Short- and Long-term Mortality Risk Associated with the Use of Antipsychotics Among 26,940 Dementia Outpatients: A Population-Based Study

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Objective: *To investigate short- and long-term mortality risk associated with the use of antipsychotics in dementia outpatients, assessing the risk over specific time frames and quantifying the risk by the individual antipsychotics.* **Methods:** *This population-based study used data from the Norwegian Prescription Database. The study sample included 26,940 dementia outpatients aged 65 years or older prescribed anti-dementia drugs and psychotropics from Norwegian pharmacies between 2004 and 2010.* **Results:** *Cox survival analyses, adjusted for age, gender, mean daily defined dose, and severe medical conditions, showed that antipsychotic use compared with other psychotropics involved approximately twice the mortality risk in outpatients with dementia. Furthermore, these results are consistent for all investigated time points after first dispensing the drugs (hazard ratio [HR]$_{30days}$ = 2.1 [95% confidence interval {CI}: 1.6–2.9] to HR$_{730–2,400days}$ = 1.7 [95% CI: 1.6–1.9]). Haloperidol was associated with higher mortality risk (HR$_{30days}$ = 1.7 [95% CI: 1.0–3.0] to HR$_{730–2,400days}$ = 1.4 [95% CI: 1.0–1.9]) than risperidone.* **Conclusion:** *This first study to observe antipsychotic use and mortality in dementia outpatients over more than 6 years clearly shows that antipsychotics involve increased short- and long-term mortality risk. Physicians may justly consider antipsychotics to be the best option for some dementia patients among available nonpharmacologic and pharmacologic treatments. However, although causal conclusions are precluded due to limited adjustments in the analyses, the findings support the current treatment recommendations that antipsychotics should be avoided or used with great caution.* (Am J Geriatr Psychiatry 2014; 22:321–331)

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INTRODUCTION

Neuropsychiatric symptoms such as agitation, depression, and psychosis are prevalent in dementia and assumed to affect as many as 90% of the patients.[1,2] Antipsychotics are associated with adverse drug reactions[3,4] and are not approved for use in dementia patients with neuropsychiatric symptoms,[5] except in some countries that sanction treatment with risperidone. Clinical judgment concerning alternative treatment regimens is left to the physicians.[6]

Several studies have found increased risk of mortality in people with dementia associated with antipsychotics,[3,7–9] whereas others have not.[10,11] Important issues must be better understood to enable clinical practice to move forward. First, only a few studies, mostly from Canada and the United States, have compared the relative mortality risk of different antipsychotics.[12–14] Furthermore, many of the studies include older individuals and do not specifically identify people with dementia (e.g.,[15–17]). This may represent important biases, particularly concerning the comparison of individual drugs where the preferred choice of treatment may vary between people with and without dementia. There has been only preliminary investigation of the time course of increased mortality, a vital parameter for informing treatment guidelines and the routine review and discontinuation of antipsychotics in clinical practice. Except for a few studies following patients for 1 year,[8,12] 2 years,[7] or 3.5 years,[18] most studies have a maximum of 180 days of observation time,[9,13,19–21] As pointed out by Gardette et al. in a recent study,[18] data are still needed to assess mortality risk among older subjects suffering from dementia during long-term follow up.

A warning from the U.S. Food and Drug Administration from 2008[6] and a more recent review[3] concluded that there are no significant differences between conventional and atypical antipsychotics—both drug groups are associated with an increased risk for all-cause mortality. The few studies that have investigated the mortality risk associated with individual antipsychotics when used by dementia patients have found that haloperidol carries a particularly high risk.[12,13] Although most studies report that use of haloperidol is low in dementia patients,[22] a substantial number of people with dementia still receive this medication.[23] A recent cohort study showed that the lowest mortality risk was associated with quetiapine compared with risperidone,[13] although the importance of this finding is unclear given the limited effectiveness of quetiapine on aggression, agitation, or psychosis in randomized controlled trials.[24,25]

Approximately 70,000 people in Norway have dementia.[26] Based on public records[27] and prior research,[28,29] we estimate that about two in five dementia outpatients are receiving antidementia drugs in Norway. An article using the same data on dementia outpatients as in the present study[29] showed that concomitant use of antipsychotics with antidementia drugs was about 16% for both men and women. Antidepressants, mild hypnotics, benzodiazepines, and opioids were used concomitantly with antidementia drugs by 36%, 29%, 25%, and 23% of women and by 27%, 24%, 21%, and 17% of men, respectively.[29]

The aim of this study was to estimate the mortality risk associated with the use of antipsychotics in a large population-based sample of dementia outpatients. The study focuses on the time course of the mortality risk associated with the use of antipsychotics as a group and on the individual antipsychotic agents.

METHODS

Study Cohort

The analyses in the present study were based on data from the Norwegian Prescription Database (NorPD; www.norpd.no) linked with data from the Cause of Death Registry (CDR).[30] Both NorPD and CDR are owned by the Norwegian Institute of Public Health and cover the entire Norwegian population of 5 million inhabitants. The NorPD contains information about all prescribed drugs (reimbursed or not) dispensed at pharmacies to individual patients by any prescriber between January 1, 2004 and December 31, 2010. Prescriptions to nursing home patients are not recorded in the NorPD, nor are over-the-counter drugs. Available information includes patients' unique identification numbers (encrypted), gender, age, prescribers' unique identification numbers (encrypted), the dates on which drugs were dispensed, drug information (e.g., package size,