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Original Study

Central Nervous System-Acting Medicines and Risk of Hospital Admission for Confusion, Delirium, or Dementia

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A B S T R A C T

Background: Most studies assessing the effect of central nervous system (CNS)-acting medicines on cognitive disturbances have focused on the use of individual medicines. The impact on cognitive function when another CNS-acting medicine is added to a patient's treatment regimen is not well known.
Objective: To determine risk of hospitalization for confusion, delirium, or dementia in older people associated with increasing numbers of CNS-acting medicines taken concurrently, as well as the number of standard doses taken each day (measured as defined daily doses).
Design: Retrospective cohort study, from July 2011 to June 2012, using health claims data.
Setting: Australian veteran population.
Participants: A total of 74,321 community-dwelling individuals aged 65 years and over, who were dispensed at least 1 CNS-acting medicine in the year before study entry. Patients with prior hospitalization for confusion or delirium, and those with dementia or receiving palliative care, were excluded.
Main outcome measure: Hospitalization for confusion, delirium, or dementia.
Results: Over the 1-year study period, 401 participants were hospitalized with confusion, delirium, or dementia. Adjusted analyses showed the risk of hospitalization was 2.4 times greater with the use of 2 CNS-acting medicines compared with no use [incident rate ratio (IRR) 2.39, 95% confidence interval (CI) 1.79–3.19, $P < .001$], and more than 19 times greater when 5 or more CNS-acting medicines were taken concurrently (IRR 19.35, 95% CI 11.10–33.72, $P < .001$). Similarly, the risk of hospitalization was significantly increased among patients taking between 1.0 and 1.9 standard doses per day (IRR 2.64, 95% CI 1.99–3.50, $P < .001$) and between 2.0 and 2.9 standard doses per day (IRR 3.43, 95% CI 2.07–5.69, $P < .001$) compared with no use.
Conclusions: Use of multiple CNS-acting medicines or higher doses is associated with an increased risk of hospitalization for confusion, delirium, or dementia. Health care professionals need to be alert to the contribution of CNS-acting medicines among patients presenting with confusion or delirium and consider strategies to reduce treatment burden where possible.

Medicines acting on the central nervous system (CNS) are commonly used by older patients. A previous systematic review reported that 12% to 43% of older, community-dwelling adults take at least 1 psychotropic medicine[1] and prevalence of use is even greater among residents of long-term care facilities.[2,3] Treatment with multiple CNS-acting medicines is also common, with several studies reporting that 30–50% of older patients using a psychotropic medicine take at least 2 concurrently.[4–7] Long-term treatment with certain CNS-acting medicines may be clinically necessary, however, evidence suggests that benzodiazepines and opioids may be overused or used inappropriately among the older population.[8,9]

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While it is well known that CNS-acting medicines are associated with cognitive disturbances, including confusion, drowsiness, dizziness, impaired memory, and dementia[10–12]; most studies have focused on the use of individual medicines. The impact on cognitive function when another CNS-acting medicine is added to a patient's treatment regimen is not well known. One study, which was conducted using administrative health data for 32,649 patients with dementia and 32,649 matched controls from Taiwan, found that the odds of dementia was more than 6 times higher in older patients using a benzodiazepine in combination with another psychotropic medicine [adjusted odds ratio (OR) 6.48, 95% confidence interval (CI) 5.90–7.12] compared with no use of CNS-acting medicines, and was higher than in patients using benzodiazepines alone (adjusted OR 2.28, 95% CI 2.00–2.59).[13] Another study, which involved 2737 older Americans, found that long-term use and higher doses of CNS-acting medicines were associated with cognitive decline (ie, a 5-point or greater reduction in modified mini mental state examination scores)[14]; however, the relationship between the number of CNS-acting medicines used and cognitive decline was not assessed, and it is unclear whether patients in this study were still taking CNS-acting medicines when the cognitive decline occurred. Another study which involved 565 older Finns found an association between the use of an opioid analgesic and another CNS-acting medicine at baseline and cognitive decline at 8-year follow-up[15]; however, results of this study are unlikely to be generalizable because only 3 patients were taking an opioid at both baseline and follow-up.

Multiple sedative use has also been associated with an increased risk of delirium among hospital inpatients,[16] however, no studies have explored the risk of hospitalization for confusion or delirium among community-dwelling patients taking multiple CNS-acting medicines. A previous study conducted within the Australian veteran population reported that 60% of older patients hospitalized with confusion were dispensed at least 3 unique psychotropic medicines in the 3 months before admission.[17] The aim of the present study was to determine the effect of the total number of CNS-acting medicines taken and total number of daily doses on the risk of hospitalization for confusion, delirium, or dementia in older people.

Methods

Study Design and Data Source

We conducted a retrospective cohort study using administrative claims data from the Australian Government Department of Veterans' Affairs (DVA). This data set includes details of all prescription medicines, hospitalizations and primary care services which have been subsidized by DVA for eligible veterans and their dependents. Medicines are coded in the dataset according to the World Health Organization (WHO) Anatomical and Therapeutic Chemical (ATC) classification,[18] and hospital admissions are coded according to the WHO International Classification of Diseases, 10th Edition, Australian Modification (ICD-10-AM).[19] The data set includes patient demographics such as date of birth, gender, and date of death.

Study Population

The study period was July 1, 2012 to June 30, 2013. People were included in the study if they were aged 65 years or over at the start of the study period, if they were eligible to receive all DVA funded health services prior to study entry, and if they had been dispensed at least 1 CNS-acting medicine in the year prior to study entry. We included this last requirement to ensure that all study participants had been recently exposed to CNS-acting medicines, so that any bias that may result from differences in patient characteristics between those exposed and unexposed to CNS-acting medicines was minimized. CNS-acting medicines were defined as opioid analgesics (identified by ATC code N02A), antimigraine preparations (N02C), anti-epileptics (N03), medicines for Parkinson disease (N04), antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), and antidepressants (N06A). We excluded people with a previous hospitalization for confusion, delirium, or dementia (identified by the ICD-10-AM codes listed in Supplementary Table 1), people with at least 1 prescription dispensed for a dementia medicine in the year prior to study entry (donepezil, galantamine, rivastigmine, or memantine; ATC code N06D), people living in a long-term care facility at study entry, and people receiving palliative care in the 6 months prior to study entry.

Exposure Assessment

We determined exposure to CNS-acting medicines on each day of the study period. Medicine use was categorized according to the total number of CNS-acting medicines taken each day and the total number of standard doses of CNS-acting medicines taken each day [measured as defined daily doses (DDDs)].[20] Prescription duration is not recorded in the claims data, so we estimated the duration of each prescription as the time within which 75% of patients obtained a refill dispensing.[21] Participants were considered to be taking the medicine from the date of dispensing plus the length of this duration estimate.

Sensitivity Analyses

We conducted 3 sensitivity analyses. The first excluded participants dispensed antipsychotics [identified by ATC code N05A, excluding prochlorperazine (N05AB04)] or anti-Parkinson medicines (N04) during the study period or in the 12 months prior to study entry. Patients taking these medicines were excluded as antipsychotics may be used to manage the behavioral and psychological symptoms of dementia, and up to one-third of older patients with Parkinson disease have coexisting dementia.[22] The second sensitivity analysis excluded hospitalizations for dementia from the primary outcome measure. The third sensitivity analysis excluded all participants dispensed an antipsychotic or anti-Parkinson medicine during the study period or in the 12 months before study entry, and dementia hospitalizations were excluded from the primary outcome.

Study Outcomes and Statistical Analysis

The primary endpoint for the study was any hospitalization with a primary diagnosis of confusion, delirium, or dementia, identified using the ICD-10-AM codes listed in Supplementary Table 1. Follow-up continued until the first hospitalization for confusion, delirium or dementia or the end of the study period (June 30, 2012), whichever occurred first. People were censored if their first hospitalization during the study period was for a diagnosis other than the primary outcome, on entry to residential aged care, initiation of dementia medicines or palliative care, or death.

We assessed the association between exposure to CNS-acting medicines and the risk of hospital admission for confusion, delirium, or dementia on the following day. We chose this method to avoid misclassifying exposure in people who started a CNS-acting medicine in hospital, on the day of admission, but who were not using a CNS-acting medicine prior to hospital admission. Days where people were not taking any CNS-acting medicines were used as the reference period. The rate of hospital admission was determined by dividing the total number of hospitalizations in each exposure category by the number of days at risk. Poisson regression models with a robust error variance were used to calculate incidence rate ratios, with adjustment for age at study entry, gender, socioeconomic index (based on area of residence),[23] number of hospitalizations in the 3 months prior to study entry, and the number of comorbidities, medicines, prescribers, and specialist visits (assessed quarterly in the