



Polypharmacy patterns in the last year of life in patients with dementia

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Abstract

Purpose To describe prescribing of medicines in primary care in the last year of life in patients with dementia.

Method A retrospective cohort analysis in UK primary care using routinely collected data from the Clinical Practice Research Datalink. Number of medications and potentially inappropriate medication prescribed one year prior to, and including death, was ascertained.

Results Dementia patients ($n = 6923$) aged 86.6 ± 7.3 years (mean \pm SD) were prescribed 4.8 ± 4.0 drugs 1 year prior to death, increasing to 5.6 ± 4.0 2 months prior, before falling to 4.9 ± 4.1 at death. One year prior to death, 50% of patients were prescribed a potentially inappropriate medication, falling to 41% at death. Cardiovascular medications were the most common, with decreases in drug count only occurring in the last month prior to death. Prescriptions for gastrointestinal and central nervous system medication increased throughout the year, particularly laxatives/analgaesics, antidepressants and hypnotic/antipsychotics. Women (vs. men) and patients with Alzheimer's (vs. vascular dementia) were prescribed 4.7% (95% CI 2.3%–7%) and 14.6% (11.7–17.3%) fewer medications, respectively. Prescribing decreased with age and increased with additional comorbidities.

Conclusions Dementia patients are prescribed high levels of medication, many potentially inappropriate, during their last year of life, with reductions occurring relatively late. Improvements to medication optimisation guidelines are needed to inform decision-making around deprescribing of long-term medications in patients with limited life-expectancy.

Keywords Dementia · Polypharmacy · Inappropriate prescribing · End-of-life

Abbreviations

CPRD	Clinical Practice Research Datalink
GP	General practice
BNF	British National Formulary
ZIP	Zero-inflated Poisson

Background

Dementia is a growing challenge for primary health care services, with an estimated 7% of over 65 s affected [1], and numbers likely to increase given our ageing population. Polypharmacy, the co-prescription of multiple drugs, is common [2, 3] and a particular concern amongst patients with dementia. Memory loss and impaired cognitive function may lead to adherence problems with complex medication regimens, and patients may have difficulty in communicating problems related to adverse drug effects [4]. There is also evidence that inappropriate prescribing is frequent [5], and altered pharmacokinetics and pharmacodynamics may make the adverse consequences more serious in this older, multimorbid population.

These issues are especially concerning in the context of limited life expectancy, given the time required for demonstrable benefits to be achieved with certain medications [6, 7]. Furthermore, the evidence for clinical effectiveness of most drugs comes from randomised controlled trials which exclude

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individuals with dementia or at the end of life [8], so the balance of risks and benefits may be less favourable than in the general population. Current evidence of prescribing practices in dementia patients is predominantly from nursing home residents [9–11] or cross-sectional studies [12–14]. There has been limited study of changes in medication use during the last phases of life in patients with dementia in the community.

The aim of this study was to describe patterns of polypharmacy in the last year of life amongst adults with a diagnosis of dementia and examine variations in prescribing by demographic and clinical factors.

Method

Study population

We conducted a descriptive analysis using routinely collected, anonymised, UK primary care health records from the Clinical Practice Research Datalink (CPRD) [15]. Approval for the study was granted by the CPRD Independent Scientific Advisory Committee (Protocol reference 15_106R). The CPRD is a large database containing electronic medical health records of over 5 million active patients from approximately 650 general (family) practices (GP) and is considered a representative sample of the general UK population [15]. Coded data available for each patient include clinical diagnoses and detailed information on drugs prescribed [16, 17].

For this study, patients who had died between May 2013 and April 2014 and had a diagnosis of dementia at or before death were identified using the electronic GP medical records and linked Office of National Statistics death registry. A dementia diagnosis was defined using Read codes, a standard clinical coding classification used in UK primary care [18], for any relevant clinical diagnosis in the GP medical record or a relevant ICD-10 code in the death registry (Appendix 1).

Measurements

Polypharmacy was ascertained at death (i.e. an ongoing prescription on the date of death) and at 2 weeks, 1, 2, 4, 6, 9 and 12 months prior to death, from primary care records. These time intervals were based on pragmatism and clinical judgement. Almost all prescriptions issued by a GP to a patient will be captured by CPRD as prescribing is conducted almost exclusively electronically. Prescription length was calculated by dividing drug quantity by number of daily doses; where missing, imputed from the population average for that drug (Appendix 2). Drugs were categorised according to the British National Formulary (BNF) [19]. Palliative care medications were also identified (Appendix 3) [20]. Appropriateness of medications was classified using a previously published list developed using a Delphi consensus

approach for adults with advanced dementia [7]. For this analysis, medications were defined as never appropriate and rarely appropriate (Appendix 3). In addition, prescribing safety indicators [21] taken from the Royal College of General Practitioners (RCGP) indicator list [22] and used in the PINCER trial [23] and a general measure of potentially hazardous prescribing (≥ 1 of 19 indicators [P1–P19]) was derived for each time point. Prescriptions were limited to enteral-administered drugs, as the duration of individual prescriptions can be determined more reliably; these accounted for three-quarters of all medications in this population. For the analysis of palliative medications, we also included injectable drugs.

A count of all ongoing prescriptions of unique drug substances at each time point was derived. Counts were also derived for selected BNF chapters (most frequent enteral-administered prescriptions identified by Guthrie et al. [24]) and inappropriate medication. Throughout the paper, the term polypharmacy is used to indicate multiple concurrent medications, without implying appropriateness of medication or any particular minimum quantity.

A list of 37 physical and mental long-term conditions established by clinical expert consensus [25–27] was used to ascertain comorbidity status in participants at 1 year prior to death. An unweighted count of clinical conditions was derived, and a seven-category measure, grouping ≥ 6 conditions, was created.

Dementia subtype (vascular, Alzheimer's disease, other and unspecified) and care home status during the last year of life were ascertained using clinical Read codes (Appendices 1 and 4, respectively). Analysis of dementia subtype was restricted to patients with a recorded diagnosis of vascular dementia or Alzheimer's.

Statistical analysis

Counts and averages were used to describe changes in the number of prescriptions over time. Zero-inflated Poisson (ZIP) regression models were fitted to investigate differences in the number of prescriptions at each time point and across different demographic and clinical factors. Robust standard errors were used which allowed for correlations across different time points within individual patients (i.e. multiple prescription counts). A ZIP regression is a two-stage process, first predicting whether individuals had any prescriptions using a logit regression model, and secondly, a Poisson model to predict the rate of prescriptions amongst patients prescribed medication; the final output combining the two models. Number of days prior to death was included as a covariate in the logit and Poisson regression model, and univariable Poisson regression models were used to investigate associations with gender, age, dementia subtype, care home status and multimorbidity score. Estimates from the models are presented in terms of the

expected relative difference (RD) and 95% confidence intervals (CI) in number of medications prescribed per unit increase in the exposure of interest.

Interactions between each exposure and number of days until death were examined using a likelihood ratio test. For age and comorbidity, non-linear associations with prescription count were investigated and the most appropriate, as determined using likelihood ratio tests, is presented. Wald tests were used to test whether the association changed over time.

All analyses were conducted using Stata 14, and all statistical tests were two sided.

Results

A total of 6923 patients (mean age 86.6 ± 7.3 years, 64% female) with a diagnosis of dementia died during the study period (Table 1). Patients with vascular dementia had a mean of 4.0 ± 2.2 additional comorbidities, of which 1.9 ± 1.3 were cardiovascular disease (CVD) related, compared with 2.9 ± 2.0 comorbidities (1.1 ± 1.1 CVD related) for those with Alzheimer's.

Of all products prescribed in the study period ($n = 219,543$), 69.2% ($n = 151,975$) were enteral administered.

Table 1 Frequency of selected characteristics of participants

		<i>n</i>	Mean (SD) (%)
Gender	Men	2513	36.3
	Women	4410	63.7
Age at death (years)		6923	86.6 (7.3)
Dementia subtype ^a	Vascular	1940	32.3
	Alzheimer's	1760	29.3
	Other	85	1.4
	Unspecified	2220	37.0
Comorbidity 1 year prior to death (excluding dementia) ^b	Mean (SD)	6923	3.3 (2.2)
	0	756	10.9
	1	815	11.8
	2	1011	14.6
	3	1209	17.5
	4	1173	16.9
	5	869	12.6
	6+	1090	15.7
Lives in a care home	No	5084	73.4
	Yes	1839	26.6

SD, standard deviation; IQR, interquartile range

^aDementia subtypes other includes dementia associated with Parkinson's, Huntington's, and Picks Disease, HIV/AIDS, and alcohol abuse. Two hundred forty-one patients diagnosed with vascular and Alzheimer's dementia, the most frequent diagnosis was used

^bComorbidity list includes 37 chronic conditions

Remaining products included topical (11.9%, $n = 26,019$), non-pharmacological (5.6%, $n = 12,208$), injected (4.9%, $n = 10,724$), inhaled (2.1%, $n = 4,532$), administered to ears, eyes, or nose (1.9%, $n = 4,133$) and unknown (4.2%, $n = 9,216$).

Changes in overall prescribing over time

On average, dementia patients were prescribed 4.8 ± 4.0 enteral-administered drugs at baseline (1 year prior to death), increasing to 5.6 ± 4.1 1 month prior to death, falling to 4.9 ± 4.1 prescriptions ongoing on the date of death (Fig. 1). In the ZIP models, the overall number of drugs prescribed increased by 3.0% (95% confidence interval 1.5 to 4.5%) between the baseline and 1 month prior, with prescribing falling by 4.3% (-5.9 to -2.6%) at death compared with 1 year prior (Appendix 5).

Palliative medication prescriptions (both enteral administered and injections) increased across the year, with a sharp rise from 0.5 ± 1.1 drugs 2 weeks prior to death to 1.2 ± 2.1 at death (Fig. 1), opioids being the most frequently prescribed. On the date of death, 41.0% ($n = 2,838$) of patients had at least one prescription for a palliative medication. In the ZIP model, the increase in palliative medication prescriptions at death represented nearly a 5-fold (474.3%; 418.0 to 538.4%) increase compared to 1 year prior.

Prescribing for specific therapeutic areas

Stratified by BNF chapter, cardiovascular medications were the most frequently prescribed drugs throughout the last year of life, and musculoskeletal the least (Fig. 2a). On average, patients were prescribed 1.7 ± 2.0 cardiovascular drugs at baseline, with 1.3 ± 2.0 continuing to be prescribed at death, representing a 17.4% (-15.1 to -19.7%) fall (Fig. 2b). Levels of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium-channel blocker, beta-blockers and diuretics (ABCD medication) remained constant (≈ 0.8 drugs) until 1 month prior to death.

There were increases in gastrointestinal medication and drugs affecting the central nervous system (CNS) over the 12 months prior to death. On average, prescriptions increased from 0.8 ± 1.0 to 0.9 ± 1.1 and 1.2 ± 1.5 to 1.5 ± 1.6 at 12 months and 1 month prior to death for gastrointestinal and CNS medication, respectively. After accounting for correlation over time, the number of gastrointestinal and CNS medication increased by 6.5% (1.7 to 11.6%) and 8.4% (5.1 to 11.9%), respectively, between 12 months and 1 month prior to death (Appendix 6). Increases were observed for laxatives and indigestion medication (Fig. 2c), and for analgaesics, antidepressants and hypnotics and anti-psychotics (Fig. 2d).

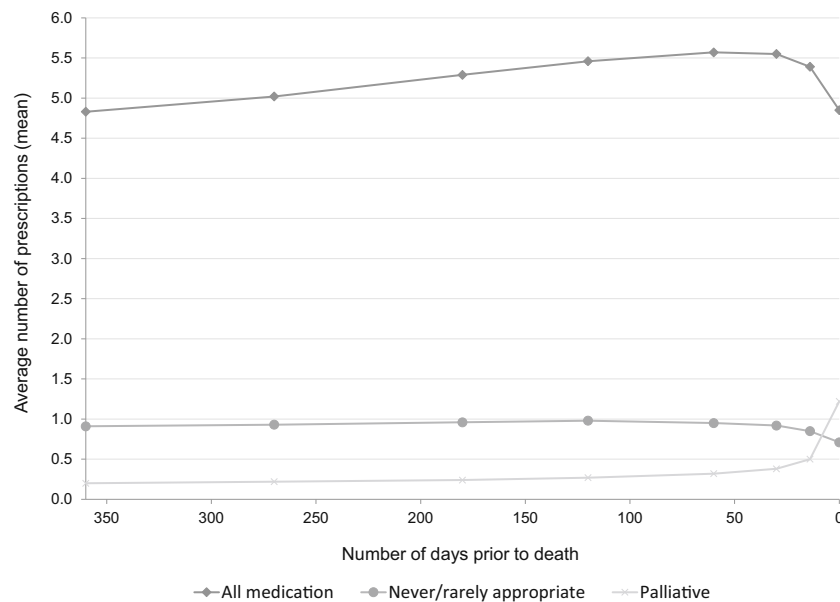


Fig. 1 Average (mean) number of prescriptions in the last year of life of dementia patients, stratified by appropriate prescribing All prescriptions restricted to enteral administered drugs. Never appropriate medication include lipid-lowering medication, cholinesterase inhibitors, antiplatelet agents (excluding aspirin), memantine, hormone antagonists, antioestrogen, leukotriene receptor antagonists, cytotoxic chemotherapy, sex hormones and immunomodulators. There were no prescriptions of

antioestrogen, leukotriene receptor antagonists, cytotoxic chemotherapy, sex hormones and immunomodulators in the last year of life amongst the study population. Rarely appropriate medication includes bisphosphonates, warfarin, digoxin, bladder relaxants, tamsulosin, antiandrogens, alpha blockers, antiarrhythmics, antispasmodics, mineralocorticoids, clonidine, hydralazine and heparin. There were no prescriptions of clonidine, hydralazine and heparin in the last year of life amongst the study population

Prescribing of inappropriate medications

One year prior to death, half (49.9%) of the patients were prescribed at least one drug considered inappropriate in severe dementia, dropping to 41.2% at death. Average number of inappropriate drugs fell from 1.0 ± 1.2 at 4 months to 0.7 ± 1.1 at death (Fig. 1). There was little change in prescribing of inappropriate medication until 1 month prior to death, when there was a 4.3% (-0.6 to -7.8%) decrease, with an even greater decrease of 11.2% (-7.1 to -15.1%) at death, compared with 1 year prior. Lipid-lowering agents and bisphosphates were the most commonly prescribed never and rarely appropriate medication, respectively (Fig. 3). Potentially hazardous prescribing followed a similar pattern, with over 16.4% of participants prescribed at least one 12 months prior to death, falling to 7.3% at death (Fig. 3a).

Factors that influence differences in prescribing

The relative differences in prescribing between key demographic and clinical factors are presented in Fig. 4. Women, older patients and those with Alzheimer's were generally prescribed fewer drugs overall compared with men (RD = -4.7% ; -2.3 to -7.0%), younger patients (oldest vs. youngest quartile, RD = -15.6% ; -12.5 to -18.5%) and those with vascular dementia (RD = -14.6% ; -11.7 to -17.3%). The

magnitude of differences in overall prescribing between dementia subtypes decreased over time (Alzheimer's vs. vascular -16.0% (-19.3 to -12.5%) at 1 year; -10.3% (-14.2 to -6.2%) at death; $p = 0.002$). Similar patterns were found for inappropriate prescribing (data not shown). There was no overall difference in prescribing between care home residency status, although inappropriate prescribing was lower in patients living in care homes compared with those not (RD = -17.4% ; -12.3 to -22.3%).

The number of drugs prescribed across the year varied by comorbidity status (p value < 0.001 ; Fig. 4d). Patients with a higher number of comorbidities experienced little change in the number of prescriptions in the last year of life, until near death when prescribing decreased. In contrast, prescribing increased amongst patients with fewer comorbidities.

Discussion

Findings from this study of electronic health records indicate that there are high levels of prescribing amongst dementia patients during their last year of life, with a significant proportion of the population prescribed an inappropriate medication throughout the year, with nearly half having such a prescription 2 weeks prior to death. The overall number of drugs increased over the last 12 months, and reductions were

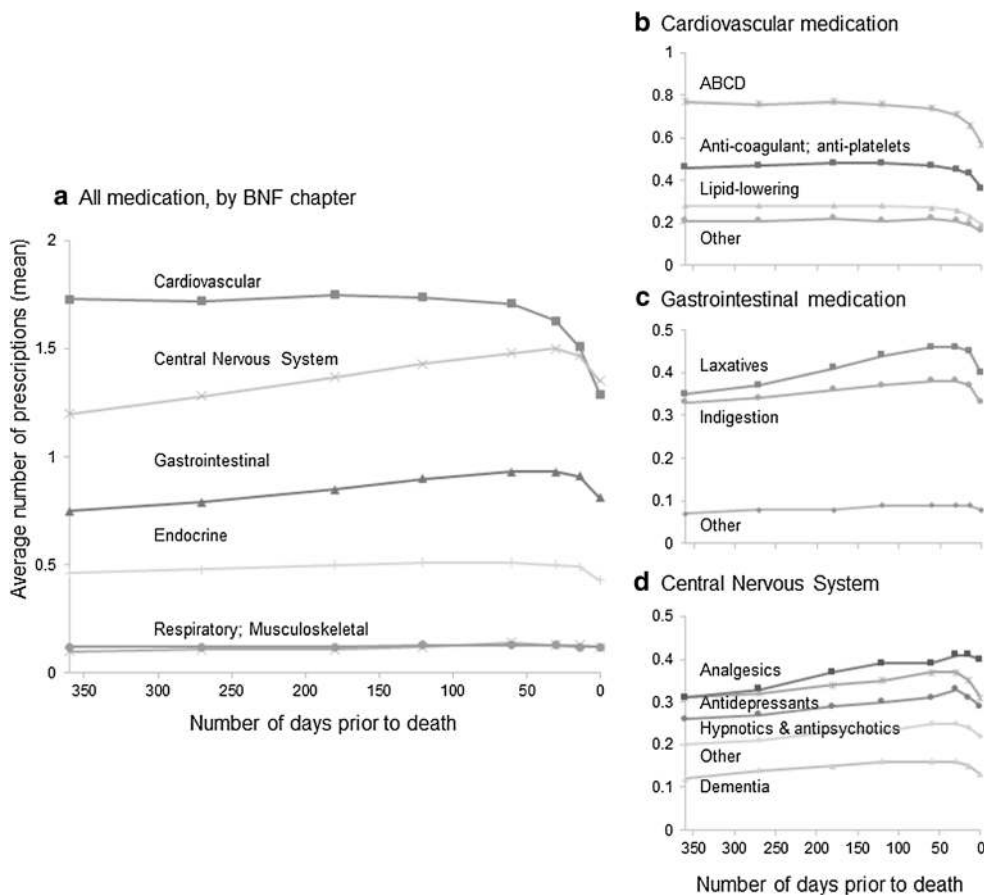


Fig. 2 Average (mean) number of enteral prescriptions in the last year of life of dementia patients, stratified by BNF chapter. **a** Selected BNF chapters; **b** Indigestion BNF sub-chapter 1.1 & 1.3, laxatives BNF sub-chapter 1.6, other includes all remaining chapter 1 sub-chapters. **c** ABCD BNF sub-chapter 2.5.5.1/2, 2.4, 2.6.2 & 2.2.1-4/8, Anti-coagulants, anti-platelets BNF subchapter 2.8/9, Lipid-lowering BNF sub-chapter 2.12, other includes all remaining chapter 2 sub-chapters. **d** Antidepressants

BNF sub-chapter 4.3, Analgesia BNF sub-chapter 4.7, Hypnotics and anti-psychoics BNF sub-chapter 4.1/2, Dementia medication BNF sub-chapter 4.11, other includes all remaining chapter 4 sub-chapters. *BNF* British National Formulary, *ABCD* angiotension-converting enzyme inhibitors, angiotensin II receptor antagonists, beta-adrenoceptor blocking drugs, calcium-channel blockers, Diuretics. All, never and rarely appropriate medication include enteral-administered drugs

generally only observed relatively close to death. In particular, a high level of cardiovascular drugs was consistently prescribed until the final month, whilst gastrointestinal and CNS medication increased.

Strengths and limitations

To our knowledge, this is the first general population study to investigate changes in the number and types of medication prescribed in primary care during the last year of life amongst patients who died with dementia. Combining primary care health records with national death registration data helped maximise identification of cases, providing a good representation of the UK population. Due to the ubiquitous nature of electronic prescribing in UK primary care, CPRD also provides full and detailed information on a patient’s prescribing history in primary care. Despite these strengths, several limitations are worth consideration, including potential misclassification and drug indication, which are common to most

studies using these types of routine clinical data. Information on prescribing outside of primary care, including in secondary care and “over the counter” were not available. Detailed clinical information on dementia diagnosis and progression, such as age at diagnosis and severity, is not captured, as demonstrated by the high level of missing information on dementia subtype. Nevertheless, the underlying pathogenesis was still available in around two-thirds of cases. The definition of inappropriate medication was drawn from a list developed for advanced dementia, despite lack of information about severity. A recent large cohort study found that patients who died with a dementia diagnosis, only one-quarter were at the severe stage of the illness [28]; thus, the appropriateness of such a list may be limited. However, there is no agreed alternative definition of inappropriate prescribing for dementia patients in the end-of-life context, and our choice was thus a pragmatic one although nevertheless clinically relevant. We compared findings using an alternative, general measure of potentially hazardous prescribing, and found levels to be three times higher

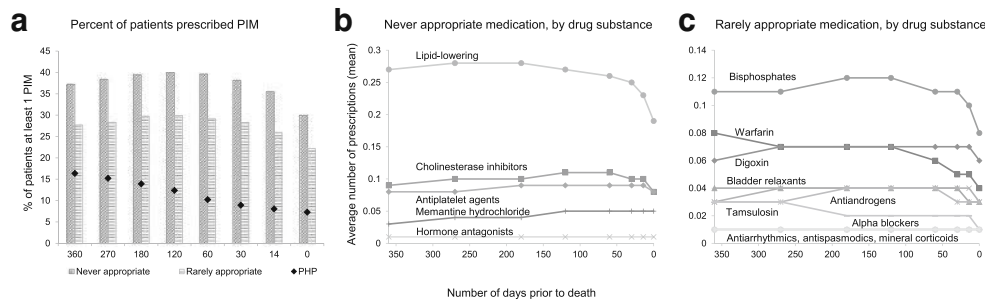
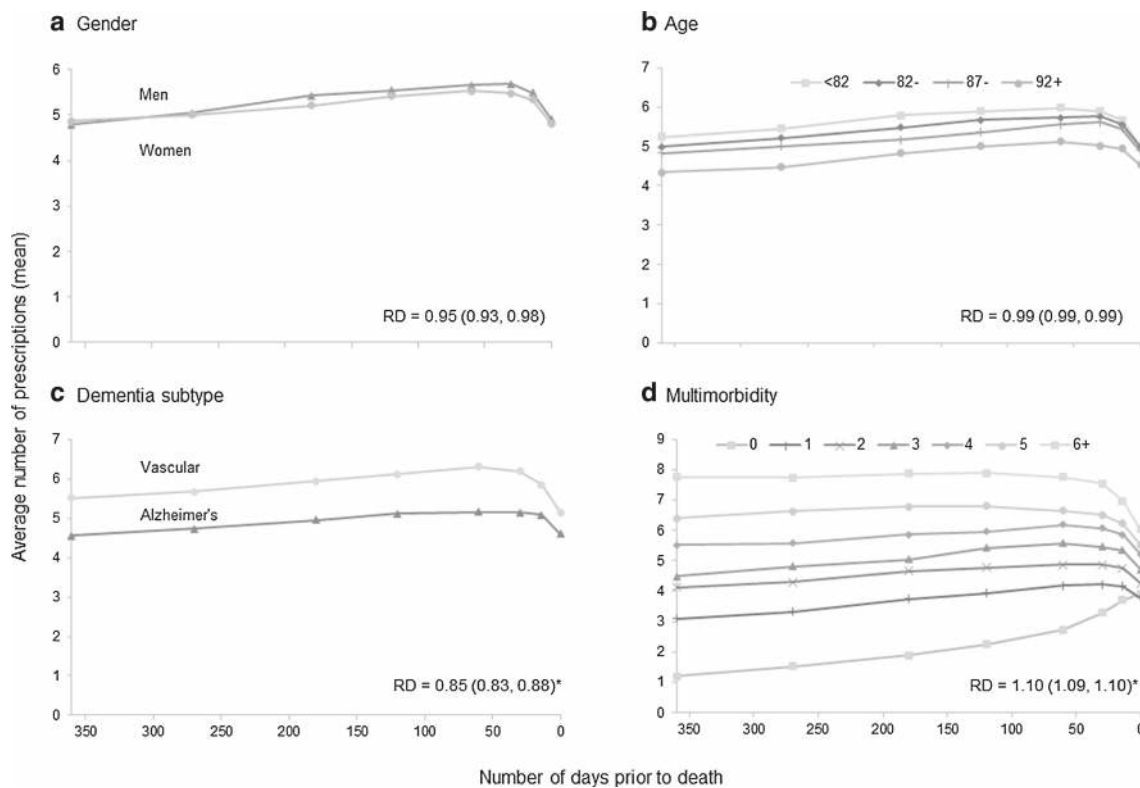


Fig. 3 Proportion of dementia patients in the last year of life prescribed at least one inappropriate medication, and average (mean) number of prescriptions, stratified by appropriate prescribing. *AP* appropriate prescription, *PHP* potentially hazardous prescription. All prescriptions restricted to enteral administered drugs. Never appropriate medication include lipid-lowering medication, cholinesterase inhibitors, antiplatelet agents (excluding aspirin), memantine, hormone antagonists, antioestrogen, leukotriene receptor antagonists, cytotoxic chemotherapy, sex hormones and immunomodulators. There were no prescriptions of

antioestrogen, leukotriene receptor antagonists, cytotoxic chemotherapy, sex hormones and immunomodulators in the last year of life amongst the study population. Rarely appropriate medication includes bisphosphonates, warfarin, digoxin, bladder relaxants, tamsulosin, antiandrogens, alpha blockers, antiarrhythmics, antispasmodics, mineralocorticoids, clonidine, hydralazine and heparin. There were no prescriptions of clonidine, hydralazine and heparin in the last year of life amongst the study population. Potentially hazardous prescribed is a composite measure of prescribing safety indicators P1-P19 [21]



CI: confidence intervals

Fig. 4 Average (mean) and relative difference (RD) in the number of enteral prescriptions in the last year of life of dementia patients by demographic and clinical factors. *CI*, confidence intervals. Zero-inflated Poisson regression models were fitted, and correlated standard errors at the patient level were used to account for the multiple measures (i.e. prescription counts) within individuals. Relative difference presented represents the average difference in drug count for a unit increase in the exposure over the year period. For age and multimorbidity, continuous

measures were used. The reference for A. gender was men, and for C. dementia subtype was vascular dementia. *Evidence of statistical interaction between exposure and time from death (p value < 0.001). All medication includes enteral-administered drugs. A list of 37 physical and mental chronic conditions was used to ascertain multimorbidity status in participants 1 year prior to death. The condition list was based on work by Barnett et al. and clinical consensus [13, 14]

in our dementia study population than those observed in the older general population [21]. Similar conclusions from these two analyses highlights that there are important opportunities to potentially improve prescribing in this population. Finally, our cohort was defined by death, and it is therefore not possible to comment on how prescribing varies with prospective assessment of life expectation, either by clinical judgement (e.g. the “surprise question” [29]) or objective risk assessment (e.g. QMortality [30]). This would be an important direction for future work.

Comparison with existing literature

This study supports previous findings of high levels of prescribing amongst dementia patients and the ongoing use of inappropriate medication in this population. The number of medications prescribed was comparable with the existing literature (range, 4 to 5.4) [2, 5, 12, 31]. Consistent with previous longitudinal studies [9–11, 32], our results indicate that dementia patients experience an overall increase in prescribing in the last year of life. Levels of inappropriate prescribing were similar to those reported elsewhere. A US study of nursing home residents with advanced dementia found half were prescribed at least 1 drug with questionable benefit [33]. Based on the RCGP safety indicators, hazardous prescribing appears to have declined over the 12 months reflecting implementation of appropriate improvements in prescription regimen, although rates were still considerably higher than the general population [21]. Furthermore, inappropriate prescribing quantified by specific therapeutic classes persisted until relatively late in life.

As indicated elsewhere [34], older patients had lower levels of prescribing compared with younger patients, suggesting physicians may be considering limited life expectancy and withholding treatments in the older age groups. Women were prescribed fewer drugs overall, with fewer high-risk medications compared with men. This may, in part, be accounted for by women being older and having fewer comorbidities. In the literature, there are mixed results relating to gender differences in prescribing, in particular with relation to inappropriate medication [9, 31]; this probably reflects variations in dementia severity and definitions of inappropriate prescribing between studies.

As in the general population, we found comorbidity to be associated with higher levels of prescribing [5, 12, 13, 35]. Dementia patients with higher levels of comorbidity experienced little change in their medication in their last year of life, whilst those with fewer comorbidities were prescribed more medications. This difference reflects low levels of medication at baseline amongst patients with no other conditions, with increases probably indicating health deterioration and prescribing related to symptom management.

Implications for research and/or practice

Findings from this study indicate that dementia patients receive considerable numbers of medications in their last year of life, many of which are considered inappropriate. Although rates of potentially hazardous prescribing did decline somewhat, these observations nevertheless support the need for improved medication optimisation strategies for patients experiencing polypharmacy [36]. Furthermore, they demonstrate that, outside of the palliative care setting, withdrawal or reduction of medications is uncommon. In part, this reflects the difficulties of predicting death 12 months in advance; clinicians may be reluctant to reduce potentially life-prolonging treatment in the face of considerable uncertainty around life expectancy, and indeed may not consider deprescribing in the first place if the patient is not obviously dying. The findings may also reflect the lack of a strong evidence base or any clinical guidelines to inform decisions around deprescribing of long-term medications [37].

Clinicians and policy makers alike need to ensure that medication optimisation remains a prominent aspect of clinical management for patients with dementia towards the end of life. There is also a pressing need to develop better evidence to support improved prescribing for these patients. This should include enhanced trial data for the effectiveness of long-term medications, improved methods for the identification of individuals with limited life expectancy and better medication optimisation strategies tailored to the specific needs of this vulnerable population.

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Compliance with ethical standards

Approval for the study was granted by the CPRD Independent Scientific Advisory Committee (Protocol reference 15_106R).

Conflict of interest The authors declare that they have no conflicts of interest.

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