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Original Study

Antipsychotic Drug Use Is Not Associated With Long-Term Mortality Risk in Norwegian Nursing Home Patients

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A B S T R A C T

Objectives: To assess the long-term mortality risk associated with antipsychotic drug (AP) use in nursing homes.
Design: A longitudinal study with 5 assessments over a 75-month follow-up period.
Setting: A representative sample of nursing home patients in 4 Norwegian counties.
Participants: At baseline, 1163 patients were included. At the last follow-up, 98 patients were still alive.
Measurements: Prevalent drug use at each assessment was registered. Level of dementia, neuropsychiatric symptoms, level of functioning, medical health, and use of restraints were recorded at each assessment. A Cox regression model with time-dependent psychotropic drug use as the main predictor was estimated and adjusted for confounders.
Results: In unadjusted Cox regression, a lower mortality risk was associated with the use of other psychotropic drugs, but not APs, compared with nonusers. In the adjusted analysis, neither use of APs nor other psychiatric drugs was associated with increased mortality risk. Higher age, male gender, not being married, medical disease burden, lower level of functioning, more severe degree of dementia, and a higher number of drugs were all associated with increased mortality risk.
Conclusion: In this long-term study of nursing home patients, AP drug use was not associated with increased risk of mortality. This is in line with results from earlier studies of clinical samples, but contrasts with results from randomized controlled trials and registry-based studies. The findings should be interpreted with caution. Taking into account the modest benefit and high risk of adverse effects of AP drug use, nonpharmacological treatment remains the first-line treatment approach.
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Antipsychotic drugs (APs) are frequently used in nursing homes with reported prevalence estimates between 25% and 46%.[1–4] Prescription rates in nursing homes were relatively stable between 1997 and 2009[5–7] but recently a significant decrease in prescription rates has been reported.[8]

APs are often used to treat neuropsychiatric symptoms, such as agitation/aggression, delusions, or hallucinations in patients with dementia. Atypical APs, such as risperidone, olanzapine, and aripiprazole have become increasingly popular because of their putatively more favorable risk profile compared with conventional APs. However, pooled analysis of data from clinical trials and registry-based studies has demonstrated an increased risk for cerebrovascular adverse events (CVAEs).[9] Furthermore, a pooled analysis of 17 randomized controlled trials (RCTs) has reported a 1.7 times increased risk of all-cause mortality associated with atypical AP use compared with placebo.[10] A number of registry-based studies that included elderly outpatients and nursing home patients have demonstrated that there is an increased mortality risk associated with not only use of atypical APs, but also, and even to a larger extent, with use of

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conventional APs.[11–16] In contrast to these results, observational clinical studies among home-dwelling elderly people and nursing home patients have not showed any increased mortality risk with the use of APs, some results have even indicated a favorable effect.[17–20] Large, prospective studies in clinical samples are needed to shed light on these questions, which are important for clinical practice. We present data on mortality risk over 6 years in the largest longitudinal nursing home study so far with adjustment for the most relevant clinical factors that may have an impact on mortality in this frail population. In line with previous research, we hypothesize that the use of APs is positively associated with mortality risk, compared with patients who do not use APs.

Methods

Study Design

This is a longitudinal study of 26 nursing homes in 19 municipalities in 4 counties in Norway. All nursing home patients with a minimum of 14 days of stay were considered eligible for the study. The baseline assessment (A_1) took place from November 2004 to January 2005. Follow-up assessments took place 12 months (A_2), 31 months (A_3), 52 months (A_4), and 75 months (A_5) after the baseline assessment. Time of death was recorded at the nursing home.

Registered nurses with wide experience from working in old age psychiatry did the data collection. All assessors received 2 days of training before the first assessment and 1 day of training before the following 4 assessments.

Participants

In all, 1165 patients were approached. Two patients or their next of kin declined participation, leaving 1163 patients for inclusion. The patients and their family members were informed about the study. Explicit consent was not required for enrollment, but the patients or their next of kin were informed that they could refuse to participate at any stage of the study. This procedure was in line with Norwegian legislation and the study was approved by the Regional Ethics Committee, the Data Inspectorate, and the Directorate for Health and Social Affairs in 2004.

Assessments

Demographic data and the use of regular medications were collected from the patients' medical records. Type of ward was categorized into regular units, special care units for persons with dementia, and "others" comprising psychogeriatric, short-term, and rehabilitation units. Psychotropic drugs were grouped into APs, anxiolytics, hypnotics and sedatives, antidepressants, and antidementia drugs according to the Anatomical Therapeutic Chemical (ATC) index. To analyze the daily given drug doses, we used the Defined Daily Dose (DDD), a World Health Organization statistical measure of drug consumption that gives the assumed average maintenance dose per day for a drug used for its main indication in adults.[21] The use of restraints (mechanical, nonmechanical, electronic surveillance, force or pressure in medical examination or treatment, force or pressure in the performance of activities of daily living) was recorded with a structured questionnaire applied in previous Norwegian nursing home studies and dichotomized into no restraints or 1 or more restraints.[22]

Neuropsychiatric symptoms were assessed with the Neuropsychiatric Inventory, Nursing Home Version (NPI-NH).[23] The NPI-NH comprises 10 items on neuropsychiatric symptoms and 2 items on neurovegetative symptoms common in dementia. Based on data from a principal component analysis of this sample,[24] subsyndromal scores on agitation (aggression/agitation + disinhibition + irritability), psychosis (delusion + hallucination), and affective symptoms (depression + anxiety) were generated. Apathy was analyzed on its own, as this symptom did not load on any of the 3 factors.

The level of dementia was assessed by means of the Clinical Dementia Rating Scale (CDR).[25] The CDR consists of 6 items rating the degree of cognitive and functional impairment considering all available information. In the analysis, we also present the CDR "sum of boxes" (range 0–18), which is strongly correlated with the CDR total score (range 0–3).[26] In the baseline sample of this study, the Spearman correlation between the CDR score and the CDR "sum of boxes" was 0.94.

The level of functioning in daily activities was assessed with the Physical Self-Maintenance Scale.[27] This 6-item scale gives a sum score ranging from 6 to 30, with higher scores indicating increasing functional impairment. Medical health was rated with the General Medical Health Rating scale (GMHR),[28] a global health rating scale including 1 item with 4 categories: good, fairly good, poor, and very poor. From the records, we collected information about ICD-10 diagnoses. The diseases were sorted into groups and scored as absent or present: cardiovascular diseases, respiratory diseases, neurological diseases, and malignant neoplasm.

Data Analysis

Baseline characteristics were presented as mean and SD for continuous variables and as frequencies and percentages for categorical variables. Comparisons of baseline characteristics between survivors and nonsurvivors, and AP users and AP nonusers were performed by t test for independent samples or χ^2 test, as suitable.

A survival analysis was used to assess the relationship between mortality and the use of psychotropic drugs, defined as a categorical variable with categories "No psychotropic drugs," "Other psychotropic drugs," and "Antipsychotics." Patients using both APs and other psychotropic drugs were included in the "Antipsychotics" group. Patients were censored at the end of the observation period or when they left the study because of a change in level of care. As the use of psychotropic drugs may change at each follow-up time point, an extended Cox model with Efron approximation for ties was estimated by using the counting process method.[29] Using the counting process method, multiple records for each individual are created. Each record corresponds to an interval of time in which the predictor remains constant. For each patient, 1 to 4 such intervals were generated. Event was coded as censored as long as the patient was alive.

Crude hazard ratios (HRs) for mortality with the corresponding 95% confidence intervals (CIs) were first estimated by unadjusted models for use of psychotropic drugs as well as basic demographic variables and variables that have been shown to be associated with mortality in previous studies: age, gender, education level, marital status, CDR "sum of boxes," psychosis subsyndrome, affective subsyndrome, agitation subsyndrome, apathy, Physical Self-Maintenance Scale (PSMS), GMHR, days in nursing home, DDD of AP drugs, number of drugs, the use of restraints, the presence of cardiovascular diseases, respiratory diseases, neurological diseases, and malignant neoplasm. Most of them were included into the model as time-dependent variables in the same manner as the use of psychotropic drugs. An adjusted model without main predictor, use of psychotropic drugs, was then estimated and reduced by a stepwise selection method with the Akaike Information Criterion (AIC) applied at each step.[30] By using this approach, a close to one probability of entry and stay in the model was chosen, and a sequence of models starting with the null model (no predictors) and ending with the full model (all predictors included) was produced. The model with a minimum of AIC calculated at each step was selected as the AIC-optimal model. AIC is considered to be one of the most preferable approaches for model selection, as it combines the goodness-of-fit of the model in terms of likelihood

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