriptions in the time that followed the launch with a monthly percent change of -5.3 (95% CI: -12.6 to 2.6). This changed around March 2011 (95% CI: August 2010 to April 2011, p-value=0.892) to a very strong trend for increased prescribing. From the second trend change in June 2011 (95% CI: April 2011 to November 2011, p-value=0.896) until the end of the study in December 2015, this trend reduced to a monthly percent change of 20.7 (95% CI: 15.3 to 26.4). This indicates a continuing increase in the prescriptions for NMDA receptor antagonists in recent years, albeit substantially reduced from the rise observed between March and June 2011. The complete output for both this analysis and that relating to AChE inhibitors is provided in Additional file 7, along with the analysis of each of the drugs individually instead of by class.

Figure 3: Indicative graph of NMDA receptor antagonist prescriptions in patients with probable Alzheimer's disease.



This graph shows the proportion of patients with probable Alzheimer's disease receiving their first prescription for an NMDA receptor antagonist (memantine) each month from January 2003 to December 2015. The fixed lines indicate events with the potential to effect prescription rates during the study period. The joinpoints, monthly percent change (MPC) for each segment and the average monthly percent change (AMPC) for the study period are also presented.

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Sensitivity analyses

We performed a sensitivity analysis to test the diagnosis definitions by calculating the sensitivity and specificity of both the code lists (possible Alzheimer's disease, probable Alzheimer's disease, non-specific dementia, other dementia, and vascular dementia) and the diagnoses (Table 3) in the CPRD dataset. For this analysis, the CPRD was compared against linked data from the Office of National Statistics (ONS) death registry and the Hospital Episode Statistics (HES) inpatient dataset. The results of this analysis are presented in Additional file 4. The linked data uses the International Statistical Classification of Diseases and Related Health Problems (ICD) codes, instead of Read codes, and so the code lists necessary for the sensitivity analysis are included in Additional file 5. In this analysis, we found there to be high specificity (HES: 40.3-98.3%; ONS: 38.1-97.5%) and low sensitivity (HES: 18.8-66.9%; ONS: 46.7-69.5%) for the code lists. The diagnoses, which rely on multiple code lists, reflected this pattern with an even higher specificity (HES: 74.5-99.9%; ONS: 73.4-99.9%) and lower sensitivity (HES: 1.3-61.2%; ONS: 6.9-65.5%). The high specificity demonstrated in this analysis reflects our conservative approach when constructing the code lists. As a consequence of this, we expected a lower sensitivity and this is in line with what we observed.

To further test the diagnosis definition, an analysis similar to the main analysis was undertaken wherein the diagnosis definition was relaxed from 'probable Alzheimer's disease' to include other codes. We did this in two ways: (1) introducing codes that represented what may be lesser degrees of confidence in the accuracy of Alzheimer's disease diagnosis (termed 'any Alzheimer's disease') and (2) introducing codes capturing other types of dementia (termed 'any dementia'). The results of these further analyses are provided in Additional files 7 and 8 and present data on 'any Alzheimer's disease' and 'any dementia' respectively. Finally, the analysis of individual drugs for each of the diagnosis definitions has also been considered and is presented in the respective Additional files (Additional file 7 for the main analysis, 8 for 'any Alzheimer's disease' and 9 for 'any dementia'). A summary of the results from all analyses (both those presented in the main analysis and those included in Additional files 7-9) can be found in Table 5. The table shows that the joinpoint analysis is consistent regardless of the diagnosis definition used for both the drug class NMDA receptor antagonists (memantine) and for one of the three AChE inhibitors, galantamine. The joinpoint estimates for the AChE inhibitor analysis vary according to the diagnosis definition used though the two sensitivity analyses are reasonably consistent with each other. This is also true for the remaining two AChE inhibitors, donepezil and rivastigmine, which are likely to cause the pattern seen in the all AChE inhibitor analysis.

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Table 5: Comparison of the sample sizes and joinpoint estimates, presented with 95% CIs, for all analyses.

	Probable AD	Any AD	Any dementia
Source	Main analysis and Additional file 7	Additional file 8	Additional file 9
Included code lists	Probable AD	Probable AD Possible AD Mixed incl. probable AD Mixed incl. possible AD	Probable AD Possible AD Vascular dementia Other dementia Mixed incl. probable AD Mixed incl. possible AD Mixed excluding AD Undiagnosed dementia
AChE inhibitors	Eligible: 10456 Treated: 5019 Joinpoint 1: Oct 2012 (Sep 2011 – Apr 2013) Joinpoint 2: May 2013 (Nov 2012 – Apr 2014)	Eligible: 23371 Treated: 6942 Joinpoint 1: Jun 1999 (Jul 1998 – Nov 2000) Joinpoint 2: Jun 2001 (Sep 2000 – Dec 2001)	Eligible: 38650 Treated: 9896 Joinpoint 1: Aug 2000 (Jun 1998 – Nov 2000) Joinpoint 2: Jan 2001 (Sep 2000 – Nov 2001)
NMDA receptor antagonists	Eligible: 9964 Treated: 1052 Joinpoint 1: Mar 2011 (Aug 2010 – Apr 2011) Joinpoint 2: Jun 2011 (Apr 2011 – Nov 2011)	Eligible: 20817 Treated: 1432 Joinpoint 1: Sep 2010 (Mar 2010 – Apr 2011) Joinpoint 2: Oct 2011 (Apr 2011 – Feb 2012)	Eligible: 35625 Treated: 1961 Joinpoint 1: Aug 2010 (Nov 2009 – Dec 2010) Joinpoint 2: Nov 2011 (Aug 2011 – Mar 2012)
Donepezil	Eligible: 10456 Treated: 4192 Joinpoint 1: Aug 2009 (Apr 2007 – Sep 2010) Joinpoint 2: None	Eligible: 23371 Treated: 5635 Joinpoint 1: Feb 2002 (Feb 2001 – Jul 2003) Joinpoint 2: May 2008 (Jul 2006 – Sep 2010)	Eligible: 38650 Treated: 7611 Joinpoint 1: Nov 2001 (Apr 2001 – Nov 2002) Joinpoint 2: Feb 2009 (Mar 2007 – Jun 2010)
Rivastigmine	Eligible: 10395 Treated: 515 Joinpoint 1: Feb 2005 (Feb 2004 – Nov 2007) Joinpoint 2: None	Eligible: 22887 Treated: 806 Joinpoint 1: Jun 2009 (Jan 2006 – May 2010) Joinpoint 2: Jul 2010 (Sep 2009 – May 2014)	Eligible: 38130 Treated: 1621 Joinpoint 1: Aug 2007 (Oct 2005 – Apr 2014) Joinpoint 2: Aug 2010 (Jul 2008 – Nov 2014)
Galantamine	Eligible: 10224 Treated: 603 Joinpoint 1: Jan 2007 (Mar 2004 – Feb 2009) Joinpoint 2: Jan 2014 (Jan 2013 – Jan 2015)	Eligible: 21888 Treated: 902 Joinpoint 1: Nov 2006 (May 2004 – Apr 2008) Joinpoint 2: Nov 2013 (Mar 2013 – Sep 2014)	Eligible: 36994 Treated: 1188 Joinpoint 1: Aug 2006 (Jan 2005 – Dec 2007) Joinpoint 2: Nov 2013 (Feb 2013 – Sep 2014)

AD: Alzheimer's disease. Donepezil, rivastigmine and galantamine are acetylcholinesterase (AChE) inhibitors and memantine is an N-Methyl-D-aspartate (NMDA) receptor antagonist.

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DISCUSSION

The first trend change for the proportion of patients with probable Alzheimer's disease receiving their first prescription for an AChE inhibitor occurred in October 2012 (CI: September 2011 to April 2013, p-value=0.816). At this time, a long term steady increasing trend became a very strong increasing trend. This surge could be related to two factors. Firstly, the patents expired on the three drugs in this class in 2012 – galantamine in January 2012; donepezil in February 2012; and rivastigmine in July 2012. Secondly, the Prime Minister's Dementia Challenge launched in May 2012. It is likely that the reduction in cost of these drugs, which resulted from their patents expiring, in combination with increased awareness of dementia due to the Prime Minister's Dementia Challenge led to this substantial change in prescription rates we observed. The second trend change in the AChE inhibitor analysis occurred in May 2013 (CI: November 2012 to April 2014, p-value=0.789), less than a year after the initial change for this drug class and with overlapping 95% CIs. This change signals the end of the surge in prescribing and the start of a decreasing trend in prescriptions. This is not unexpected as patent expiry may have led to a form of 'catch up prescribing', whereby people who were previously denied access to the drug were granted access at this time because of its newly reduced cost. This would result in the apparent decreasing trend once 'catch up prescribing' was complete, which is suggested by the trend analysis but is not as clear when considering the raw data points.

The trend changes in the NMDA receptor antagonist analysis occurred in March 2011 (CI: August 2010 to April 2011, p-value=0.891) and June 2011 (CI: April 2011 to November 2011, p-value=0.896). Notably the 95% CI for the first trend change ends in April 2011, which is when the 95% CI for the second trend change begins. This suggests that the trend changes may be related. The first of these trend changes marks the start of a strong increasing trend that changes to a steady increasing trend following the second trend change. In May 2011 NICE introduced guidelines that recommended the prescription of memantine for patients with moderate to severe Alzheimer's disease, or those people who could not tolerate AChE inhibitors. This replaced existing guidelines that restricted access to memantine to patients participating in clinical trials. It would therefore seem that these trend changes relate to the transition between the existing guidelines and those introduced in May 2011. Interestingly, neither of the trend changes in the NMDA receptor antagonist analysis align with those observed for the AChE inhibitors. This suggests that the NICE guidelines, which were implemented at the same time for both drug classes, may not have been effective for AChE inhibitors. This is likely due to the fact that these drugs were available outside of clinical trials prior to the restrictive guidelines recommended in 2006.

Looking at the results of all analyses, presented in Table 5, we observed that the joinpoint analysis is consistent, regardless of the diagnosis definition used, for the NMDA receptor antagonists but not for AChE inhibitors. All analyses of the NMDA receptor antagonists found two joinpoints to be optimum. The first of the joinpoints occurred in the seven-month period between August 2010 and March 2011 and the second occurred in the six-month period between June 2011 and November 2011. This high level of consistency across diagnosis definitions indicates a clear pattern in prescribing of the NMDA receptor antagonists, suggestive of a distinct change in practice. This provides additional support for our inferences concerning the impact of the 2011 NICE guidance on this drug class. Prescriptions for AChE

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inhibitors on the other hand lacked consistency and this is likely due to the variation observed in the estimates for two of the three drugs in this class: donepezil and rivastigmine. For both drugs, estimates were reasonably consistent in the 'any Alzheimer's disease' and 'any dementia' analyses but differed for the main analysis i.e. 'probable Alzheimer's disease'. Notably the trend analysis found one joinpoint to be optimum in the main analyses of these drugs but two joinpoints in the additional analyses. The lack of a second joinpoint in the main analysis for donepezil and rivastigmine suggests that prescribing for patients with probable Alzheimer's disease was more consistent, as one might expect, across the study than for other groups. This could indicate that patients with dementias other than probable Alzheimer's disease, i.e. with unlicensed indications, were receiving these drugs and that their prescribing was subject to change over the period studied. Further to this, large increases in prescriptions are observed as the diagnosis definition is relaxed. This could provide further evidence for the possible unlicensed use of this drug class. Alternatively, it could be attributed to the fluctuating course of symptoms that some people with dementia experience or increased recognition of mixed diagnoses, where there is evidence of Alzheimer's disease in addition to other forms of dementia; both of which might lead to treatment changes. However, it is also important to remember that we took a conservative approach when defining diagnosis so that some patients with the correct indication for these drugs will be included in the additional but not the main analysis.

Strengths and limitations

The key strength of this study is the large sample of primary care data with prescribing information, provided by the CPRD. As highlighted before, the CPRD is "broadly representative of the UK general population" and was generally comparable to the last census in 2011 for age, sex, and ethnicity. [21,22] Our data extract contains 40,202 patients diagnosed with dementia in England up to 1st January 2016 (note data is restricted to practices with a last data collection date in 2016). This includes 10,651 with probable Alzheimer's disease and a further 12,167 with possible Alzheimer's disease. Additional file 1 presents a sensitivity analysis that investigates whether the representativeness of the CPRD is maintained in our study data. The analysis concludes that as the proportion of patients included from England is similar to that included from the CPRD as a whole and the majority of patients in the CPRD are from English practices, the representativeness of the CPRD is likely preserved. A further strength of our study is the long follow up of patients that allowed us to consider patients who did not receive immediate treatment. This is important as pharmacological interventions for Alzheimer's disease have historically considered severity as part of the prescribing decision and so there is likely to be a treatment delay after initial diagnosis for those presenting with mild disease.

The main limitation of our study is the likelihood of missed diagnoses. This is demonstrated within our dataset, as there are 1,231 patients receiving one of the treatments of interest who do not have any form of recorded dementia diagnosis (including unspecified dementia). These missed diagnoses are likely to be due to: (1) outdated or non-specific diagnoses (i.e. type of dementia is not updated once established); (2) diagnoses received outside of primary care (i.e. from a specialist service); and (3) unrecorded diagnoses in primary care (i.e. a diagnosis is given but not added to a record). Missed diagnoses have been explored in sensitivity analyses by relaxing the diagnosis definition from 'probable Alzheimer's disease' to include other less certain codes for the disease and other types of dementia. The results of these analyses are

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summarized in Table 5 and presented in full in Additional files 7 and 8 for the diagnoses 'any Alzheimer's disease' and 'any dementia' respectively. They show that the joinpoint estimates are consistent for the drug class NMDA receptor antagonists but not for the drug class AChE inhibitors, due to variation observed in the individual analyses of donepezil and rivastigmine. This variation may be attributable to the increased number of treated patients in the 'any Alzheimer's disease' and 'any dementia' analyses. Treated patient numbers may be increased in these groups because those with mixed diagnoses, where the initial or predominant diagnosis was not Alzheimer's disease but a secondary presence of the disease later appeared, will not necessarily have been included in the main analysis. We also performed further sensitivity analyses that calculated the sensitivity and specificity of our code lists and diagnosis definitions, which are summarized in the results section and presented in full in Additional file 4. This analysis concluded that there was high specificity and low sensitivity for both the code lists and diagnoses, which was in line with the conservative approach we took when constructing the code lists. A final limitation of this study is the difficulty in determining the lag time between an event and a trend change in order to assess the impact of the event. To allow for this, we have opted to include only events that are considered to be high impact – for example changes at a national level – and so we expect any effect associated with them to be evident if present.

CONCLUSIONS

Initially we suggested four categories of events that may have influenced prescribing trends, these were: NICE guidance on the prescribing of drugs for dementia, inclusion of dementia in QOF, government dementia strategies, and expiry of drug patents. Analysis of both drug classes indicates that inclusion of dementia in QOF had no effect on prescribing trends and the other factors had mixed effects. NICE guidance on the prescribing of drugs for dementia aligned with trend changes for NMDA receptor antagonists but not AChE inhibitors. The guidance that had the noticeable effect was released in May 2011 and allowed the NMDA receptor antagonist, memantine, to be used outside of clinical trials. All other guidance for both this drug and AChE inhibitors, including that which recommended restricting access, did not align with trend changes. Government dementia strategies also appear to have had mixed results. The first National Dementia Strategy launched in February 2009, during the time when NICE recommended restricted access to AChE inhibitors, did not appear to have an impact on prescribing. There was also no noticeable effect of the Prime Minister's Challenge on Dementia 2020. However, as this strategy started within a year of the end of our study, it is possible that an impact on prescribing has yet to be realized. The government dementia strategy that may have influenced prescribing is the Prime Minister's Dementia Challenge, which was launched in May 2012 and may explain trend changes observed in AChE inhibitor prescribing in October 2012. Although this strategy is likely to have increased awareness of dementia at this time, we feel the more likely cause of this trend change is the patent expiry of the drugs in this class. This will have reduced the cost of these drugs and potentially led to a surge in prescribing, such as that observed in our trend analysis. The events considered here highlight the many factors that may have influenced prescribing rates and the challenges in assessing the impact of a given event. Overall it would seem that the proportion of patients receiving prescriptions increased over the period studied, irrespective of changing guidelines and other initiatives. Furthermore, given the increased rates of dementia reported in the CPRD (Figure 1), the absolute number of prescriptions has increased considerably over the period studied.

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Given the lack of previous literature investigating the factors effecting prescription rates of drugs for dementia, there are a number of implications of this study. We have observed that prescription rates in England do not always respond to factors such as regulatory guidance, recommendations or patent expiry and, when they do, not necessarily in a predictable way. This suggests that communication with clinicians may need to be improved to use drugs for dementia more cost effectively. In addition to this, the study has provided insight into the factors that may have influenced prescription rates of drugs for dementia in England since their launch in 1997. This is essential for accurate assessment of the effectiveness of these treatments and to adjust for them in other forms of analyses, particularly as factors that may modify the rates of disease progression. This study may also help to inform the handling of regulatory guidance and recommendations concerning drugs for dementia in the future.

LIST OF ABBREVIATIONS

AD: Alzheimer's Disease
AChE: AcetylCholinEsterase
AMPC: Average Monthly Percent Change
CPRD: Clinical Practice Research Datalink
HES: Hospital Episode Statistics
MMSE: Mini Mental State Examination
MPC: Monthly Percent Change
NICE: National Institute of health and Care Excellence
NMDA: N-Methyl-D-Aspartate
ONS: Office of National Statistics
QOF: Quality and Outcomes Framework

DECLARATIONS

Ethics approval and consent to participate

The protocol for this study has been approved by the CPRD's Independent Scientific Advisory Committee [ISAC Protocol 15_246R]. This study does not directly involve patients so further ethical approval is not required.

Consent for publication

Not applicable

Availability of data and material

The data that support the findings of this study are available from the CPRD but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

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Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to planning the analysis. VMW conducted the analysis and drafted the manuscript. All others edited and revised the manuscript. PGK and RMM were responsible for securing the funding.

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