

Adverse effects of Z-drugs for sleep disturbance in people living with dementia: a population-based cohort study

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List of abbreviations

ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CPRD	Clinical Practice Research Datalink
DDD	Defined Daily Doses
GP	General Practitioner
HES	Hospital Episode Statistics
ICD-10	International classification of diseases 10 th revision
MEDALZ	Medicine use and Alzheimer's disease
NNH	Number Needed to Harm
ONS	Office of National Statistics
PlwD	People living with Dementia
PPI	Patient and Public Involvement
TCA	Tricyclic Antidepressant

ABSTRACT

Background: Sleep disturbance is common in dementia and often treated with Z-drugs (zopiclone, zaleplon, and zolpidem). While some observational studies suggest that Z-drugs are associated with adverse events such as falls and fracture risks in older people, this has not been studied in dementia.

Methods: We used data from 27,090 patients diagnosed with dementia between January 2000 and March 2016 from the Clinical Practice Research Datalink linked to Hospital Episodes Statistics data in England. We compared adverse events for 3,532 patients newly prescribed Z-drugs by time-varying dosage to (1) 1,833 non-sedative-users with sleep disturbance, (2) 10,214 non-sedative-users with proximal GP consultation matched on age, sex, and antipsychotic use, and (3) 5,172 patients newly prescribed benzodiazepines. We defined higher dose Z-drugs and benzodiazepines as prescriptions equivalent to ≥ 7.5 mg zopiclone or >5 mg diazepam daily. Cox regression was used to estimate hazard ratios (HR) for incident fracture, hip fracture, fall, mortality, acute bacterial infection, ischaemic stroke/transient ischaemic attack, and venous thromboembolism over 2-year follow-up, adjusted for demographic and health related covariates.

Results: The mean (SD) age of patients was 83 (7.7) years and 16,802 (62%) were women. Of 3,532 patients prescribed Z-drugs, 584 (17%) were initiated at higher doses. For patients prescribed higher dose Z-drugs relative to non-users with sleep disturbance, the HRs (95% confidence interval) for fractures, hip fractures, falls and ischaemic stroke were 1.67 (1.13-2.46), 1.96 (1.16-3.31), 1.33 (1.06-1.66) and 1.88 (1.14-3.10). We observed similar associations when compared to non-sedative-users with proximal GP consultation. Minimal or inconsistent excess risks were observed at ≤ 3.75 mg zopiclone or equivalent daily, and for mortality, infection, and venous thromboembolism. We observed no differences in adverse events for Z-drugs compared to benzodiazepines, except lower mortality rates with Z-drugs (HR [95% confidence interval] of 0.73 [0.64-0.83]).

Conclusions: Higher dose Z-drug use in dementia is associated with increased fracture and stroke risks, similar or greater to that for higher dose benzodiazepines. Higher dose Z-drugs should be avoided, if possible, in people living with dementia, and non-pharmacological alternatives preferentially considered. Prescriptions for higher dose Z-drugs in dementia should be regularly reviewed.

TRIAL REGISTRATION: EUPAS18006 (ENCePP e-register of studies)

Background

Around 60% of people living with dementia (PlwD) are affected by sleep disturbance [1,2], including insomnia, fragmented night time sleep, night-time wandering, or excessive day sleep [3]. Sleep disturbance affects the quality of life of PlwD and their informal carers, and often leads to care home admission [4].

Benzodiazepines are frequently used for insomnia in PlwD and act by binding to gamma-aminobutyric acid, an inhibitory neurotransmitter [5]. Benzodiazepines are associated with a range of adverse side-effects including cognitive impairment, daytime sedation, tolerance, dependence and falls [6–9]. Z-drugs (zaleplon, zopiclone, eszopiclone and zolpidem), a class of non-benzodiazepine gamma-aminobutyric acid agonists have shorter half-lives and were originally believed to be safer than benzodiazepines, but their adverse effects are increasingly recognised [10,11]. Observational studies report Z-drugs are associated with increased risks of falls, fractures, stroke, mortality and infection in older adults [12–16]. However, these studies are generally subject to residual confounding by sleep disturbance and comorbidity. Studies have also not typically examined how the timing and dosages of Z-drugs might modify risk. More importantly, the adverse effects of Z-drugs have rarely been studied in PlwD, where these side-effects can be particularly catastrophic [17]. A recent Cochrane review found insufficient evidence to guide drug treatment of sleep problems in dementia [18], despite wide scale prescribing [19]. In addition, the effectiveness of Z-drugs to improve sleep in older people is uncertain and considered limited [11], with cognitive behaviour therapy demonstrated to be more effective at managing insomnia than zopiclone in older adults [20].

We examined the association between first Z-drug prescription and subsequent risk of falls, fractures, mortality, infection, ischaemic stroke, and venous thromboembolism in PlwD. To reduce confounding, we

compared Z-drug users with (1) non-users with sleep disturbance, (2) non-users with a proximal GP consultation, and (3) new benzodiazepine use.

Methods

Study Design

We performed a series of cohort studies, using data from the Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics (HES), Office for National Statistics (ONS) mortality data, and Index of Multiple Deprivation data in England. CPRD collates all diagnoses, referrals and prescribing records for over 11.3 million patients broadly representative of the UK population [21]. Diagnosis information is electronically entered as UK Read codes [22]. HES records all diagnoses made during a hospital admission (coded using the International classification of diseases 10th revision [ICD-10]) and demographic information [23], and ONS provides date and cause of death (ICD-10 coded) [24]. The Index of Multiple Deprivation combines a number of indicators of housing, employment, income, education, environment at the general practice level [25]. CPRD obtained ethical approval from a National Research Ethics Service Committee, allowing researchers to access anonymized data for observational studies upon approval from an Independent Scientific Advisory Committee.

Study Population

We defined dementia patients by record of a dementia diagnosis in CPRD (codes in Additional file 1) or HES (ICD-10 F00-F03, G30, G31.0 or G31.1) *or* prescription of a cognitive enhancer (i.e. memantine, donepezil, rivastigmine, or galantamine), occurring after January 2000 when aged ≥ 55 years. We excluded patients with < 3 months of 'up-to-standard' (research quality) data or with severe mental illness or Down syndrome before dementia diagnosis (codes in Additional file 1) [21].

Exposures

Our primary exposure was new prescription of Z-drugs. We considered three comparator groups to reduce confounding [26]. The primary comparator was record of sleep disturbance without sedative-hypnotic prescription. Secondary comparators were (a) non-users at a proximal GP consultation and (b) new benzodiazepine users. To facilitate these comparisons, three main cohorts were constructed, with their index date as the first date after dementia diagnosis of (a) prescription for a Z-drug (World Health Organization's Anatomic Therapeutic Classification [ATC] system category N05CF), (b) prescription of any benzodiazepine (ATC N05BA or N05CD except midazolam injection), and (c) code for sleep disturbance (codes in Additional file 1) but without a concurrent sedative-hypnotic (ATC N05C or N05BA) prescription.

Two additional cohorts were created by matching the Z-drug and BZD cohorts on age, sex and antipsychotic use, to non-users (not prescribed sedative-hypnotics) with proximal GP consultation. We matched three non-users to each Z-drug or benzodiazepine user, without replacement, and assigned an index date as the closest GP consultation within one month of the corresponding Z-drug or benzodiazepine index date. Patients could be members of different cohorts over time.

Exclusion criteria for all cohorts were (1) <12 months data history, (2) sedative-hypnotic prescription in last 12 months, (3) prior diagnosis of sleep apnoea, sleep related respiratory failure, or alcohol abuse (codes in Additional file 1), (4) prescription of multiple sedative-hypnotics, and (5) newly prescribed antipsychotics or low dose tricyclic or related antidepressants (≤ 25 mg Amitriptyline or ≤ 50 mg Trazodone per day). We additionally performed a separate validation study on the accuracy of our patient selection (details in Additional file 2). In summary, GP practices confirmed dementia diagnoses in 96% of cases, however uncertainty was raised regarding the accuracy of those identified with sleep disturbance.

To test dose-response relationships we determined the number of daily defined doses (DDDs) of Z-drugs and benzodiazepines at each prescription. The DDD is the assumed average maintenance dose per day for a drug based on its main indication in adults. We used DDD values from the World Health Organisation's Collaborating Centre for Drug Statistics Methodology (www.whooc.no/atc_ddd_index), where the DDDs for zopiclone, zolpidem and zaleplon are 7.5mg, 10mg and 10mg per day. The British National Formulary recommends these daily doses for adults with insomnia, but to halve them for elderly patients. Missing dosing frequency data was assumed once daily, except diazepam where we applied the most common frequency for the product and quantity prescribed amongst the complete prescription data.

Outcomes

The selected outcomes were identified from previous studies or were priorities identified by our Patient and Public Involvement (PPI) group members or by an advisory group of healthcare professionals established to support this project. The main outcomes were, in order of importance: (1) Incident (a) fracture in any location, (b) hip fracture, and (c) forearm/wrist/hand fracture, (2) Incident fall, (3) mortality, (4) acute bacterial infection, (5) Ischaemic stroke/transient ischemic attack, and (6) Venous thromboembolism. These were identified via first mention of a relevant Read code in CPRD or ICD-10 code in HES or ONS (codes in Additional file 3). We also examined further healthcare utilization outcomes: (7) number of (a) hospital admissions, and (b) GP consultations, and (8) new prescription of (a) antipsychotics (b) antidepressants, and (c) antibiotics.

Covariates

We considered as potential confounders variables suspected to be linked to dementia, sleep disturbance, benzodiazepine or Z-drug use or the outcomes examined. They were measured on the index date and covered domains of demographics, health behaviours, dementia subtype, proxies for dementia severity, proxies for sleep disturbance severity, comorbidities, recent medical history (e.g. GP consultations, hospital admissions, falls, fractures, infections, immunisations, body mass index [BMI], systolic blood pressure), and concurrent prescriptions (details in additional file 4).

Statistical analysis

The primary analysis estimated the association between new prescription of sleep disturbance medication and incidence of each outcome, compared to other groups. We followed patients until the earliest of: death, leaving the GP practice, last data extraction, new sedative-hypnotic or antipsychotic prescription, 2-years post index date, or 31st March 2016. Z-drug and benzodiazepine new-users were also censored 90 days following their last Z-drug/benzodiazepine prescription. Matched patients were additionally censored at the censoring date of their corresponding case. Specific exclusion criteria applied at the index date to reduce the chance of repeated coding of the same event are described in Additional file 5 table S1.

Cox proportional hazards regression was used for binary outcomes. We used robust standard errors to account for the correlation due to repeat measurements in some patients [27]. The proportional hazards assumption was checked using Schoenfeld residuals [28]. Negative binomial regression was used to model number of hospital admissions and GP consultations. Estimates were adjusted for age and sex, and all covariates in additional file 4. Age, BMI, systolic blood pressure, duration since dementia

diagnosis, index date, and number of prior GP consultations were modelled using restricted cubic splines (with five knots) to allow non-linear effects [29]. We included an interaction between sex and BMI, due to known sex differences in the relationship between BMI and fracture risk [30]. Absolute risk differences of adverse events and numbers needed to harm (NNH) were estimated using standard formulae for time to event analysis [31].

We examined average daily Z-drug dose over follow-up, but in post-hoc secondary analysis, to reflect changes in dose, we examined time-varying daily DDDs. In sensitivity analysis, we excluded those with record of >6 hours sleep per night from the sleep-disturbance comparator group (see validation study in Additional file 2 for more detail). This was to increase the chance that the sleep-disturbance group had more comparable insomnia to the Z-drug group. Finally, in the comparison of Z-drug to benzodiazepine new-users, we restricted to benzodiazepines likely prescribed for sleep disturbance (loprazolam, lormetazepam, nitrazepam, temazepam, or other benzodiazepine with dosing instructions to take only at night or with a concurrent record of sleep disturbance).

Multiple imputation by chained equations was used to impute missing values of BMI, smoking, alcohol use, residence, ethnicity and blood pressure (see Additional file 4 for details) [32]. To account for multiple outcomes tested, we used the Benjamini-Hochberg procedure to control the false discovery rate at <5% for each analysis [33]. Stata version 15.1 was used throughout.

Results

There were 51,117 eligible dementia patients with ≥ 12 months data history in the linked CPRD-HES database (additional file 5 figure S1). Of these, 3,532 and 5,172 patients were newly prescribed Z-drugs or benzodiazepines respectively and met our inclusion criteria. Z-drug and benzodiazepine new users were matched to 10,214 and 15,174 non-users, respectively. Finally, 1,833 dementia patients had recorded sleep disturbance, but without prescription of sedative-hypnotics.

Patient characteristics

The mean (SD) age of patients at index date was 83 (7.7) years, and 16,802 (62%) were women. Patients were registered with their GP for a median (IQR) of 19 (11-32) years and diagnosed with dementia for a median (IQR) of 12 (4-25) months.

The patient cohorts were similar across measured characteristics (Table 1 with missing data described in additional file 5 table S2). Recent hospital admissions were more likely among Z-drug users. Concurrent antipsychotics and antidepressants, and previous benzodiazepine or Z-drug use was more likely among benzodiazepine and Z-drug users. Benzodiazepine users more frequently lived in care homes, had agitation/psychosis and anxiety and dementia for longer. Those with sleep disturbance (no sedative-hypnotics) were more likely from a deprived neighbourhood, consume alcohol, have urinary incontinence, and insomnia history before dementia. Finally, the non-users with proximal GP consultation had more recent GP consultations and fewer recent falls and fractures.

Of 3532 patients prescribed Z-drugs, 3358 (95%) were prescribed zopiclone, with 2801 (83%) prescribed 3.75mg daily on the index date. For 598 (17%) the prescription instructions were “pro re nata” (PRN / as needed). Of 5172 patients prescribed benzodiazepines, the most common were diazepam (n=2077, 40%), lorazepam (n=1669, 32%) and temazepam (n=1168, 23%). Patients were followed for a median

(IQR) of 3.5 (3.0-10.3) months and mainly censored due to no further Z-drug or benzodiazepine prescriptions. See additional file 5 table S3 for initial and follow-up doses.

Falls and fractures

We estimated HRs (95% CI) of 1.32 (0.99-1.75) and 1.34 (1.08-1.67) for Z-drugs and fracture compared to sleep disturbance (without sedative-hypnotics) and non-use with proximal GP consultation, respectively (Table 2). For hip fracture, the HRs (95% CI) were 1.38 (0.92-2.06) and 1.59 (1.15-2.19) for Z-drugs compared to sleep disturbance and non-use with proximal GP consultation, respectively. Z-drug use was associated with increased falls compared to non-use with proximal GP consultation (HR 1.43, 95% CI 1.26-1.62), but not compared to sleep disturbance (HR 1.02, 95% CI 0.87-1.21). New benzodiazepine use was associated with increased fractures and falls compared to non-use with proximal GP consultation, but the HR (95% CI) for hip fractures was 1.17 (0.87-1.57) (additional file 5 table S4). There were no large differences in fall and fracture rates between new Z-drug and benzodiazepine users (Table 2).

There was evidence of differing associations with the outcomes according to the prescribed daily dose of Z-drugs or benzodiazepines (Table 3 and additional file 5 table S5). Compared to sleep disturbance without sedative-hypnotics, the adjusted HR (95% CI) for fractures, hip fractures and falls for Z-drug prescriptions equivalent to ≥ 7.5 mg zopiclone daily were 1.67 (1.13-2.46), 1.96 (1.16-3.31) and 1.33 (1.06-1.66). The adjusted HR (95% CI) for Z-drug prescriptions equivalent to ≤ 3.75 mg zopiclone daily and fractures, hip fractures and falls were 1.22 (0.90-1.66), 1.21 (0.78-1.90) and 0.95 (0.80-1.13). Similar associations were observed when compared to non-users with proximal GP consultation.

Absolute risks. Use of zopiclone at ≥ 7.5 mg or equivalent is associated with absolute annual risks of fracture of 12.4% (compared to 7.6% in the sleep disturbance cohort). For hip fracture, the corresponding

figures are 6.6% annual risk associated with zopiclone at ≥ 7.5 mg or equivalent compared to 3.4%. This is equivalent to NNH of 21 and 32, and extra cases per 1000 treated of 48 and 32 for fractures and hip fractures, respectively.

Mortality, infection and cardiovascular outcomes

Although Z-drug use was associated with greater mortality compared to those with sleep disturbance (HR 1.38, 95% CI 1.14-1.66), there was no strong evidence of excess risk compared to non-users with a proximal GP consultation (HR 1.08, 95% CI 0.94-1.23) (Table 2). Further, the associations with mortality seemed unrelated to dose (Table 3). Z-drug prescription was associated with less mortality than benzodiazepines (HR 0.73, 95% CI 0.64-0.83).

We did not detect any strong associations between new Z-drug prescription and greater infection or venous thromboembolism rates, compared either to the non-users or benzodiazepine users.

When examining new Z-drug prescription overall, we did not detect strong associations with incident stroke rates (HR 1.14 [95% CI 0.86-1.50], compared to non-users with proximal GP consultation).

However, higher dose (≥ 7.5 mg zopiclone or equivalent) Z-drugs were associated with more ischaemic strokes (HR 1.88 [95% CI 1.14-3.10] and 1.90 [1.30-2.79] compared to sleep disturbance and non-users with proximal GP consultation). The association for higher dose Z-drugs appeared greater than that for higher dose (>5 mg diazepam or equivalent) benzodiazepine use, with a HR (95% CI) for higher dose benzodiazepine and stroke of 1.37 (0.91-2.08) compared to non-use with proximal GP consultation (additional file 5 table S5).

Absolute risks. Use of zopiclone at ≥ 7.5 mg or equivalent is associated with absolute annual risks of stroke of 8.1% (compared to 4.4% in the sleep disturbance cohort). This is equivalent to an NNH of 27 and 37 extra cases per 1000 treated.

Additional medication and healthcare utilisation

The adjusted rate ratios (95% CI) for hospital visits for Z-drug users were 1.26 (1.13-1.40), compared to sleep disturbance and 1.17 (1.07-1.27), compared to non-use with proximal GP consultation. The rates between Z-drugs and benzodiazepines were similar. For GP consultations the corresponding rate ratios were 1.17 (1.12-1.23) and 1.07 (1.04-1.11), respectively. However, when analysed by time-varying prescribed dose, more frequent hospital admissions and GP consultations were generally only observed for higher dose Z-drugs (Table 5) and higher dose benzodiazepines (additional file 5 table S6).

Z-drug users were more likely prescribed a new antipsychotic (HR 2.37, 95% CI 1.84-3.04) or antidepressant (HR 2.32, 95% CI 1.65-3.25) during follow-up compared to non-users with sleep disturbance (Table 4). There was a small increase in antibiotic prescribing subsequent to new Z-drug prescription compared to non-users with proximal GP consultation (HR 1.19, 95% CI 1.08-1.30). Rates of new prescribing were generally similar post Z-drug prescription to post benzodiazepine prescription and were greater with increasing Z-drug dose (Table 5).

Additional analyses

Similar associations to those for time-varying prescribed dose were observed when analysing the (non-time-varying) average number of doses prescribed over the exposure period (additional file 5 table S7-

S8). In the sensitivity analysis using a comparator of those with sleep disturbance and no associated mention of >6 hours sleep, associations for Z-drug use were generally slightly reduced (additional file 5 tables S9-S10). Finally, associations for Z-drug use compared to the 1601 patients prescribed benzodiazepines for sleep disturbance were very similar to when comparing to any benzodiazepine (additional file 5, table S11).

Discussion

We found evidence of increased risks of falls, fractures and ischaemic stroke in people with dementia prescribed Z-drugs at higher doses. The associations observed were similar or greater in magnitude to those for higher dose benzodiazepine prescription. One in six Z-drug prescriptions were commenced at higher doses of equivalent to 7.5mg zopiclone daily or greater. We did not detect any consistent or clinically significant increased risks of mortality, infection or venous thromboembolism with Z-drug use. PlWD prescribed higher dose Z-drugs were also more likely to be admitted to hospital, visit their GP, and be further prescribed antipsychotics, antidepressants and antibiotics.

We designed the study to minimize possible sources of bias [34]. Although we were unable to measure dementia severity, we adjusted for duration since the dementia diagnosis, prescription of dementia medications and antipsychotics, history of agitation/psychosis, and end of life care. However, there may be residual confounding by dementia severity for some comparisons. Although underlying severity was unclear, the mortality results suggest that, compared to Z-drug users, the sleep disturbance group not prescribed sedatives may have less severe dementia, however that the non-users with proximal GP consultation had comparable dementia severity. Residual confounding by sleep disturbance severity is also a possibility. Sleep disturbance was challenging to identify within the electronic primary care record

as highlighted in our validation study, where only 42% of our selected 'sleep disturbance' patients had sleep disturbance confirmed by their GP practice. This could be partly due to the sometimes contradictory 'sleep pattern' records or that the sleep disturbance recorded was transient or due other causes, such as urinary incontinence or alcohol abuse. The comparable falls risk in the Z-drug and 'sleep disturbance' group could be due to urinary incontinence and alcohol use being more common in the 'sleep disturbance' group. The coding of 'sleep disturbance' was often vague and may represent conditions other than insomnia. It may be that some of the 'sleep disturbance and no sedative' group had milder cases of sleep disturbance than those prescribed Z-drugs. Performing a sensitivity analysis on the sleep disturbance definition reduced our effects slightly. Residual confounding by severity of insomnia or dementia could also affect the associations with higher Z-drug doses. We also had no data on genetic information and environmental factors, which may influence falls risk in people living with dementia [35]. There was likely some small residual confounding due to new admission to a care home, however we were unable to accurately ascertain the admission date to control for this.

Our study was strengthened by additional comparisons to non-users with a proximal GP visit and new benzodiazepine users. As benzodiazepines are also prescribed for anxiety and behavioural disturbances of dementia, there may be residual confounding by dementia and sleep disturbance severity in the comparison between Z-drug and benzodiazepine users. However, when instead restricting to benzodiazepines likely prescribed for sleep disturbance our findings were very similar. Dosing instructions were often missing for benzodiazepines, and although we made plausible assumptions based on the complete prescriptions, some misclassification of exposures is possible. Recording of prescriptions issued in primary care is accurate, however we lacked data on medications prescribed in secondary care or obtained elsewhere. Medication adherence is unknown, therefore the Z-drug effects may be underestimated if many patients prescribed Z-drugs had not taken them. Studies report high positive

predictive values for patients coded with our study outcomes in UK primary care data [36–41]. Potential under-reporting in CPRD was improved through linkage to HES and ONS. However, we likely underestimated forearm fracture incidence as many do not require hospital admission. Similarly, GP records of falls may under-represent all falls that occur in the older population, but more accurately represent ‘injurious falls requiring medical attention’ [42]. Our study was strengthened by using a new-user design and careful selection and follow-up of patients taking Z-drugs alone and not concurrent with other sedative-hypnotics [43,44]. Our findings are generalizable to most people with diagnosed dementia and sleep disturbance. Few patients were prescribed zaleplon or zolpidem and none eszopiclone; however as they exert the same pharmacological action as zopiclone, the adverse effects of these agents are likely similar.

Comparison with other studies

Fractures

Few studies have examined Z-drug dose and fracture risk. Greater risks of hip fracture were reported among older US care-home residents taking higher dose Z-drugs, although limited by small numbers [45]. Additionally, few studies have examined fracture risk in PlWD taking Z-drugs. Consistent with our findings, a study of hospital records of PlWD in Japan reported increased fracture risks with Z-drug use, but they were unable to ascertain whether the prescription was given before or after the fracture [46]. Various studies report associations between Z-drugs and fracture risk, and specifically hip fracture risk, in older adults [12,13]. However, our study and others suggest this relative risk is lower in PlWD [47,48]. For example in US nursing home residents, greater odds ratios were estimated between non-benzodiazepine hypnotic drug use and hip fracture in residents with no or only mild cognitive impairment than with

moderate-severe cognitive impairment [47]. Z-drugs likely increase fracture risk through their effects on gait and balance [49,50]. A randomised trial reported more tandem walk failures upon night-time awakening among older adults randomized to 5mg zolpidem compared to placebo [51].

Falls

Z-drugs were originally claimed to cause fewer falls than benzodiazepines [52], however, we found similar or larger effects. This is consistent with findings from older men in the Osteoporotic Fractures in Men study [53]. More fall-related injuries were observed with Z-drug use in older people in Taiwan, with greater frequencies when prescribed >0.6 DDDs [54]. Increased fall rates have also been observed with dose increases in sedative-hypnotics in nursing home residents with dementia [55].

Cardiovascular outcomes

Similar to us, more strokes were observed in the Medicine use and Alzheimer's disease (MEDALZ) cohort prescribed Z-drugs and adults in Taiwan prescribed zolpidem [15,56]. Unfortunately, neither study estimated dose-specific risks. Mechanisms for Z-drugs causing increased stroke risk are uncertain, but could relate to decreased local cerebral blood flow [56]. However, as prolonged sleep disturbances likely increase stroke risk, residual confounding by sleep disturbance severity and duration could underlie reported associations [57].

Infections

Analysis of RCT data, generally in younger adults, indicated possible 1.5-2 fold increased infection risks when taking zopiclone and zolpidem [58]. We found inconsistent evidence of increased bacterial infection risk with higher dose Z-drugs. Other studies in older adults, including a MEDALZ cohort study, report no association between Z-drug use and risk of pneumonia [59–61]. Together these suggest that if acute infection risk increases with higher dose Z-drug use in PlwD, then it is likely to be small, and our study was underpowered to detect it.

Mortality

Consistent with our findings, a MEDALZ cohort study found benzodiazepine use associated with increased mortality, but not Z-drugs [62]. Studies on Z-drug or benzodiazepine use and mortality in adults have been conflicting, and reported associations may simply stem from increased usage of benzodiazepines with approaching death [63].

Healthcare Utilization

We observed greater subsequent initiation of antipsychotics and antidepressants among Z-drug users, similarly observed by older people prescribed Z-drugs in a Taiwan study [54]. This likely reflects the increased behavioural and psychological symptoms of dementia as it progresses. The increased hospital visits we observed post Z-drug initiation could partly reflect the increased fracture and stroke rates in these patients. The Taiwan study also reported greater rates of fall-related injuries requiring hospitalization among Z-drug users [54].

Conclusions

Higher doses of Z-drugs should be avoided in PlwD due to increased fracture and stroke risks. One in six PlwD in our study were commenced at 7.5mg zopiclone or equivalent daily. Prescribers should use the lowest effective dose in the elderly, use simple specific drug regimens, and this advice needs implementing in national guidelines [64,65]. Our findings suggest that the safety profile of Z-drugs should be considered similar to benzodiazepines in PlwD. Although the risks associated with low dose Z-drugs were small, as the effectiveness of Z-drugs is also unproven in dementia, we advise adhering to the Beers criteria guidelines of avoiding Z-drug use in PlwD, where possible [66]. Alternative strategies should be sought for sleep disturbance other than Z-drug or benzodiazepine dose escalation. Where pharmacological management of sleep disturbance is initiated, fracture risk management plans are implemented, and prescriptions regularly reviewed to mitigate potential adverse health outcomes. This gives a clear and important steer for the use of hypnotics in people with dementia in clinical practice. This evidence is currently particularly important as social isolation related to the COVID-19 pandemic may increase the frequency of neuropsychiatric symptoms in dementia [67], and limit resources to offer non-pharmacological management approaches.

Declarations

Ethical approval: The study was approved by the Independent Scientific Advisory Committee for CPRD for Clinical Practice Research Datalink research (protocol 16_181). No further ethical approval was required for the analysis of the data. The CPRD Group has obtained ethical approval from a multi-centre research ethics committee for all purely observational research using CPRD data.

Consent for publication: Not applicable

Availability of data and materials: This study is based on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency (MHRA). However, the interpretation and conclusions contained in this report are those of the authors alone. Linked data from the Clinical Practice Research Datalink is available directly from CPRD. Full code lists for the covariates are available from the corresponding author at kathryn.richardson@uea.ac.uk.

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Authors' contributions: KR, YKL, CF, IM, GMS, NS, AA, CB and RH conceived and developed the initial study. KR and GMS drafted the statistical analysis plan. KR, NS, IM, CF, RH and YKL developed the code

lists. KR conducted the statistical analysis and wrote the first manuscript draft, and all authors contributed to the interpretation of findings and revision of the manuscript.

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Additional material

Additional file 1.doc – Read codes to define dementia in CPRD, excluded patients and sleep disturbance

Additional file 2.doc - Dementia and sleep disturbance validation study

Additional file 3.doc - Read codes in CPRD and ICD-10 codes in HES and ONS to define the outcomes

Appendix file 4.doc – Study protocol registration, Definition of covariates and Multiple Imputation

Methods

Additional file 5.doc - Additional exclusion criteria, frequency of missing data, dose changes during follow-up, additional analysis results tables and flowchart of patient selection

References

- 1 Guarnieri B, Adorni F, Musicco M, *et al.* Prevalence of Sleep Disturbances in Mild Cognitive Impairment and Dementing Disorders: A Multicenter Italian Clinical Cross-Sectional Study on 431 Patients. *Dement Geriatr Cogn Disord* 2012;**33**:50–8. doi:10.1159/000335363
- 2 Gitlin LN, Hodgson N, Piersol CV, *et al.* Correlates of quality of life for individuals with dementia living at home: the role of home environment, caregiver, and patient-related characteristics. *Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry* 2014;**22**:587–97. doi:10.1016/j.jagp.2012.11.005
- 3 McCurry SM, Logsdon RG, Teri L, *et al.* Characteristics of Sleep Disturbance in Community-Dwelling Alzheimer’s Disease Patients. *J Geriatr Psychiatry Neurol* 1999;**12**:53–9. doi:10.1177/089198879901200203
- 4 Pollak CP, Perlick D. Sleep problems and institutionalization of the elderly. *J Geriatr Psychiatry Neurol* 1991;**4**:204–10.
- 5 Ashton H. Guidelines for the rational use of benzodiazepines. When and what to use. *Drugs* 1994;**48**:25–40. doi:10.2165/00003495-199448010-00004
- 6 Tannenbaum C, Paquette A, Hilmer S, *et al.* A Systematic Review of Amnestic and Non-Amnestic Mild Cognitive Impairment Induced by Anticholinergic, Antihistamine, GABAergic and Opioid Drugs. *Drugs Aging* 2012;**29**:639–58.
- 7 Swift CG, Swift MR, Hamley J, *et al.* Side-effect ‘tolerance’ in elderly long-term recipients of benzodiazepine hypnotics. *Age Ageing* 1984;**13**:335–43. doi:10.1093/ageing/13.6.335
- 8 Brett J, Murnion B. Management of benzodiazepine misuse and dependence. *Aust Prescr* 2015;**38**:152–5. doi:10.18773/austprescr.2015.055
- 9 Woolcott JC, Richardson KJ, Wiens MO, *et al.* Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med* 2009;**169**:1952–60. doi:10.1001/archinternmed.2009.357
- 10 Gunja N. The Clinical and Forensic Toxicology of Z-drugs. *J Med Toxicol* 2013;**9**:155–62. doi:10.1007/s13181-013-0292-0
- 11 Glass J, Lanctôt KL, Herrmann N, *et al.* Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ* 2005;**331**:1169. doi:10.1136/bmj.38623.768588.47
- 12 Treves N, Perlman A, Kolenberg Geron L, *et al.* Z-drugs and risk for falls and fractures in older adults—a systematic review and meta-analysis. *Age Ageing* 2018;**47**:201–8. doi:10.1093/ageing/afx167
- 13 Donnelly K, Bracchi R, Hewitt J, *et al.* Benzodiazepines, Z-drugs and the risk of hip fracture: A systematic review and meta-analysis. *PLOS ONE* 2017;**12**:e0174730. doi:10.1371/journal.pone.0174730
- 14 Huang C-Y, Chou FH-C, Huang Y-S, *et al.* The association between zolpidem and infection in patients with sleep disturbance. *J Psychiatr Res* 2014;**54**:116–20. doi:10.1016/j.jpsychires.2014.03.017

- 15 Huang W-S, Tsai C-H, Lin C-C, *et al.* Relationship Between Zolpidem Use and Stroke Risk: A Taiwanese Population-Based Case-Control Study. *J Clin Psychiatry* 2013;**74**:e433–8. doi:10.4088/JCP.12m08181
- 16 Parsaik AK, Mascarenhas SS, Khosh-Chashm D, *et al.* Mortality associated with anxiolytic and hypnotic drugs—A systematic review and meta-analysis. *Aust N Z J Psychiatry* 2015;:0004867415616695. doi:10.1177/0004867415616695
- 17 Givens JL, Sanft TB, Marcantonio ER. Functional Recovery After Hip Fracture: The Combined Effects of Depressive Symptoms, Cognitive Impairment, and Delirium. *J Am Geriatr Soc* 2008;**56**:1075–9. doi:10.1111/j.1532-5415.2008.01711.x
- 18 McCleery J, Cohen DA, Sharpley AL. Pharmacotherapies for sleep disturbances in dementia. *Cochrane Database Syst Rev* Published Online First: 2016. doi:10.1002/14651858.CD009178.pub3
- 19 Gustafsson M, Karlsson S, Gustafson Y, *et al.* Psychotropic drug use among people with dementia – a six-month follow-up study. *BMC Pharmacol Toxicol* 2013;**14**:56. doi:10.1186/2050-6511-14-56
- 20 Sivertsen B, Omvik S, Pallesen S, *et al.* Cognitive Behavioral Therapy vs Zopiclone for Treatment of Chronic Primary Insomnia in Older Adults: A Randomized Controlled Trial. *JAMA* 2006;**295**:2851–8. doi:10.1001/jama.295.24.2851
- 21 Herrett E, Gallagher AM, Bhaskaran K, *et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;**44**:827–36. doi:10.1093/ije/dyv098
- 22 Chisholm J. The Read clinical classification. *Br Med J* 1990;**300**:1092–1092. doi:10.1136/bmj.300.6732.1092
- 23 Herbert A, Wijlaars L, Zylbersztejn A, *et al.* Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *Int J Epidemiol* 2017;**46**:1093–1093i. doi:10.1093/ije/dyx015
- 24 Patel V. Deaths registered in England and Wales: 2017. London, UK: : Office for National Statistics 2018.
- 25 Department for Communities and Local Government, UK Government. English indices of deprivation 2015. <https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015> (accessed 22 Oct 2019).
- 26 Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. *Int J Epidemiol* 2016;**45**:1866–86. doi:10.1093/ije/dyw314
- 27 Rogers W. Regression standard errors in clustered samples. *Stata Tech Bull* 1994;**3**.https://econpapers.repec.org/article/tsjstbull/y_3a1994_3av_3a3_3ai_3a13_3asg17.htm (accessed 11 Dec 2019).
- 28 Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994;**81**:515–26. doi:10.1093/biomet/81.3.515
- 29 Groenwold RHH, Klungel OH, Altman DG, *et al.* Adjustment for continuous confounders: an example of how to prevent residual confounding. *CMAJ Can Med Assoc J* 2013;**185**:401–6. doi:10.1503/cmaj.120592

- 30 De Laet C, Kanis JA, Odén A, *et al.* Body mass index as a predictor of fracture risk: A meta-analysis. *Osteoporos Int* 2005;**16**:1330–8. doi:10.1007/s00198-005-1863-y
- 31 Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999;**319**:1492–5.
- 32 White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011;**30**:377–99. doi:10.1002/sim.4067
- 33 Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J R Stat Soc Ser B Methodol* 1995;**57**:289–300. doi:10.2307/2346101
- 34 Sterne JA, Hernán MA, Reeves BC, *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;**355**:i4919. doi:10.1136/bmj.i4919
- 35 Sharma S, Mueller C, Stewart R, *et al.* Predictors of Falls and Fractures Leading to Hospitalization in People With Dementia: A Representative Cohort Study. *J Am Med Dir Assoc* 2018;**19**:607–12. doi:10.1016/j.jamda.2018.03.009
- 36 Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract* 2010;**60**:e128–36. doi:10.3399/bjgp10X483562
- 37 Staa T-PV, Abenhaim L. The quality of information recorded on a UK database of primary care records: A study of hospitalizations due to hypoglycemia and other conditions. *Pharmacoepidemiol Drug Saf* 1994;**3**:15–21. doi:10.1002/pds.2630030106
- 38 Huerta C, Johansson S, Wallander M, *et al.* Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the united kingdom. *Arch Intern Med* 2007;**167**:935–43. doi:10.1001/archinte.167.9.935
- 39 Ruigómez A, Martín-Merino E, Rodríguez LAG. Validation of ischemic cerebrovascular diagnoses in the health improvement network (THIN). *Pharmacoepidemiol Drug Saf* 2010;**19**:579–85. doi:10.1002/pds.1919
- 40 Gibbs RG, Newson R, Lawrenson R, *et al.* Diagnosis and initial management of stroke and transient ischemic attack across UK health regions from 1992 to 1996: experience of a national primary care database. *Stroke* 2001;**32**:1085–90. doi:10.1161/01.str.32.5.1085
- 41 Derby LE, Myers MW, Jick H. Use of dexfenfluramine, fenfluramine and phentermine and the risk of stroke. *Br J Clin Pharmacol* 1999;**47**:565–9. doi:10.1046/j.1365-2125.1999.00928.x
- 42 Gribbin J, Hubbard R, Smith C, *et al.* Incidence and mortality of falls amongst older people in primary care in the United Kingdom. *QJM* 2009;**102**:477–83. doi:10.1093/qjmed/hcp064
- 43 Ray WA. Evaluating Medication Effects Outside of Clinical Trials: New-User Designs. *Am J Epidemiol* 2003;**158**:915–20. doi:10.1093/aje/kwg231
- 44 Schneeweiss S, Patrick AR, Stürmer T, *et al.* Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. *Med Care* 2007;**45**:S131-142. doi:10.1097/MLR.0b013e318070c08e

- 45 Dore DD, Zullo AR, Mor V, *et al.* Age, Sex, and Dose Effects of Nonbenzodiazepine Hypnotics on Hip Fracture in Nursing Home Residents. *J Am Med Dir Assoc* 2018;**19**:328-332.e2. doi:10.1016/j.jamda.2017.09.015
- 46 Tamiya H, Yasunaga H, Matusi H, *et al.* Hypnotics and the Occurrence of Bone Fractures in Hospitalized Dementia Patients: A Matched Case-Control Study Using a National Inpatient Database. *PLoS ONE* 2015;**10**:e0129366. doi:10.1371/journal.pone.0129366
- 47 Berry SD, Lee Y, Cai S, *et al.* Nonbenzodiazepine sleep medication use and hip fractures in nursing home residents. *JAMA Intern Med* 2013;**173**:754–61. doi:10.1001/jamainternmed.2013.3795
- 48 Tolppanen A-M, Taipale H, Tanskanen A, *et al.* Comparison of predictors of hip fracture and mortality after hip fracture in community-dwellers with and without Alzheimer’s disease – exposure-matched cohort study. *BMC Geriatr* 2016;**16**:204. doi:10.1186/s12877-016-0383-2
- 49 Finkle WD, Der JS, Greenland S, *et al.* Risk of Fractures Requiring Hospitalization After an Initial Prescription for Zolpidem, Alprazolam, Lorazepam, or Diazepam in Older Adults. *J Am Geriatr Soc* 2011;**59**:1883–90. doi:10.1111/j.1532-5415.2011.03591.x
- 50 Brandt J, Leong C. Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. *Drugs RD* 2017;**17**:493–507. doi:10.1007/s40268-017-0207-7
- 51 Frey DJ, Ortega JD, Wiseman C, *et al.* Influence of Zolpidem and Sleep Inertia on Balance and Cognition During Nighttime Awakening: A Randomized Placebo-Controlled Trial. *J Am Geriatr Soc*; **59**:73–81. doi:10.1111/j.1532-5415.2010.03229.x
- 52 Allain H, Bentué-Ferrer D, Polard E, *et al.* Postural instability and consequent falls and hip fractures associated with use of hypnotics in the elderly: a comparative review. *Drugs Aging* 2005;**22**:749–65.
- 53 Diem SJ, Ewing SK, Stone KL, *et al.* Use of non-benzodiazepine sedative hypnotics and risk of falls in older men. *J Gerontol Geriatr Res* 2014;**3**:158. doi:10.4172/2167-7182.1000158
- 54 Yu N-W, Chen P-J, Tsai H-J, *et al.* Association of benzodiazepine and Z-drug use with the risk of hospitalisation for fall-related injuries among older people: a nationwide nested case–control study in Taiwan. *BMC Geriatr* 2017;**17**:140. doi:10.1186/s12877-017-0530-4
- 55 Sterke CS, van Beeck EF, van der Velde N, *et al.* New insights: dose-response relationship between psychotropic drugs and falls: a study in nursing home residents with dementia. *J Clin Pharmacol* 2012;**52**:947–55. doi:10.1177/0091270011405665
- 56 Taipale H, Koponen M, Tanskanen A, *et al.* Use of benzodiazepines and related drugs is associated with a risk of stroke among persons with Alzheimer’s disease. *Int Clin Psychopharmacol* 2017;**32**:135–41. doi:10.1097/YIC.000000000000161
- 57 Hermann DM, Bassetti CL. Role of sleep-disordered breathing and sleep-wake disturbances for stroke and stroke recovery. *Neurology* 2016;**87**:1407–16. doi:10.1212/WNL.0000000000003037
- 58 Joya FL, Kripke DF, Loving RT, *et al.* Meta-analyses of hypnotics and infections: eszopiclone, ramelteon, zaleplon, and zolpidem. *J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med* 2009;**5**:377–83.

- 59 Nakafero G, Sanders RD, Nguyen-Van-Tam JS, *et al.* The association between benzodiazepines and influenza-like illness-related pneumonia and mortality: a survival analysis using UK Primary Care data. *Pharmacoepidemiol Drug Saf* 2016;;n/a-n/a. doi:10.1002/pds.4028
- 60 Wang M-T, Wang Y-H, Chang H-A, *et al.* Benzodiazepine and Z-drug use and risk of pneumonia in patients with chronic kidney disease: A population-based nested case-control study. *PLOS ONE* 2017;**12**:e0179472. doi:10.1371/journal.pone.0179472
- 61 Taipale H, Tolppanen A-M, Koponen M, *et al.* Risk of pneumonia associated with incident benzodiazepine use among community-dwelling adults with Alzheimer disease. *CMAJ* 2017;**189**:E519–29. doi:10.1503/cmaj.160126
- 62 Saarelainen L, Tolppanen A-M, Koponen M, *et al.* Risk of death associated with new benzodiazepine use among persons with Alzheimer disease: A matched cohort study. *Int J Geriatr Psychiatry* 2018;**33**:583–90. doi:10.1002/gps.4821
- 63 Neutel CI, Johansen HL. Association between hypnotics use and increased mortality: causation or confounding? *Eur J Clin Pharmacol* 2015;**71**:637–42. doi:10.1007/s00228-015-1841-z
- 64 Walley T, Scott AK. Prescribing in the elderly. *Postgrad Med J* 1995;**71**:466–71.
- 65 Milton JC, Hill-Smith I, Jackson SHD. Prescribing for older people. *BMJ* 2008;**336**:606–9. doi:10.1136/bmj.39503.424653.80
- 66 By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc* 2019;**67**:674–94. doi:10.1111/jgs.15767
- 67 Brown EE, Kumar S, Rajji TK, *et al.* Anticipating and Mitigating the Impact of the COVID-19 Pandemic on Alzheimer’s Disease and Related Dementias. *Am J Geriatr Psychiatry* Published Online First: 18 April 2020. doi:10.1016/j.jagp.2020.04.010

Table 1. Characteristics of patients with dementia prescribed Z-drugs and benzodiazepines and comparison cohorts

Characteristic	Z-drug (n=3532)		Sleep disturbance, no sedative- hypnotic (n=1833)		No Z-drug, proximal GP consultation (n=10214)		Benzodiazepine (n=5172)		No benzodiazepine, proximal GP consultation (n=15174)	
	n	%	n	%	n	%	n	%	n	%
Women	2087	59%	1145	62%	6074	59%	3222	62%	9491	63%
Age, years ^a	82.9	7.7	83.1	7.1	83.1	7.5	82.5	7.8	82.6	7.8
White ethnicity ^b	3072	87%	1539	84%	8816	86%	4470	86%	13042	86%
Care home ^b	892	25%	434	24%	2108	21%	1509	29%	2979	20%
Lives alone ^b	760	22%	545	30%	2848	28%	993	19%	4785	32%
GP practice area IMD quintile ^a	3.2	1.4	3.4	1.4	3.1	1.4	3.2	1.4	3.1	1.4
Current smoker ^b	312	9%	142	8%	722	7%	355	7%	1124	7%
Ex-smoker ^b	765	22%	428	23%	2226	22%	1163	22%	3322	22%
Alcohol drinker ^b	715	20%	489	27%	2142	21%	1127	22%	3297	22%
Body mass index ^{ab}	24.9	4.9	24.5	4.6	24.9	4.8	24.5	4.8	24.8	4.9
Systolic blood pressure ^{ab}	133.5	19.0	133.9	18.8	134.3	19.1	133.6	18.9	134.5	18.8
Dementia										
Months since dementia diagnosis ^c	11.4	3.6-26.2	11.0	3.8-24.1	13.5	5.2-27.4	15.6	5.1-32.4	10.3	3.7-22.0
Dementia subtype										
Alzheimer's disease	1355	38%	746	41%	4224	41%	2140	41%	6612	44%
Vascular dementia	940	27%	487	27%	2773	27%	1375	27%	4046	27%
Other/mixed dementia	409	12%	192	10%	1013	10%	600	12%	1377	9%
Unspecified dementia	828	23%	403	22%	2184	21%	1057	20%	3139	21%
Agitation/psychosis history	619	18%	409	22%	1261	12%	1363	26%	1341	9%
End of life care	197	6%	77	4%	564	6%	416	8%	726	5%
Sleep disturbance										
Sleep disturbance pre dementia	825	23%	615	34%	1982	19%	1064	21%	2918	19%
History of benzodiazepine use	869	25%	222	12%	1376	13%	982	19%	2009	13%
History of Z-drug use	304	9%	113	6%	597	6%	481	9%	852	6%
Medical history in past year										
Falls	1003	28%	542	30%	2165	21%	1241	24%	3359	22%
Fractures	360	10%	131	7%	657	6%	409	8%	1071	7%
Dizziness/unsteadiness	214	6%	127	7%	652	6%	294	6%	817	5%
Faints/syncope	184	5%	120	7%	533	5%	357	7%	712	5%
Urinary tract infection/acute LRTI	928	26%	423	23%	2054	20%	1242	24%	3114	21%
Influenza vaccination	2480	70%	1340	73%	7747	76%	3739	72%	11350	75%
Pneumonia vaccination	166	5%	103	6%	506	5%	234	5%	773	5%
Physician consultations ^a	12.5	10.3	11.2	9.4	14.9	12.7	12.9	10.7	13.7	12.0
Hospital admissions ^a	1.3	3.0	1.0	2.2	0.9	1.6	1.1	1.9	0.9	2.3
Comorbidities										
Depression	894	25%	493	27%	2633	26%	1,512	29%	3,723	25%
Depression symptoms	692	20%	368	20%	1898	19%	1,175	23%	2,804	18%
Anxiety	576	16%	311	17%	1648	16%	1,204	23%	2,451	16%
Anxiety symptoms	446	13%	261	14%	1181	12%	877	17%	1,751	12%
Parkinson's disease	208	6%	109	6%	530	5%	290	6%	723	5%
Urinary incontinence	520	15%	465	25%	1640	16%	841	16%	2,273	15%

Benign prostatic hyperplasia	361	10%	175	10%	1075	11%	487	9%	1,474	10%
Asthma	366	10%	165	9%	1056	10%	517	10%	1,590	10%
Cancer	743	21%	313	17%	2114	21%	1,002	19%	3,074	20%
COPD	266	8%	147	8%	782	8%	369	7%	1,209	8%
Osteoporosis	417	12%	215	12%	1224	12%	581	11%	1,885	12%
Other musculoskeletal conditions	448	13%	248	14%	1395	14%	664	13%	2,036	13%
Osteoarthritis/Rheumatoid Arthritis	1426	40%	756	41%	3980	39%	2,063	40%	5,906	39%
Other joint conditions	2901	82%	1,537	84%	8463	83%	4,293	83%	12,615	83%
Headache/migraine	720	20%	363	20%	2020	20%	1,101	21%	2,955	19%
Back/neck pain	1959	55%	1,009	55%	5640	55%	2,910	56%	8,380	55%
Age-related macular degeneration	189	5%	115	6%	648	6%	348	7%	923	6%
Cataract	992	28%	547	30%	2940	29%	1,400	27%	4,284	28%
Glaucoma	356	10%	186	10%	1011	10%	445	9%	1,459	10%
Retinal disorder	295	8%	138	8%	944	9%	415	8%	1,390	9%
Diabetes	531	15%	245	13%	1712	17%	718	14%	2,483	16%
Hyperlipidaemia	470	13%	269	15%	1443	14%	754	15%	2,152	14%
Hypertension	1822	52%	1,006	55%	5736	56%	2,762	53%	8,521	56%
Stroke/transient ischemic attack	783	22%	397	22%	2177	21%	1,091	21%	3,022	20%
Myocardial infarction	310	9%	172	9%	909	9%	433	8%	1,307	9%
Heart failure	314	9%	182	10%	988	10%	444	9%	1,350	9%
Atrial fibrillation	528	15%	260	14%	1666	16%	775	15%	2,365	16%
Angina	532	15%	308	17%	1646	16%	811	16%	2,263	15%
Venous thromboembolism	236	7%	123	7%	737	7%	341	7%	1,029	7%
Prescriptions in last 90 days										
Anticholinesterase/memantine	850	24%	385	21%	2417	24%	1237	24%	3662	24%
Antipsychotic	811	23%	371	20%	1586	16%	1125	22%	851	6%
SSRI antidepressant	763	22%	352	19%	1855	18%	1174	23%	2616	17%
Tricyclic antidepressant	363	10%	192	10%	835	8%	596	12%		
Other antidepressant	294	8%	153	8%	575	6%	483	9%	771	5%
Antiepileptic	241	7%	110	6%	610	6%	424	8%	825	5%
Analgesic	1730	49%	808	44%	4107	40%	2338	45%	5805	38%
Inhaled corticosteroid	191	5%	96	5%	507	5%	196	4%	742	5%
Lipid regulating medication	1217	34%	630	34%	3492	34%	1644	32%	5324	35%
Diuretic	1188	34%	633	35%	3322	33%	1456	28%	4779	31%
Beta blocker	645	18%	328	18%	1907	19%	850	16%	2771	18%
ACE inhibitor	709	20%	379	21%	2222	22%	991	19%	3357	22%
Angiotensin II receptor antagonist	235	7%	124	7%	724	7%	330	6%	1123	7%
Calcium channel blocker	643	18%	339	18%	1947	19%	849	16%	2980	20%
Anticoagulant	204	6%	103	6%	739	7%	295	6%	1056	7%
Antiplatelet	1603	45%	878	48%	4390	43%	2171	42%	6439	42%
Cardiac glycoside	281	8%	155	8%	768	8%	345	7%	1032	7%
NSAID	352	10%	156	9%	815	8%	468	9%	1206	8%
Bisphosphonate	375	11%	194	11%	1074	11%	477	9%	1618	11%
Calcium/Vitamin D	677	19%	377	21%	1854	18%	888	17%	2754	18%
Antibiotic (in last 30 days)	1098	31%	567	31%	2590	25%	1370	26%	3640	24%

Abbreviations: ACE, Angiotensin-converting enzyme; COPD, Chronic Obstructive Pulmonary Disease; IMD, Index of Multiple Deprivation; GP, general practitioner; LRTI, Lower respiratory tract infection; NSAID, Nonsteroidal anti-inflammatory drug; SSRI, Selective serotonin reuptake inhibitor

a mean (standard deviation)

b Characteristic contains missing data as described in Additional file 5 table S2.

c median (inter-quartile range)

Table 2. Adjusted hazard ratios for new Z-drug prescription and adverse events for people with dementia

Outcome	Z-drug (n=3532)	Comparator		
		Sleep disturbance, no sedative-hypnotic (n=1833)	No Z-drug, proximal GP consultation (n=10214)	Benzodiazepine (n=5172)
Fracture				
Incidence rate per 100PY (events)	11.4 (164)	7.6 (130)	8.4 (269)	12.5 (223)
Age, sex adjusted HR (95% CI)	NA	1.39 (1.08-1.78)	1.40 (1.14-1.70)	0.93 (0.76-1.14)
Fully adjusted HR (95% CI) ^a	NA	1.32 (0.99-1.75)	1.34 (1.08-1.67) ^b	0.99 (0.80-1.23)
Hip fracture				
Incidence rate per 100PY (events)	5.7 (84)	3.4 (60)	3.5 (115)	5.1 (94)
Age, sex adjusted HR (95% CI)	NA	1.53 (1.07-2.18)	1.64 (1.23-2.19)	1.11 (0.82-1.49)
Fully adjusted HR (95% CI) ^a	NA	1.38 (0.92-2.06)	1.59 (1.15-2.19) ^b	1.10 (0.87-1.65)
Forearm/wrist/hand fracture				
Incidence rate per 100PY (events)	2.0 (29)	1.1 (20)	1.5 (48)	2.5 (46)
Age, sex adjusted HR (95% CI)	NA	1.80 (0.95-3.41)	1.35 (0.85-2.14)	0.81 (0.51-1.28)
Fully adjusted HR (95% CI) ^a	NA	1.44 (0.60-3.47)	1.33 (0.77-2.31)	1.00 (0.59-1.70)
Fall				
Incidence rate per 100PY (events)	37.1 (473)	27.3 (384)	25.8 (767)	35.8 (585)
Age, sex adjusted HR (95% CI)	NA	1.12 (0.97-1.29)	1.52 (1.36-1.71)	1.06 (0.94-1.20)
Fully adjusted HR (95% CI) ^a	NA	1.02 (0.87-1.21)	1.43 (1.26-1.62) ^b	1.08 (0.95-1.22)
Mortality				
Incidence rate per 100PY (events)	28.4 (436)	16.7 (301)	24.1 (799)	39.0 (736)
Age, sex adjusted HR (95% CI)	NA	1.51 (1.29-1.77)	1.20 (1.06-1.34)	0.72 (0.64-0.81)
Fully adjusted HR (95% CI) ^a	NA	1.38 (1.14-1.66) ^b	1.08 (0.94-1.23)	0.73 (0.64-0.83) ^b
Acute bacterial infection				
Incidence rate per 100PY (events)	47.8 (416)	43.6 (220)	40.6 (1325)	57.8 (371)
Age, sex adjusted HR (95% CI)	NA	1.13 (0.94-1.37)	1.24 (1.09-1.42)	1.01 (0.86-1.18)
Fully adjusted HR (95% CI) ^a	NA	1.02 (0.82-1.27)	1.13 (0.98-1.31)	0.92 (0.78-1.10)
Ischemic stroke/ transient ischemic attack				
Incidence rate per 100PY (events)	6.2 (93)	4.4 (77)	5.5 (178)	6.0 (110)
Age, sex adjusted HR (95% CI)	NA	1.32 (0.95-1.83)	1.20 (0.94-1.54)	1.03 (0.78-1.36)
Fully adjusted HR (95% CI) ^a	NA	1.35 (0.90-2.04)	1.14 (0.86-1.50)	1.05 (0.78-1.43)
Venous thromboembolism				
Incidence rate per 100PY (events)	1.5 (22)	1.3 (21)	1.4 (43)	2.5 (47)
Age, sex adjusted HR (95% CI)	NA	1.64 (0.97-2.79)	1.14 (0.74-1.76)	0.79 (0.50-1.25)
Fully adjusted HR (95% CI) ^a	NA	1.65 (0.74-3.69) ^c	1.12 (0.67-1.85)	0.82 (0.50-1.34)

Abbreviations: HR, hazard ratio; CI, confidence interval; GP, general practitioner; PY, person-years.

a Adjusted for all covariates listed in Table 1.

b Fully-adjusted HR remaining statistically significant after controlling the false discovery rate to <5% (based on 13 outcomes)

c not adjusted for antiepileptics, antiplatelet drugs, pneumonia vaccine and anxiety symptoms due to model instability

Table 3. Adjusted hazard ratios for Z-drug prescription and adverse events for people with dementia according to prescribed Daily Defined Dose of Z-drugs

Outcome and Daily Defined Dose prescribed ^a	No. events in Z-drug cohort	Sleep disturbance and no sedative-hypnotic (n=1833)		No Z-drug, proximal GP consultation (n=10214)	
		Age, sex adjusted	Fully adjusted ^b	Age, sex adjusted	Fully adjusted ^b
Fracture					
≤0.5	117	1.30 (0.99-1.70)	1.22 (0.90-1.66)	1.33 (1.07-1.65)	1.28 (1.01-1.63)
0.6-0.9	5	1.28 (0.51-3.20)	1.06 (0.39-2.89)	1.24 (0.50-3.05)	1.08 (0.42-2.76)
≥1	42	1.70 (1.19-2.42)	1.67 (1.13-2.46) ^c	1.66 (1.18-2.34)	1.58 (1.09-2.28) ^c
Hip fracture					
≤0.5	55	1.30 (0.88-1.93)	1.21 (0.78-1.90)	1.42 (1.03-1.97)	1.43 (1.00-2.06)
0.6-0.9	<5	1.10 (0.26-4.67)	0.79 (0.15-4.11)	1.27 (0.31-5.22)	1.05 (0.24-4.64)
≥1	27	2.30 (1.45-3.65)	1.96 (1.16-3.31) ^c	2.50 (1.61-3.89)	2.36 (1.44-3.87) ^c
Forearm fracture					
≤0.5	20	1.66 (0.81-3.40)	1.22 (0.48-3.12)	1.28 (0.77-2.15)	1.29 (0.73-2.27)
≥0.6	9	2.18 (0.98-4.85)	1.91 (0.67-5.47)	1.53 (0.72-3.24)	1.42 (0.59-3.38)
Fall					
≤0.5	335	1.05 (0.90-1.22)	0.95 (0.80-1.13)	1.43 (1.26-1.63)	1.35 (1.17-1.56) ^c
0.6-0.9	14	0.84 (0.49-1.44)	0.73 (0.41-1.29)	1.19 (0.70-2.02)	1.07 (0.61-1.87)
≥1	124	1.42 (1.15-1.74)	1.33 (1.06-1.66) ^c	1.92 (1.58-2.35)	1.81 (1.46-2.34) ^c
Mortality					
≤0.5	321	1.49 (1.26-1.77)	1.38 (1.14-1.68) ^c	1.18 (1.03-1.34)	1.07 (0.93-1.24)
0.6-0.9	16	1.56 (0.95-2.56)	1.60 (0.96-2.70)	1.25 (0.77-2.02)	1.22 (0.75-1.99)
≥1	99	1.56 (1.24-1.96)	1.33 (1.03-1.71)	1.26 (1.02-1.55)	1.06 (0.85-1.33)
Acute bacterial infection					
≤0.5	297	1.15 (0.98-1.36)	1.00 (0.83-1.20)	1.37 (1.20-1.57)	1.23 (1.06-1.43) ^c
0.6-0.9	13	0.98 (0.56-1.72)	0.86 (0.47-1.57)	1.20 (0.69-2.08)	1.12 (0.63-1.99)
≥1	106	1.40 (1.12-1.76)	1.25 (0.98-1.60)	1.64 (1.32-2.04)	1.52 (1.21-1.91) ^c
Ischemic stroke/transient ischemic attack					
≤0.5	55	1.04 (0.72-1.51)	1.12 (0.71-1.75)	0.96 (0.71-1.30)	0.95 (0.68-1.31)
0.6-0.9	5	1.97 (0.78-4.96)	1.98 (0.74-5.28)	1.74 (0.72-4.19)	1.71 (0.74-3.98)
≥1	33	2.07 (1.36-3.15)	1.88 (1.14-3.10) ^c	1.90 (1.30-2.79)	1.61 (1.08-2.42)
Venous thromboembolism					
≤0.5	26	2.01 (1.16-3.49)	2.00 (0.90-4.47)	1.35 (0.85-2.13)	1.26 (0.74-2.12)
≥0.6	<5	0.78 (0.27-2.25)	0.85 (0.21-3.39)	0.56 (0.21-1.54)	0.66 (0.22-1.95)

Abbreviations: HR, hazard ratio; CI, confidence interval; GP, general practitioner

a The reference group for all comparisons is no Z-drug prescription. Most patients assigned to the '0.6-0.9 DDD' Z-drug group were prescribed 3.75mg zopiclone with instructions similar to "TAKE ONE OR TWO AT NIGHT".

b Adjusted for all covariates listed in table 1.

c Fully-adjusted HR remaining statistically significant after controlling the false discovery rate to <5% (based on 37 tests; 11 outcomes with three dose categories and two outcomes with two dose categories)

Table 4. Adjusted hazard and rate ratios for new Z-drug prescription and new prescriptions, GP consultations and hospital admissions for people with dementia

Outcome	Z-drug (n=3,532)	Comparator		
		Sleep disturbance, no sedative-hypnotic (n=1833)	No Z-drug, proximal GP consultation (n=10214)	Benzodiazepine (n=5172)
Number of hospital admissions				
Rate per 100PY (events)	126.7 (1944)	93.0 (1671)	107.7 (3563)	129.4 (2441)
Age, sex adjusted RR (95% CI)	NA	1.34 (1.20-1.49)	1.26 (1.15-1.39)	0.98 (0.89-1.09)
Fully adjusted RR (95% CI) ^a	NA	1.26 (1.13-1.40) ^b	1.17 (1.07-1.27) ^b	0.92 (0.84-1.01)
Number of GP consultations				
Rate per 100PY (events)	1387.8 (21292)	1124.6 (20209)	1511.7 (50021)	1502.6 (28335)
Age, sex adjusted RR (95% CI)	NA	1.29 (1.22-1.37)	0.97 (0.93-1.01)	0.94 (0.90-0.98)
Fully adjusted RR (95% CI) ^a	NA	1.17 (1.12-1.23) ^b	1.07 (1.04-1.11) ^b	0.96 (0.93-1.00)
New antipsychotic prescription				
Incidence rate per 100PY (events)	38.7 (331)	10.3 (130)	15.2 (227)	75.4 (532)
Age, sex adjusted HR (95% CI)	NA	2.53 (2.03-3.14)	3.68 (3.10-4.37)	0.79 (0.68-0.90)
Fully adjusted HR (95% CI) ^a	NA	2.37 (1.84-3.04) ^b	3.85 (3.18-4.65) ^b	0.86 (0.74-0.99)
New antidepressant prescription				
Incidence rate per 100PY (events)	23.8 (172)	8.2 (82)	10.3 (199)	30.3 (242)
Age, sex adjusted HR (95% CI)	NA	2.24 (1.70-2.94)	2.52 (2.05-3.10)	0.86 (0.71-1.05)
Fully adjusted HR (95% CI) ^a	NA	2.32 (1.65-3.25) ^b	2.65 (2.09-3.37) ^b	0.88 (0.71-1.10)
New antibiotic prescription				
Incidence rate per 100PY (events)	109.1 (791)	61.2 (517)	89.5 (1738)	111.0 (1096)
Age, sex adjusted HR (95% CI)	NA	1.46 (1.30-1.65)	1.27 (1.17-1.38)	1.01 (0.92-1.10)
Fully adjusted HR (95% CI) ^a	NA	1.34 (1.17-1.52) ^b	1.19 (1.08-1.30) ^b	1.05 (0.95-1.15)

Abbreviations: HR, hazard ratio; CI, confidence interval; PY, person-years; RR, rate ratio.

a Adjusted for all covariates listed in table 1.

b Fully-adjusted HR remaining statistically significant after controlling the false discovery rate to <5% (based on 13 outcomes)

Table 5. Adjusted hazard ratios for Z-drug prescription and new prescriptions, GP consultations and hospital admissions for people with dementia according to prescribed Daily Defined Doses (DDD) of Z-drugs

Outcome and daily defined dose prescribed ^a	No. events in Z-drug cohort	No sedative-hypnotic, sleep disturbance (n=1833)		No Z-drug, proximal GP consultation (n=10214)	
		Age, sex adjusted	Fully adjusted ^b	Age, sex adjusted	Fully adjusted ^b
Number of hospital admissions ^c					
≤0.5	1403	1.24 (1.10-1.39)	1.18 (1.05-1.32)	1.19 (1.07-1.31)	1.10 (1.00-1.20)
0.6-0.9	63	1.06 (0.76-1.49)	1.22 (0.88-1.69)	1.03 (0.74-1.43)	1.10 (0.80-1.51)
≥1	472	1.35 (1.15-1.58)	1.29 (1.10-1.50) ^d	1.32 (1.15-1.52)	1.22 (1.06-1.39) ^d
Number of GP consultations ^c					
≤0.5	9230	1.21 (1.14-1.29)	1.10 (1.05-1.16) ^d	0.89 (0.85-0.94)	1.00 (0.96-1.04)
0.6-0.9	690	1.12 (0.96-1.32)	1.10 (0.95-1.26)	0.83 (0.71-0.97)	1.02 (0.88-1.17)
≥1	4823	1.23 (1.12-1.34)	1.16 (1.08-1.25) ^d	0.91 (0.84-0.98)	1.06 (0.99-1.13)
Incident antipsychotic prescription					
≤0.5	214	2.08 (1.64-2.62)	2.00 (1.54-2.61) ^d	3.09 (2.56-3.74)	3.31 (2.69-4.07) ^d
0.6-0.9	18	3.35 (2.04-5.50)	2.75 (1.57-4.81) ^d	5.15 (3.19-8.32)	4.82 (2.81-8.25) ^d
≥1	99	4.05 (3.10-5.31)	3.56 (2.61-4.85) ^d	5.81 (4.55-7.42)	5.82 (4.44-7.63) ^d
Incident antidepressant prescription					
≤0.5	124	1.25 (1.14-1.37)	1.16 (1.05-1.28) ^d	2.47 (1.91-3.19)	2.39 (1.90-2.99) ^d
0.6-0.9	8	1.20 (0.83-1.73)	1.13 (0.76-1.68)	2.67 (1.19-5.99)	3.00 (1.49-6.01)
≥1	40	1.37 (1.17-1.61)	1.31 (1.11-1.54) ^d	3.47 (2.32-5.18)	2.93 (2.04-4.19) ^d
Incident antibiotic prescription					
≤0.5	583	1.43 (1.27-1.63)	1.30 (1.13-1.49) ^d	1.25 (1.14-1.37)	1.16 (1.05-1.28) ^d
0.6-0.9	27	1.36 (0.93-2.00)	1.20 (0.79-1.81)	1.20 (0.83-1.73)	1.13 (0.76-1.68)
≥1	181	1.57 (1.32-1.88)	1.46 (1.21-1.76) ^d	1.37 (1.17-1.61)	1.31 (1.11-1.54) ^d

Abbreviations: HR, hazard ratio; CI, confidence interval; GP, general practitioner.

^a The reference group for all comparisons is no Z-drug prescription. Most patients assigned to the ‘0.6-0.9 DDD’ Z-drug group were prescribed 3.75mg zopiclone with instructions similar to “TAKE ONE OR TWO AT NIGHT”.

^b Adjusted for all covariates listed in table 1.

c Estimates provided are Rate Ratios (95% confidence intervals)

d Fully-adjusted HR remaining statistically significant after controlling the false discovery rate to <5% (based on 37 tests; 11 outcomes with three dose categories and two outcomes with two dose categories)