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**ORIGINAL ARTICLE**

# Impact of deprivation, dementia prevalence and regional demography on prescribing of antedementia drugs in England: A time trend analysis

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**Aim:** This study aimed to examine trends in prescribing of antedementia drugs in primary care in England between 2009 and 2019, and investigate the impact of deprivation, regional demography and disease prevalence on prescribing practices.

**Methods:** Analysis of publicly available government data from various sources pertaining to primary care prescribing and demographics was conducted. All primary care prescription data pertaining to antedementia drugs in England between 2009 and 2019 were extracted and adjusted for inflation and population changes. Data across English clinical commissioning regions were compared to explore the association between prescribing trend, deprivation, regional demography and dementia prevalence.

**Results:** The number of prescription items for antedementia drugs in England increased by approximately 3-fold (195.4%) from 24 items/1000 population in 2009 to 70.9 items/1000 population in 2019. In 2019, the least-deprived areas had approximately twice the rate of prescribing of antedementia drugs compared to the most-deprived areas (median [IQR] values of 46.7 [36.6–64.8] vs 91.23 [76.2–95.1] items/1000 population, respectively). In the multivariable analysis, the number of prescription items showed an inverse relationship with deprivation (coefficient  $-0.046$ , 95% CI  $-0.47$  to  $-0.045$ ) after adjustment for number of populations aged 65+ years and prevalence of dementia.

**Conclusions:** The 3-fold rise in the number of prescription items for antedementia drugs in the study period reflects the policy emphasis on early diagnosis and treatment of dementia. Higher rates of prescribing in the least-deprived areas may be reflective of better and early diagnoses and access to treatments. Such inequality in access to the treatments needs to be investigated further.

Principal investigator statement: The principal investigator for this study is Dr Vibhu Paudyal. This study involves analyses of publicly available government data from various sources pertaining to primary care prescribing and demographics. Hence, participants were not subjected to intervention as part of the research.

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**KEYWORDS**

acetylcholinesterase inhibitor, antipsychotic drugs, dementia, *N*-methyl-*D*-aspartate receptor antagonist, prescription patterns

**1 | INTRODUCTION**

Globally, there are over 47 million people living with dementia, with this figure set to reach 135.46 million by 2050.<sup>1</sup> As of 2019, a total of 472 890 people in England have a coded diagnosis of dementia.<sup>2</sup>

The National Institute of Clinical Excellence (NICE) guideline on Dementia in England recommends acetylcholinesterase (AChE) inhibitors (donepezil, galantamine and rivastigmine) as monotherapies for the management of mild-to-moderate Alzheimer's disease (AD).<sup>3</sup> The NICE guideline recommends that the *N*-methyl-*D*-aspartate (NMDA) receptor antagonist, memantine, be used to treat moderate AD in patients who are intolerant or have a contraindication to AChE inhibitors. Memantine is also recommended to be used in patients with an established diagnosis of AD when AChE inhibitors are already being used. The NICE guidelines also recommend AChE inhibitors for the treatment of non-Alzheimer's dementia, but they do not have UK marketing authorisation for this purpose and therefore must be prescribed off-label.<sup>3</sup>

In addition to AChE inhibitors and memantine, antipsychotics are recommended for the management of noncognitive symptoms of dementia. These symptoms of dementia include agitation, aggression, distress and psychosis. In the UK, risperidone and haloperidol are the only antipsychotics with a UK marketing authorisation to treat noncognitive symptoms associated with dementia.<sup>3</sup>

In the last decade, there has been an increased emphasis on the diagnoses and management of dementia in primary care, prior to any psychiatric referrals. The National Dementia Strategy (NDS), published in 2009 in England, emphasised the need to improve public and professional awareness and understanding of dementia and early diagnosis and treatment.<sup>4</sup> The Quality and Outcomes Framework (QoF) is a voluntary annual reward and incentive programme for all English general practices. It incorporates better diagnosis and management of dementia, including a follow-up care plan in primary care as one of the key quality indicators.<sup>5</sup>

Evaluation of prescribing practices in dementia has predominantly focused on minimising the potentially inappropriate use of antipsychotics to treat noncognitive symptoms<sup>6–9</sup> as overprescribing of antipsychotics can contribute to cardiovascular morbidity and mortality mainly caused by stroke and ischaemic heart diseases; the drugs therefore should only be prescribed where patients are severely distressed and there is a risk of harm to themselves or carers.<sup>10,11</sup> A time trend analysis of prescribing of drugs used in the management of dementia is necessary in the context of recent policy emphases on better diagnosis and management of dementia in primary care. In addition, the link between deprivation, prevalence and prescribing for dementia remains poorly understood. Geographical and deprivation level variations in prescribing practices can inform stratification of

**What is already known about this subject**

- There has been increasing policy emphasis on early diagnoses and management of dementia in primary care.
- Evaluation of prescribing practices in dementia has predominantly focused on minimising the potentially inappropriate use of antipsychotics for the treatment of noncognitive symptoms.
- The link between policy changes, prescribing practices, deprivation and disease prevalence remains poorly understood.

**What this study adds**

- In the last 10 years, there has been a nearly 3-fold rise (195.4%) in the number of prescription items for antedementia drugs, potentially reflecting the impact of policy emphases on early diagnosis and treatment.
- Least-deprived areas demonstrate up to twice the rate of prescriptions compared to most-deprived areas.
- Results indicate better and early diagnoses and access to antedementia drugs in affluent areas compared to deprived areas and this warrants further research.

targeted interventions to identify linked comorbidities and reduce health inequalities. The aim of this study was to analyse the trends in prescribing of antedementia drugs in primary care in England from 2009 to 2019 and to investigate the impact of deprivation and regional demography on prescribing practices.

**2 | METHODS****2.1 | Ethical consideration**

This study represents a secondary analysis of the information retrieved from publicly available anonymised datasets and does not warrant formal ethical approval.

**2.2 | Study design and population**

A longitudinal study of national primary care prescribing datasets was undertaken using NHS Digital sources, namely, **OpenPrescribing.net**

and Prescription Cost Analysis (PCA).<sup>12,13</sup> **OpenPrescribing.net** is a national online prescribing data resource hosted by the Evidence-Based Medicine DataLab at the University of Oxford. The resource provides general practice level prescribing data published each month from NHS Digital for all prescriptions written by general practitioners and other nonmedical prescribers attached to the practices. This includes the number of items prescribed and the actual cost of the medication.<sup>14</sup> PCA statistics are provided by NHS Digital and present prescription data regarding the number of items and the net ingredient cost (NIC) of all prescriptions dispensed by the NHS in the community in England.<sup>15</sup>

### 2.3 | Data extraction and analysis

Prescription data from January 2009 to December 2019 for antedementia drugs, relating to British National Formulary (BNF) Section 4.11,<sup>16</sup> were included. Data on donepezil, galantamine, rivastigmine and memantine were extracted. Prescription patterns relating to 10 of the most- and the 10 of the least-deprived clinical commissioning groups (CCGs) as per the Office of National Statistics (ONS) Index of Multiple Deprivation (IMD) in 2015<sup>17</sup> (Supporting Information Table S1) were also extracted and analysed to explore the link between prescribing patterns and deprivation. The CCGs are clinically led autonomous NHS bodies involved in planning and commissioning healthcare services for their locality. The 10 most-deprived and the 10 least-deprived CCGs included in the analysis covered a population of 2.8 million and 2.3 million, respectively. All data were adjusted for population estimates for each year at national, regional and CCG level.<sup>18</sup> Costs of prescription items were adjusted for inflation using the ONS Consumer Price Index (CPI) for pharmaceutical products.<sup>19</sup>

In the univariate analysis, the independent-samples Mann-Whitney U test was used to examine prescription items' variations and costs across deprivation. *P* values of <.05 were considered significant. We used multivariable logistic regression to assess the association of deprivation on prescription items after adjusting for population aged 65+ years and prevalence of dementia. A frequency weight was added into the model to denote that each row represented aggregate data.

Trends in relation to prescribing of antipsychotic drugs from 2009 to 2019 from all English general practices were also extracted. Such data included antipsychotic prescriptions for all causes. To identify the extent of antipsychotic prescribing in patients with dementia, data in relation to the proportion of patients with dementia who were prescribed antipsychotic drugs in the last 6 weeks, including those with or without a comorbid diagnosis of psychosis, were extracted from the most- and least-deprived CCGs.<sup>20,21</sup>

All data were extracted, independently checked for accuracies and analysed using Microsoft Excel, SPSS V21 and Stata V16.

## 3 | RESULTS

### 3.1 | Prescribing of antedementia drugs between 2009 and 2019

The number of prescription items dispensed in England for the pharmacological treatment of dementia (antedementia drugs, BNF Section 4.11) increased by approximately 3-fold (195.4%) from 24 prescription items per 1000 population in 2009 to 70.9 prescription items per 1000 population in 2019, reflecting an increase of 195.4% (Table 1 and Figure 1).

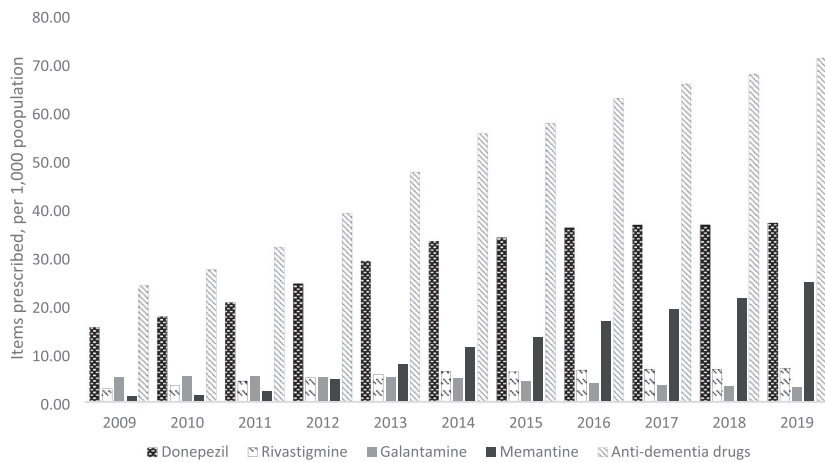
**TABLE 1** Prescription items and costs of all antedementia drugs (BNF Section 4.11) and antipsychotic drugs in England in 2009 and 2019

	Prescription items per 1000 population, n (%)		Prescription costs (GBP) per 1000 population, n (%)		Cost (GBP) per prescription item		Percentage (%) change in cost 2009-2019
	2009	2019	2009	2019	2009	2019	
<b>Antedementia drugs</b>							
Donepezil <sup>a</sup>	15.37 (64.04)	36.88 (52.02)	1277.04 (64.39)	35.68 (8.70)	83.09	0.96	- 98.84
Rivastigmine <sup>a</sup>	2.65 (11.04)	6.85 (9.66)	199.20 (10.45)	157.14 (38.33)	75.17	22.94	- 69.48
Galantamine <sup>a</sup>	4.90 (20.41)	2.94 (4.15)	350.95 (18.42)	90.74 (22.13)	71.62	30.86	- 56.91
Memantine <sup>a</sup>	1.08 (4.5)	24.6 (34.70)	78.57 (4.12)	127.09 (31.00)	72.75	5.17	- 92.89
Total antedementia drugs	24.00	70.90	1905.77	410.00			
<b>Antipsychotic drugs</b>							
Haloperidol and risperidone, n (%) <sup>b</sup>	31.81 (23.38)	36.00 (19.23)	421.10 (7.53)	301.79 (19.62)			
All antipsychotic drugs	136.06	187.21	5592.72	1538.17			
Total: antedementia drugs + antipsychotic drugs	160.06	258.11	7498.49	1948.17			

Abbreviations: BNF, British National Formulary; GBP, Great British Pound.

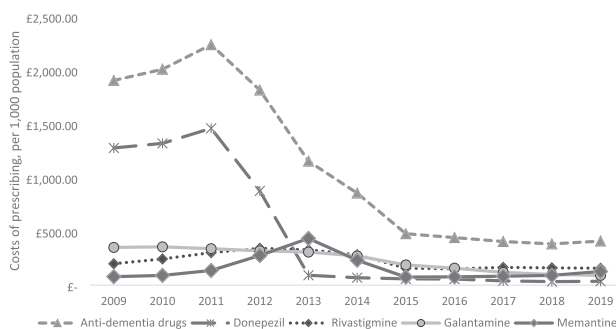
<sup>a</sup>Percentage refers to proportion of all antedementia prescription items.

<sup>b</sup>Percentage refers to proportion of all antipsychotic prescription items.



**FIGURE 1** Prescription items of all antedementia drugs (British National Formulary Section 4.11) per 1000 population in England from 2009 to 2019

BNF: British National Formulary



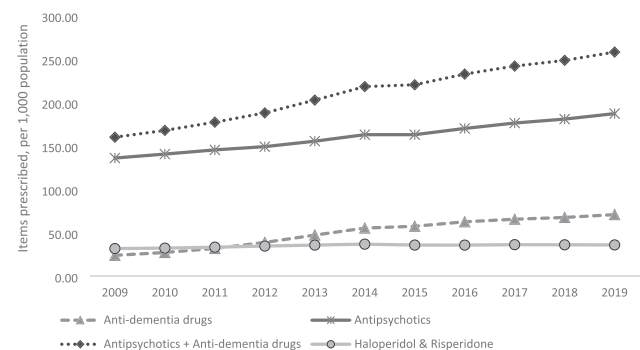
BNF: British National Formulary

**FIGURE 2** Costs of prescribing for all antedementia drugs (British National Formulary Section 4.11) per 1000 population in England from 2009 to 2019, adjusted for inflation

Donepezil was the most commonly prescribed antedementia drug in both 2009 and 2019, accounting for 64.0% and 52.0% of all antedementia prescriptions, respectively. Of all antedementia drugs, the highest increase was noted for prescribing of memantine, which increased from 4.5% in 2009 to 34.7% in 2019. Prescriptions for galantamine decreased over the same period by 40% (Table 1).

The results presented an overall decrease in the cost incurred from prescribing drugs for dementia, increasing by 17.5% from 2009 to 2011 but then drastically decreasing by 82.0% from 2011 to 2019. This resulted in an overall decrease in costs of 81.7% from 2009 to 2019 (Table 1 and Figure 2).

The costs of prescribing rivastigmine peaked in 2012 at £342.69 per 1000 population, followed by a substantial reduction in costs by 88.8% in the following year between 2012 and 2013. Overall, memantine costs increased by 61.8% from 2009 to 2019, peaking in 2013 at £434.54 per 1000 population. A significant reduction in the costs of donepezil by 40.0% was observed between 2011 and 2012. Donepezil's cost per item decreased by the largest proportion from 2019 to 2009, reducing by 98.8% over the 10 years (Table 1 and Figure 2).



BNF: British National Formulary

**FIGURE 3** Prescription items for antedementia drugs (British National Formulary Section 4.11) and all antipsychotic drugs per 1000 population in England from 2009 to 2019

### 3.2 | Prescribing of antipsychotics drugs: 2009-2019

The prescribing of all antipsychotic drugs showed a steady increase of 37.6% over the 10 years (Table 1 and Figure 3). Antipsychotic prescribing was consistently higher than prescribing of antedementia drugs, however, the rate of increase in prescribing for antedementia drugs was higher during the study period. In particular, haloperidol and risperidone prescriptions increased from 2009 to 2019 by 13.2% (Table 1 and Figure 3). Costs of prescribing all antipsychotic drugs decreased by 71.4% from 2009 to 2019 (Table 1 and Supporting Information Figure S1). Both antipsychotics and antedementia drugs presented an initial increase in costs from 2009 to 2011, followed by a decrease from 2011 to 2016. Haloperidol and risperidone showed a reduction in costs from £421.10 to £301.79 (−28.3%) per 1000 population from 2009 to 2019 (Supporting Information Figure S1).

The proportion of patients with diagnosed dementia who were prescribed an antipsychotic drug in the last 6 weeks of 2019 ranged

from 6.99% to 15.54% within the 20 CCGs. The proportion of dementia patients who were prescribed antipsychotic drugs without a psychosis diagnosis ranged from 4.88% to 12.52% (Table 3).

### 3.3 | Association between deprivation and prescribing

Prescribing in the least-deprived areas was substantially higher than that in the most-deprived areas from 2015 to 2019 (Table 2). The median (IQR) prescription items for the least deprived areas for all five observations was 75.68 (72.32-86.67) compared with 44.62 (43.03-44.85) items per 1000 population in the most deprived areas ( $P = .008$ ). Similarly, the median (IQR) costs of prescribing per 1000 population in the most-deprived areas across all five observations were £255.18 (233.48-320.74) compared with £625.87 (563.25-654.78) in the least-deprived areas ( $P = .008$ ) (Table 2). There was a larger observed variation in both items and cost data within the most-deprived areas compared to the least-deprived areas (Table 2). In the multivariable analysis, the prescription items per 1000 population showed an inverse relationship with deprivation after adjustment with population 65+ years and prevalence of dementia (coefficient  $-0.046$ , 95% CI  $-0.47$  to  $-0.045$ ,  $P < .001$ ) (Supporting Information Table S2).

### 3.4 | Variations across NHS England commissioning regions

Prescription items for dementia increased from 2015 to 2019 in every NHS England commissioning region (Supporting Information Table S3). Prescribing was consistently highest in the North-East and Yorkshire region and lowest in the Midlands for the measured time period. In 2009, 85.6 prescription items per 1000 population were prescribed in the North-East and Yorkshire region compared with

41.2 per 1000 population in the Midlands. Similarly, in 2019, the North-East and Yorkshire region prescribed 101.4 items per 1000 population, 96% higher than the 51.8 items prescribed in the Midlands ( $P = .015$ ). A significant difference in the median costs of prescribing across the regions was also observed ( $P = .001$ ).

## 4 | DISCUSSION

This overall aim of this study was to examine prescribing trends and associated costs of antidementia drugs in primary care in England and to investigate the impact of deprivation, regional demography and disease prevalence on prescribing practices and patient access to these drugs. This study demonstrated a 3-fold rise in prescribing of antidementia drugs in England in the last 10 years. The increase is reflective of the policy emphases on the early and better diagnosis and management of dementia in primary care in England. AD and other dementias currently rank as the leading and second most common causes of death amongst females and males in England, respectively.<sup>22</sup> In 2011 and 2014, there were updates to the coding framework in primary care used to code the cause of death. These changes also required dementia to be identified as the underlying cause of death rather than "other health conditions". An updated national strategy was launched in England, in 2020 which aimed to continue to emphasise early diagnoses, treatment and support for investigation and provision of newer therapies.<sup>23</sup> The prescription data analysed in this study triangulate well with the increasing prevalence and mortality data.

The number of prescription items for the NMDA receptor antagonist memantine presented the largest percentage increase over the 10 years. This notable increase emerged in 2011 and may be causally linked with an update to the NICE guidelines in the same year. Prior to 2011, memantine was only recommended for use in clinical trials for patients with moderate to severe AD.<sup>24</sup> However, following the NICE guideline update, memantine was recommended for patients

**TABLE 2** Prescription items and costs of antidementia drugs (BNF Section 4.11) in the 10 most- and 10 least-deprived CCGs in England per 1000 population from 2015 to 2019

	Prescription items per 1000 population median (IQR)		Inflation adjusted costs, GBP per 1000 population median (IQR)	
	Most deprived	Least deprived	Most deprived	Least deprived
Year, n <sup>a</sup>				
2015	43.24 (32.99-59.53)	70.28 (63.51-76.06)	367.21 (166.61-470.95)	688.03 (623.80-784.88)
2016	45.45 (37.20-65.32)	74.36 (66.18-82.19)	335.18 (149.71-453.13)	650.57 (529.58-716.50)
2017	45.63 (38.58-68.42)	77.27 (69.56-85.29)	279.52 (140.16-393.67)	551.49 (540.57-657.57)
2018	45.79 (37.81-65.70)	82.11 (75.57-86.70)	271.74 (133.09-341.85)	581.75 (438.52-634.60)
2019	46.65 (36.63-64.76)	91.23 (76.18-95.13)	310.2 (116.36-344.07)	666.4 (515.08-787.68)
Percentage (%) median change from 2015 to 2019	7.88	29.81	-15.53	-3.14
Median all years	44.62 (43.03-44.85)	75.68 (72.32-86.67)	255.18 (233.48-320.74)	625.87 (563.25-654.78)

BNF, British National Formulary; CCG, clinical commissioning group; GBP, Great British Pound; IQR, inter-quartile range

<sup>a</sup>n = sum of prescriptions and costs for 10 CCGs for each year per 1000 population.

**TABLE 3** Deprivation, dementia prevalence and prescribing of antedementia and antipsychotic drugs across various clinical commissioning groups

Clinical commissioning group	Population estimates 2019	% aged 65+	Prescription items per 1000 population (2019)	Dementia prevalence %	Patients with dementia who had a prescription for antipsychotic drugs in the last 6 weeks (%)		
					Antipsychotic prescription %	With psychosis diagnosis %	Without psychosis diagnosis %
NHS Bradford City	84 600	7.33	59.63	0.68	15.54	4.15	11.40
NHS Barking and Dagenham	219 600	9.29	66.48	0.39	10.83	1.75	9.08
NHS Sandwell and West Birmingham	507 500	12.93	15.46	0.60	12.75	2.51	10.24
NHS Blackpool	138 900	20.45	102.61	1.34	7.22	1.94	5.28
NHS City and Hackney	293 000	7.78	24.75	0.33	6.99	2.92	4.07
NHS Knowsley	149 200	17.43	49.76	0.79	11.74	1.77	9.97
NHS Tower Hamlets	322 000	6.30	36.60	0.30	9.51	3.72	5.79
NHS Liverpool	498 600	14.80	43.53	0.69	13.78	2.19	11.59
NHS Newham	359 800	7.48	36.71	0.31	8.31	3.43	4.88
NHS Hull	261 600	15.10	89.34	0.89	9.48	1.46	8.02
NHS Rushcliffe	117 600	21.34	73.65	1.14	7.45	1.19	6.26
NHS Surrey Downs	295 600	20.60	91.91	1.01	10.71	0.87	9.84
NHS Guildford and Waverley	211 100	18.85	90.55	0.91	9.84	1.47	8.37
NHS Horsham and Mid-Sussex	240 000	20.29	79.78	1.03	9.81	1.78	8.03
NHS Surrey Heath	97 600	19.51	93.51	0.93	7.62	1.55	6.08
NHS North-East Hampshire and Farnham	97 600	17.90	196.96	1.90	7.78	1.19	6.59
NHS Richmond	200 200	15.68	102.49	0.72	9.38	1.32	8.06
NHS Harrogate and Rural District	160 700	23.65	95.68	1.22	8.13	0.77	7.36
NHS North Hampshire	226 500	18.54	63.24	0.78	14.23	1.71	12.52
NHS West Hampshire	570 200	23.61	74.98	0.98	12.82	1.50	11.32

with moderate to severe AD who had a contraindication to AChE inhibitors.<sup>25</sup> This increase in memantine prescribing in 2011 is concurrent with the trends observed in another study.<sup>26</sup>

From 2009 to 2019, the cost per item of all antedementia drugs (BNF Section 4.11) decreased by over 50%. Donepezil and memantine saw the largest reduction in value, decreasing by 98.8% and 92.9% respectively. The observed reduction in costs coincides with galantamine's patent in January 2012, donepezil's in February 2012 and rivastigmine's in July 2012. Memantine, the NMDA receptor antagonist, lost exclusivity in April of 2014.

Analysis at CCG level found an inverse relationship between deprivation and prescribing patterns. This is concurrent with previous findings reporting that in English practices, patients with dementia are 27% more likely to receive a dementia prescription in the least-deprived areas than those in the most-deprived areas.<sup>27</sup> The differences in the number of prescription items for antedementia drugs were evident even after adjusting for the number of population aged 65 years and over and dementia prevalence. Therefore, further investigation is required to establish factors that might be contributing to the disparities in access to antedementia drugs. There is a lack of studies in the UK investigating factors that relate to such differential prescribing rates. Data from international literature and under-representative UK studies suggest that patients of minority ethnicity, younger age during diagnosis and those with fewer academic qualifications are less likely to be prescribed antedementia drugs.<sup>28-31</sup> There is a need for clinical guidelines to emphasise early diagnosis and equitable access to dementia drugs. Qualitative study of prescribers, patients and/or carers is needed. Patients with diagnosed dementia are often residents of care homes, and therefore future interventions to improve practice also need to focus on residential care settings.

The variations in prescribing rates were higher in the most-deprived regions compared to the least-deprived regions. Regional variations in prescribing rates were also observed with no clear-cut north-south divide observed in the datasets. The data are suggestive of the presence of pockets of "deprivation" and "affluence" in all regions.<sup>32,33</sup> These differences need to be investigated further.

This study also shows that the prescription of all antipsychotic medication increased during the 10-year study period. As shown in our data, the proportion of dementia patients prescribed antipsychotic drugs without a confirmed diagnosis of psychosis ranged from 4.0 to 12.5%. The NDS, published in 2009, aimed to reduce antipsychotic use among people with dementia. However, the trends in prescribing antipsychotics from 2009 to 2019 have not reflected a change in prescribing practices.<sup>4,34</sup> Previous studies which looked into prescribing of antipsychotics following the launch of the NDS also suggested no notable change in prescribing rates 4 years after the implementation of this strategy.<sup>6</sup>

## 5 | STRENGTHS AND LIMITATIONS

National prescribing datasets covering all patients registered with a general practice in England were included in this study. We did not

investigate the record of the indications, reasons or length of treatment for the drugs prescribed. Furthermore, the 10 most- and 10 least-deprived CCGs are only representatives of the two extremes, and they do not represent the entire population of England. It is important to note that the data regarding the prescriptions and costs of antipsychotics were not exclusively related to prescribing for dementia. Antipsychotics can be used to treat multiple other disorders, such as psychosis, schizophrenia, bipolar disorder and major depression, and other off-label uses.<sup>35,36</sup> However, dementia is the only condition where AChE inhibitors are prescribed.<sup>16</sup> The available prescription data analysed in this study related to all active patients in the primary care medical records. Records of any patients who died during the study period are not available.

## 6 | IMPLICATIONS FOR PRACTICE AND RESEARCH

Quality, appropriateness and off-label prescribing of drugs for dementia treatment need to be investigated in light of the rising trends in the data. With a greater emphasis on diagnosis and treatment in primary care, evaluations of prescriber behaviours, expertise and skills are important to ensure that prescribing is evidence-based. The deprivation level differences in rates of prescribing need to be investigated further. In addition, wide variations in the rate of prescribing within the most-deprived areas warrant further investigation. The continued rising trend observed for prescribing of antipsychotic drugs requires further research to identify the contribution of dementia to the observed trend.

## 7 | CONCLUSIONS

In the last 10 years there has been a nearly 3-fold rise in the number of prescription items for antedementia drugs. The rising trend in primary care prescribing demonstrates greater participation of the sector in the diagnosis and treatment of dementia and specialist psychiatry care. The least-deprived regions have a prescribing rate that is approximately twice as high as that in the most-deprived regions. Higher rates of prescribing in the least-deprived areas may reflect better and early diagnoses and access to treatment than offered in the most-deprived areas. Such differences in access to treatments need to be investigated further.

### ACKNOWLEDGEMENTS

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### COMPETING INTERESTS

All authors declare no conflicts of interest.

### CONTRIBUTORS

N.V., V.P., M.H. and S.K. designed the study. N.V. was the main researcher, and extracted, cleaned and undertook descriptive



analysis of the data. V.P. was the principal investigator and performed duplicate checks on the extracted data. N.V. led the write-up, to which all authors contributed through editing and expert input. O.P.K. led the multivariable analysis of the data, checked descriptive analysis for accuracy and made significant contribution to the revision of the paper. All authors agreed to the final versions of the manuscript.

## DATA AVAILABILITY STATEMENT

All data pertaining to this study are reported in this manuscript.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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