Non-benzodiazepine hypnotic use for sleep disturbance in people aged over 55 years living with dementia: a series of cohort studies

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Scientific summary

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Background

Dementia is a debilitating disorder affecting memory and cognition. Many neuropsychiatric symptoms are also present, including issues with sleep. Sleep disturbance can encompass insomnia, fragmented sleep, night-time wandering and excessive daytime sleeping, and it affects around 60% of people living with dementia. Sleep is critical for body function, cognitive performance, mood and memory consolidation. This reduction in sleep can have a devastating impact on the quality of life of people living with dementia and their carers, and can hasten care home admission. Pharmacological intervention is commonly used to help initiate and maintain sleep, including the use of hypnotic Z-drugs (zolpidem, zopiclone and zaleplon). These drugs are similar to benzodiazepine hypnotics but were thought to have fewer of the associated side effects, including increased risk of falls, fractures, infections and death, particularly in the older population.

There is now emerging evidence that Z-drug use is also significantly associated with increased risk of falls, fractures, death, infections and cerebrovascular events. Although these drugs are widely prescribed to people living with dementia, there has been little evidence showing their harms and benefits in this population. People living with dementia are already at higher risk of falls and fractures, so understanding any additional harms of Z-drug use is important.

There have also not been studies to address whether or not these drugs are actually effective in people living with dementia (e.g. we do not know if their use improves cognition or quality of life). Improving sleep could be a critical intervention to increase quality of life and improve daily functioning of both patient and carer; however, the risks associated with hypnotic use must be understood to allow a balanced decision-making process when prescribing Z-drugs to people living with dementia.

Objectives

Primary care study

This study was designed to target people living with dementia suffering with sleep disturbance who were prescribed Z-drugs, to estimate the harms associated with first prescription of Z-drugs compared with alternative treatments and no treatment. We also performed a general practitioner validation study to investigate the validity of dementia and sleep disturbance coding in primary care data sets.

Clinical cohort studies

We also investigated what the potential benefits of concurrent use of these medications are, using patient-reported outcomes (including cognition and quality of life) and dementia-based clinical data sets (which were repurposed for analysis in this study).

Design

A series of observational cohort studies using existing data from (1) primary care, linked to hospital admission data and Office for National Statistics data and (2) three clinical cohort studies of people living with dementia.

Data sources

Primary care study

Clinical Practice Research Datalink from English practices, representing 7% of the population linked to Hospital Episode Statistics and Office for National Statistics mortality data.

Clinical cohort studies

1. Resource Use and Disease Course in Dementia – Nursing Homes (REDIC): a longitudinal study of patients admitted to a nursing home who were followed for 3 years and assessed every 6 months, based in Norway.
2. Improving Well-being and Health for People with Dementia (WHELD) in nursing homes: a randomised controlled trial that evaluated an intervention to improve the quality of life of people with dementia living in care homes, based in the UK.
3. National Alzheimer's Coordinating Centre (NACC) clinical data set: a clinical data set based in the USA.

Setting

Primary care study

A total of 371 primary care practices in England.

Clinical cohort studies

Forty-seven nursing homes in Norway, 69 care homes in England and 34 Alzheimer's disease centres in the USA.

Participants

Primary care study

NHS England primary care patients from January 2000 to March 2016, followed for up to 2 years.

Patients were included if they satisfied all the following criteria:

- Their general practice was in England.
- They were diagnosed with dementia, defined as the first of a code for dementia or prescription of a cognitive enhancer (memantine, donepezil, rivastigmine or galantamine), occurring after 1 January 2000.
- They were aged $\geq$ 55 years when diagnosed with dementia.
- There was evidence of a sleep disorder, defined as the first record of a Read code for sleep disorder diagnosis, symptom or referral, or prescription of a Z-drug, low-dose tricyclic antidepressant or melatonin, on or after the dementia diagnosis date and before 31 March 2016 (this first sleep disturbance date defined the 'index date').
- Their records contained at least 3 months of good-quality data before the dementia diagnosis and at least 12 months of data before the index date.

Patients were excluded if there was:

- uncertainty regarding the timing of dementia diagnosis
- a diagnosis of severe mental illness or Down syndrome prior to dementia diagnosis
- a diagnosis of sleep apnoea, sleep-related respiratory failure or alcohol abuse prior to the index date
- a diagnosis of neuropathic pain in the 12 months prior to the index date

- a prescription of sedatives, tricyclic antidepressants or benzodiazepines in the 12 months prior to the index date
- a prescription of multiple sleep medications on the index date
- a prescription of a new antipsychotic, other sedative or other tricyclic antidepressant on the index date
- no linkage possible between Clinical Practice Research Datalink and Hospital Episode Statistics data.

Clinical cohort studies

The REDIC study included people living with dementia or mild cognitive impairment admitted to a nursing home in Norway, with follow-up every 6 months for up to 3 years. The NACC data set included people living with dementia in the USA, followed up annually for up to 12 years. The WHELD trial included people living with dementia admitted to a nursing home in England, with follow-up at 9 months.

Exposures

The primary exposure was prescription or use of Z-drugs. Secondary exposures included prescription or use of benzodiazepines, low-dose tricyclic antidepressants and antipsychotics. Details were extracted for sleep medication prescribed during the follow-up period, including prescription date, dose and duration.

Main outcome measures

In the primary care study, the 16 outcomes assessed were incident (1) fracture in any location; (2) hip fracture; (3) forearm/wrist/hand fracture; (4) fall; (5) mortality; (6) acute bacterial infection; (7) urinary tract infection or acute lower respiratory tract infection; (8) ischaemic stroke/transient ischaemic attack; (9) venous thromboembolism; (10) agitation or psychosis; and additional use of (11) sedatives and other sleep medications; (12) antipsychotics; (13) antidepressants; (14) antibiotics; and health-care utilisation of the number of (15) general practitioner visits and (16) hospital admissions.

The clinical cohort studies examined outcomes of cognition, quality of life, neuropsychiatric symptoms and disability. Specifically, the REDIC study included cognitive outcomes (using the Mini-Mental State Examination, a short eight-item version of the Severe Impairment Battery and the Clinical Dementia Rating – Sum of Boxes); neuropsychiatric symptoms (sleep, anxiety, agitation measured using the Neuropsychiatric Inventory and as part of the Cornell Scale for Depression in Dementia); quality of life (using the Quality of Life in Late-Stage Dementia, using the EuroQol-5 Dimensions and the visual analogue scale); and disability (using the Lawton Physical Self-Maintenance Scale). The NACC data set measured outcomes of cognition (using the Clinical Dementia Rating – Sum of Boxes, Mini Mental State Examination, animal naming and the Trail Making Test delta trail time); neuropsychiatric outcomes (using the Neuropsychiatric Inventory sleep scores, anxiety, agitation and Neuropsychiatric Inventory excluding sleep); the Geriatric Depression Scale (as a proxy of quality of life); and disability (measured using 10 questions on the amount of help needed with each of 10 different activities). The WHELD trial measured neuropsychiatric outcomes (using the Neuropsychiatric Inventory excluding sleep and Neuropsychiatric Inventory sleep scores) and quality of life (using the Quality of Life in Late-Stage Dementia).

Analysis

In the primary care study, Cox proportional hazards regression was used to estimate the association between sleep medication prescription and binary outcomes adjusted for the potential confounders. Negative binomial regression was used to estimate the association between sleep medication and number of general practitioner visits and hospital admissions.

Using the REDIC and NACC data sets, we explored the dynamics and predictors of use of any of three hypnotics (Z-drugs, benzodiazepines or antipsychotics). We used several different analytical approaches to explore associations between use or change in use of hypnotics with changes in cognitive, neuropsychiatric characteristics and quality-of-life outcomes.

In the REDIC study and the NACC data set, linear regression models were used to estimate the association between pattern of hypnotic use and change in each outcome, adjusting for participant age, their baseline cognitive function and visit number. Clustered standard errors were estimated to account for multiple observations per patient. To control for time-varying covariates, inverse probability of treatment weights were also generated, using logistic regression models estimating the probability of treatment at each visit, conditional on previous treatment and previous values of all covariates. Following the method of marginal structural models, these models were used to generate weights reflecting the inverse probability of observed treatment at the current visit, and these weights were applied to simple linear regression models estimating the effect of current hypnotic use on change in outcome measures between waves.

In the WHELD trial, negative binomial regression was used to estimate the association between Z-drug use at baseline and the Quality of Life in Late-Stage Dementia, Neuropsychiatric Inventory excluding sleep and Neuropsychiatric Inventory sleep scores at baseline. Logistic regression was used to estimate the association between baseline Z-drug use and mortality by 9 months' follow-up. Linear regression was used to estimate the mean decline in the Quality of Life in Late-Stage Dementia, Neuropsychiatric Inventory excluding sleep and Neuropsychiatric Inventory sleep scores from baseline to 9 months' follow-up.

Results

A total of 6809 patients were included in the primary care study and 3089 were prescribed Z-drugs. New use of Z-drugs was associated with a greater risk of fractures (hazard ratio 1.40, 95% confidence interval 1.01 to 1.94), with risk increasing with greater cumulative dose ($p = 0.002$). For 42 prescribed defined daily doses onwards, the hazard ratio for a fracture increased to 1.70 (95% confidence interval 1.17 to 2.48). We found evidence of Z-drug use associated with an increased risk of hip fracture (hazard ratio 1.59, 95% confidence interval 1.00 to 2.53) and this rose to a hazard ratio of 2.24 (95% confidence interval 1.29 to 3.91) when cumulatively prescribed ≥ 42 defined daily doses. We also found evidence of Z-drug use associated with mortality (hazard ratio 1.34, 95% confidence interval 1.10 to 1.64), but this association was similar regardless of cumulative exposure to Z-drugs. We also found that people living with dementia who were prescribed Z-drugs were more likely to be initiated on antipsychotics and antidepressants and have more general practitioner and hospital visits. There was no excess risks of falls (hazard ratio 1.05, 95% confidence interval 0.87 to 1.25), acute bacterial infections (hazard ratio 1.09, 95% confidence interval 0.92 to 1.29), ischaemic stroke/transient ischaemic attack (hazard ratio 1.33, 95% confidence interval 0.85 to 2.07), or venous thromboembolism (hazard ratio 1.66, 95% confidence interval 0.69 to 3.98) detected.

In the general practitioner validation study, we found good validity of dementia diagnoses, with 96% of selected patients confirmed to have dementia by their general practitioner. However, we found less validity for sleep disturbance, as only 63% of patients had sleep disturbance confirmed.

In 678 people living with dementia or mild cognitive impairment in the REDIC study, we found that those with better cognitive function were more likely to start using Z-drugs, whereas those with worse cognitive function were more likely to start antipsychotics. Neuropsychiatric symptoms (sleep disturbance, agitation and anxiety) predicted the new use of hypnotics, but there was no evidence that the use of hypnotics causes any significant change in any of the measures that we examined.

In the 17,055 people living with dementia in the NACC data set, we did not observe any significant additional cognitive impairment associated with the use or initiation of Z-drugs, whereas we observed cognitive decline among those taking benzodiazepines or antipsychotics, and those with more severe cognitive function were more likely to be initiated on these drugs. With respect to neuropsychiatric symptoms, there was a significant association between symptom levels and subsequently starting an associated medication, and between starting medications and a concurrent increase in symptoms. As with the REDIC study, there also appears to be no wider impact of hypnotics on quality of life (here as measured by the Geriatric Depression Scale, capturing a patient's own assessment of their mood).

In 926 people living with dementia in the WHELD trial, we observed greater neuropsychiatric symptoms in those taking Z-drugs at baseline (rate ratio 1.24, 95% confidence interval 1.00 to 1.54), but Z-drug use at baseline was not associated with greater improvement in neuropsychiatric symptoms over the following 9 months (mean additional improvement of 0.60 points, 95% confidence interval –3.26 to 4.46 points). We also observed no greater mortality risk in those taking Z-drugs (odds ratio 0.66, 95% confidence interval 0.38 to 1.15).

Limitations

Residual confounding may be possible in the primary care study because of difficulties identifying patients with sleep disturbance and by dementia severity. The limited numbers of people living with dementia taking Z-drugs and not recording medication use and the outcomes continuously restricted analyses in the clinical cohort studies.

Conclusions

Sleep is critical for the health and well-being of an individual; however, in people living with dementia, sleep disturbance is common and often treated with hypnotic medications. To the best of our knowledge, the clinical effectiveness and safety of these drugs have not been assessed in people living with dementia. Using primary care patient data, we observed a dose-dependent increase in fracture and hip fracture risk with Z-drug use in dementia; however, multiple outcomes were examined, increasing the risk of false-positive findings. We also found an association between Z-drug use and mortality, but findings suggest that this is not a causal association. There was also an increase in other prescriptions and higher health-care utilisation in those taking a Z-drug. However, there were no increased risks detected for falls, infections or cerebrovascular events in people living with dementia with sleep disturbance. Further research is needed to confirm the associations observed with Z-drugs and fracture risk, in order to establish whether or not these risks need consideration when prescribing Z-drugs, when balancing the impact of improved sleep of the patient and the carer.

Our clinical studies found no evidence for improved quality of life or cognition with Z-drug use in people living with dementia, but the studies were of insufficient power to address this. Our findings suggest that further research is needed into non-pharmacological alternatives for sleep disturbance in dementia, and into whether or not the prescription of Z-drugs concurrently needs inclusion of risk management strategies to minimise potential fracture risks and adverse health outcomes.

Study registration

This study is registered as European Union electronic Register of Post-Authorisation Studies (EU PAS) 18006.

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