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Association between Prescription of Conventional or Atypical Antipsychotic Drugs and Mortality in Older Persons with Alzheimer's Disease

Massimo Musicco[a, b] Katie Palmer[b] Antonio Russo[d] Carlo Caltagirone[b, c]
Fulvio Adorni[a] Carla Pettenati[e] Luigi Bisanti[d]

[a]Institute of Biomedical Technologies, National Research Council, Segrate, [b]Foundation IRCCS 'Santa Lucia' and [c]Tor Vergata University, Rome, [d]Epidemiology Service, Local Health Unit, Milan, and [e]Alzheimer Centre, Garbagnate Hospital, Passirana di Rho, Italy

Key Words
Alzheimer's disease · Antipsychotic drugs · Mortality · Population study

Abstract
Background/Aims: To evaluate whether dementia patients prescribed antipsychotic drugs have a higher mortality compared to unexposed patients, and to investigate whether there are differences in mortality associated with exposure to conventional versus atypical antipsychotic drugs. ***Methods:*** Retrospective population cohort study with information gathered from the Italian Health Information System. All 4,369 residents of Milan (Italy) aged 60 years or older who were newly prescribed an antidementia drug (donepezil, rivastigmine or galantamine) from January 2002 to June 2008 were included. All new users of antipsychotic drugs in this cohort were categorized according to conventional (n = 156) or atypical (n = 806) drug exposure. The mortality risks of users of conventional or atypical antipsychotics compared to nonusers were evaluated with survival analysis, considering exposure to antipsychotic drugs as a time-dependent variable. ***Results:*** Mortality was increased two- and fivefold in users of atypical and conventional antipsychotics, respectively, with respect to nonusers. ***Conclusions:*** Dementia patients prescribed antipsychotic drugs had a higher risk of death. This risk was highest for those prescribed conventional antipsychotics. At least part of the excess mortality may be due to the underlying neuropsychiatric symptoms that prompted the use of antipsychotics rather than a direct medication effect.

Introduction

Behavioral and psychological symptoms (BPSD) are common in persons with dementia [1]. Although nonpharmacological interventions are considered the first-choice approach in BPSD, drug use is often unavoidable [2, 3]. The most commonly used psychotropic drugs are antidepressants and antipsychotics (neuroleptics), because depression, agitation, and psychosis are the most frequent BPSD [4, 5].

In recent years, atypical antipsychotic drugs such as risperidone, olanzapine, and quetiapine have largely replaced conventional medications (e.g. haloperidol and thioridazine) as they have been considered as effective as conventional drugs and better tolerated [4]. In particular, physicians prefer to prescribe atypical antipsychotics to

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Massimo Musicco
Institute of Biomedical Technologies, National Research Council
Via Fratelli Cervi 93
IT–20093 Segrate (Italy)
Tel. +39 0226 422 629, E-Mail m.musicco@hsantalucia.it

elderly and frail patients, particularly those with dementia [6]. However, atypical antipsychotics were shown to have efficacy limitations for the treatment of BPSD in a double-blind randomized placebo-controlled trial [7].

Efficacy limitations are not the only problem with atypical antipsychotics. Ongoing randomized, clinical trials have reported excess mortality and cerebrovascular events in dementia patients treated with olanzapine and risperidone [8, 9]. A small excess risk of death was also confirmed for these two drugs and quetiapine in a meta-analysis of 15 randomized, placebo-controlled trials [10]. In response, health authorities throughout the world took steps to limit the prescription of atypical antipsychotics. In Italy, as in other countries, the warnings did not extend to conventional antipsychotics, although there is no current evidence that conventional antipsychotics have a better safety profile than the newer atypical drugs.

Some observational studies on major adverse events in large populations of elderly persons taking conventional versus atypical antipsychotics have been published. A study on a Canadian cohort of about 37,000 persons with dementia reported no difference in hospitalization rates for stroke between users of conventional and atypical drugs [11]. A self-controlled case series study found that the risk of stroke was increased for users of antipsychotic drugs, particularly for atypical antipsychotics [12]. Further, large studies from America [13–15] and Canada [16] reported significantly greater mortality among users of conventional compared to atypical antipsychotics. An increased risk of death for users of atypical antipsychotics compared to persons not using antipsychotics was reported in persons with dementia, but the risk was even higher for users of conventional drugs [17]. All these observational studies are prone to bias, particularly those comparing outcomes of persons exposed to antipsychotic drugs with unexposed persons, since an excess of undesired outcomes may not be due to a direct medication effect but to the underlying neuropsychiatric symptoms that prompted antipsychotic use. This is particularly true when the outcome of interest is mortality since antipsychotics are used for delirium, and this disturbance is frequent in old persons with advanced diseases [18]. Moreover, even studies comparing persons taking conventional and atypical drugs are not immune to indication bias because conventional antipsychotic drugs, such as haloperidol, are preferentially prescribed by clinicians to persons near to the end of life [19].

To provide further data on the role of conventional and atypical antipsychotics on mortality, we carried out a mortality study on elderly persons with dementia, resident in the municipality of Milan, northern Italy, with a total population of about 1.3 million persons. In persons with dementia, antipsychotics are prescribed almost always to control BPSD. For this reason, differences in undesired outcomes between dementia patients who are exposed to conventional or atypical antipsychotic drugs are less frequently due to differences in the symptoms that conditioned the use of the specific type of antipsychotic drug. However, even in persons with dementia, differences in the occurrence of negative outcomes between people exposed or unexposed to antipsychotics might be due to the presence of BPSD rather than being a negative consequence of drug consumption. The aim of the current study was to examine mortality risks associated with the use of conventional and atypical antipsychotic drugs in elderly persons with dementia.

Methods

Data Collection, Study Population, and Exposure Definition

Data was taken during the period January 1st 2002 to June 15th 2008, from the computerized health information database of Milan, which collects individual information on mortality, hospital discharge diagnoses, and drug prescriptions.

The study population consisted of 4,369 Milan residents aged 60 and above who were prescribed an acetylcholinesterase inhibitor (AChEI) – either donepezil, rivastigmine or galantamine – for the first time during the 6-year study period. In Italy, AChEIs are prescribed and reimbursed by the health service only for persons with mild to moderate Alzheimer's disease by physicians expert in dementia (neurologists, psychiatrists, geriatricians) in certified special units [20]. For this reason, we relied on the assumption that almost all persons prescribed AChEIs had Alzheimer's disease. Moreover, in newly diagnosed (incident) patients current guidelines recommend the initiation of treatment with an AChEI. Thus, in the current study, the date of first prescription of an AChEI was considered to be reasonably near to the date of first diagnosis of dementia [2, 6].

Information on the 4,369 persons with dementia was obtained from the database concerning prescription of antipsychotic drugs. We considered only the period of 2 years from the diagnosis of dementia (date of first prescription of AChEIs) to limit the possibility that antipsychotics were prescribed as an end-of-life treatment. The median survival of persons with dementia is about 5 years from diagnosis [21, 22] and thus few patients are expected to die from dementia within 2 years of the diagnosis.

Atypical antipsychotic drugs included risperidone, olanzapine, quetiapine, and clozapine. Conventional antipsychotic drugs included haloperidol, thioridazine, clotiapine, chlorpromazine, trifluoperazine, levomepromazine, amisulpride, periciazine, fluphenazine, pimozide, tiapride, levosulpiride, bromperidol, dixyrazine, zuclopentixol, sulpiride, pipamperone, and perphenazine. The whole period of observation of each member of the cohort was characterized according to exposure to conventional or atypical antipsychotics. Persons prescribed an antipsychotic were con-

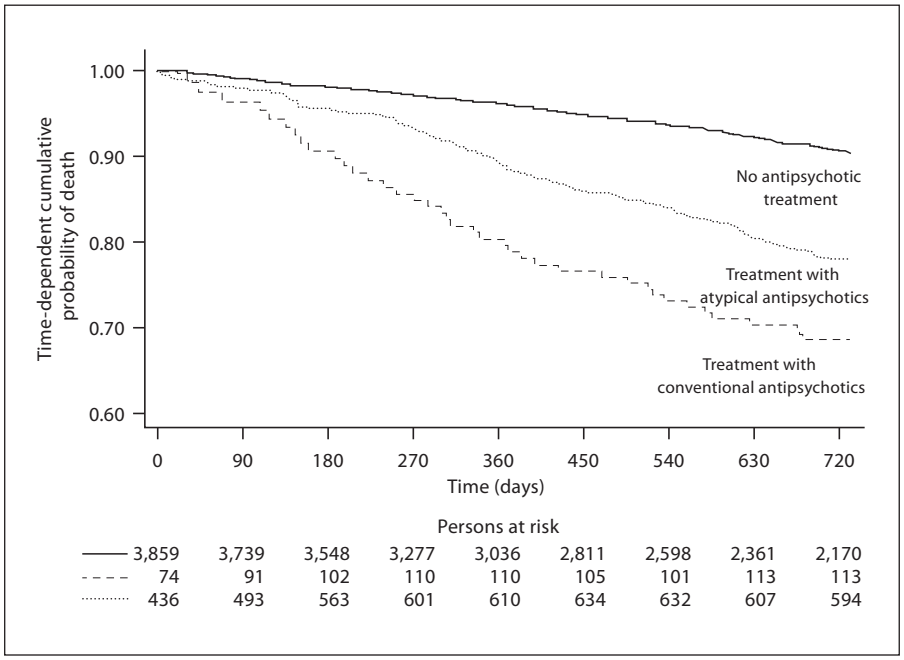

Fig. 1. Survival in the first 2 years since Alzheimer's disease diagnosis by antipsychotic drug exposure. Kaplan-Meier survival estimates.

sidered exposed to the specific type of drug (i.e. conventional or atypical) from the date of prescription until the end of the observation or until the date of prescription of a different type of drug. For this reason, each member of the cohort could contribute, in terms of person-time, to the group of the unexposed as well as the groups exposed to conventional or atypical antipsychotics.

Comorbidities and Outcomes

We considered hospitalizations occurring over the 12 months prior to dementia diagnosis (first prescription of the AChEI), and individual comorbidities were determined from the diagnoses reported on the hospital discharge forms. The discharge diagnoses were categorized according to Modified Elixhauser comorbidity categories. In the current study, we considered both (i) the 20 Elixhauser comorbidity categories as binary variables, and (ii) a hierarchical grouping of 4 categories: tumors, cardio-/cerebrovascular diseases, other diseases, and no comorbidities [23].

The outcome of this study was survival during the 2 years following the diagnosis of dementia. Death causes were derived from death certificates and grouped into 9 large categories: cancer, diabetes and other metabolic diseases, dementia, ischemic heart disease, other heart disease, stroke and other cerebrovascular diseases, respiratory infections, injury/poisoning, and other.

Statistical Analyses

With the Kaplan-Meier method, we calculated the time-dependent probability of death during the first and the second year from dementia diagnosis according to treatment and type of antipsychotic drug prescribed. Drug exposure was treated as a time-dependent variable, and each person might spend part of the 2 years after dementia diagnosis in each of the 3 considered groups (no antipsychotics, atypical antipsychotics, and conventional antipsychotics).

Crude and adjusted relative risks of death (hazard ratios) were calculated with Cox's proportional hazard models. In the comparison with nonexposure to antipsychotic drugs, exposure to antipsychotics was considered as a time-dependent variable. Persons were therefore considered unexposed as long as they did not initiate an antipsychotic treatment, if any. Risks were adjusted for 4 covariates: age, sex, comorbidities, and a score of propensity of being prescribed an antipsychotic drug that was calculated considering all 20 Elixhauser comorbidity categories. Use of antipsychotic drugs was considered as the dependent variable in a logistic regression with the Elixhauser categories (binary variables) as independent variables. The probability of being prescribed an antipsychotic drug was calculated for each cohort member and this probability was also considered as individual propensity score.

Results

Of the 4,369 persons who initiated AChEI treatment during the study period, 3,045 (69.7%) were never prescribed an antipsychotic drug (fig. 1).

Of the 1,324 (30.3%) prescribed an antipsychotic drug, 323 (24.4%) had the prescription more than 2 years after dementia diagnosis and were considered unexposed to antipsychotics. About ten percent (n = 144, 10.9%) of the exposed patients were prescribed both a conventional and an atypical antipsychotic.

The clinical and demographic characteristics of the study population by type of antipsychotic drug prescribed

Table 1. Demographic and clinical characteristics of the studied cohort according to the type of antipsychotic drug prescribed

	Treatment with antipsychotic drugs				
	no (n = 3,276)	typical only (n = 136)	atypical only (n = 854)	typical and atypical (n = 103)	total population (n = 4,369)
Sex, n					
Women	2,145 (65.5)	94 (69.1)	544 (63.7)	56 (54.4)	2,839 (65.0)
Men	1,131 (34.5)	42 (30.9)	310 (36.3)	47 (45.6)	1,530 (35.0)
Mean age ± SD, years	78.5 ± 6.7	79.2 ± 6.1	78.7 ± 6.4	76.8 ± 6.6	78.5 ± 6.6
Comorbidities, n					
None	2,753 (84.0)	105 (77.2)	709 (83.0)	82 (79.6)	3,649 (85.6)
Tumors	69 (2.1)	10 (7.4)	15 (1.8)	3 (2.9)	97 (2.2)
Cardiovascular	282 (8.6)	11 (8.1)	69 (8.1)	11 (10.7)	373 (8.5)
Other	172 (5.3)	10 (7.4)	61 (7.1)	7 (6.8)	250 (5.7)
Deaths total, n	291 (8.9)	26 (19.1)	139 (16.3)	21 (20.4)	477 (10.9)

Figures in parentheses indicate percentages.

are reported in table 1. Men were more likely to be prescribed atypical than conventional antipsychotics, whereas there were no differences in the mean age, which was about 79 years in the three groups. Comorbidities were more frequent in the group prescribed typical antipsychotic drugs but the differences among the three groups were not statistically significant.

The Kaplan-Meier survival curves in the first 2 years after dementia diagnosis are reported in figure 1. The crude and adjusted relative risks of death calculated as hazard ratios, with exposure to antipsychotic drugs as a time-dependent variable, are presented in table 2. When persons were prescribed a conventional antipsychotic drug, they had a crude risk of death that was about fourfold increased with respect to persons who were not prescribed any antipsychotic drug. The risk of death was 2.5 times increased in persons prescribed an atypical antipsychotic compared to persons unexposed to antipsychotic drugs. Adjustment for age, sex, comorbidities, and propensity score did not modify the size or the statistical significance of the risk estimates. The risk of death was 50% higher in persons prescribed a conventional antipsychotic drug with respect to those prescribed an atypical drug, and this increase was statistically significant.

In terms of death causes, the mortality excess observed in persons prescribed antipsychotic drugs was mostly explained by deaths attributed to dementia (table 3). This excess was higher for persons who were prescribed both typical and atypical antipsychotic drugs. Causes of death attributed to respiratory infections were more frequent in persons exposed to atypical and to both types of antipsychotics. Other causes more represented in persons exposed to antipsychotics were tumors in those exposed to conventional antipsychotics and nonischemic heart diseases in people exposed to atypical antipsychotics. However, these differences were largely compatible with chance variations.

Table 2. Relative risks of death (hazard ratio) by exposure to antipsychotic drugs, sex, age, and comorbidities

	Crude risk of death[a]	Adjusted risk of death[a, b]
Exposure to antipsychotic drugs		
None	1.0 (reference)	1.0 (reference)
Typical	3.8 (2.7–5.2)	3.7 (2.6–5.1)
Atypical	2.5 (2.1–3.1)	2.5 (2.0–3.0)
Typical vs. atypical	1.5 (1.1–2.1)	1.5 (1.1–2.1)
Sex		
Women	1.0 (reference)	1.0 (reference)
Men	1.4 (1.1–1.8)	1.5 (1.2–1.8)
Age, years (continuous)	1.07 (1.05–1.08)	1.07 (1.05–1.09)
Comorbidities		
None	1.0 (reference)	1.0 (reference)
Tumors	4.3 (3.0–6.2)	4.0 (2.8–5.8)
Cardio-/cerebrovascular	1.8 (1.3–2.3)	1.6 (1.2–2.1)
Other	1.4 (0.9–1.9)	1.3 (0.9–1.9)

[a] Hazard ratio with 95% confidence intervals.
[b] Adjusted for exposure, sex, and comorbidity as appropriate, and for propensity score as a continuous variable.

Table 3. Causes of death by exposure and type of antipsychotic drug prescribed

	Treatment with antipsychotic drugs			
	no (n = 3,276)	typical (n = 136)	atypical (n = 854)	typical and atypical (n = 103)
Causes of death, n				
Cancer	52 (1.6)	8 (5.9)	16 (1.2)	2 (1.9)
Diabetes and other metabolic diseases	11 (0.3)	0	2 (0.2)	1 (0.1)
Dementia	51 (1.6)	7 (5.0)	43 (5.0)	9 (8.7)
Ischemic heart disease	27 (0.8)	2 (1.5)	5 (0.6)	0
Nonischemic heart disease	18 (0.5)	1 (0.7)	14 (1.6)	0
Stroke and other cerebrovascular diseases	36 (1.1)	2 (1.5)	16 (1.9)	3 (2.9)
Respiratory infections	31 (1.0)	1 (0.7)	17 (2.0)	4 (3.9)
Injury/poisoning	15 (0.5)	0	4 (0.5)	1 (0.1)
Other	50 (1.5)	5 (3.7)	22 (2.6)	1 (0.1)

Figures in parentheses indicate percentages.

Discussion

In the current study, we found an increased mortality risk associated with use of antipsychotic drugs in elderly persons with dementia in Milan, Italy. Mortality was about twofold and fourfold increased in persons with dementia who were prescribed atypical or conventional antipsychotic drugs, respectively, compared to persons unexposed to antipsychotics. Further, conventional antipsychotics were associated with a 50% increased risk of death compared to exposure to atypical antipsychotics.

Our results of an increased mortality risk in users of antipsychotic drugs are in agreement with other studies on mortality and use of either conventional or atypical antipsychotic drugs in elderly populations [13–17]. In particular, we found almost identical results to those of a large study that compared mortality of persons with dementia exposed and unexposed to antipsychotic drugs [17]. When investigating mortality and antipsychotic use in the elderly, it is likely that observational studies on persons with dementia are less affected by potential distortions related to biases of indication. In persons with dementia, antipsychotics are mostly prescribed to control neuropsychiatric symptoms such as hallucinations, delusions, and more commonly to control psychomotor agitation. For this reason, in a population of demented persons, the prescription of antipsychotics as end-of-life treatment is less frequent than in the general population where these drugs, on the contrary, are frequently used for this indication [19]. However, even in persons affected by dementia, the conditions of those who were prescribed antipsychotic drugs may be regarded as potential determinants of death. Thus, the association between higher risk of death and exposure to antipsychotic drugs cannot be immediately considered to be causal. We studied a large cohort of persons with dementia, and it is very likely that those who were prescribed antipsychotic drugs had psychoses or psychomotor symptoms such as agitation and aggressiveness [24]. Therefore, it is plausible that at least part of the excess death observed in persons with dementia who were prescribed antipsychotic drugs may be due to the presence of these behavioral disturbances rather than an undesired effect of the drugs. It can be argued that psychoses and psychomotor agitation in older and probably frail persons can cause behavior and traumatic injuries that may directly or indirectly cause their death. Unfortunately, we have no sound evidence that this was the case or not in our studied population. Only deaths attributed to dementia were clearly increased among persons prescribed antipsychotic drugs, whereas there were only small differences in the frequency of deaths for other causes. This result has two possible explanations. First, antipsychotics were prescribed to persons with more severe forms of dementia that, independently from the potential negative effect of antipsychotics, have an inherent reduced life expectancy. In fact, disturbances like psychoses and psychomotor agitation are more frequently observed in the more advanced stages of Alzheimer's disease [25] and, therefore, patients with more severe forms of the disease are also expected

to be more frequently prescribed an antipsychotic drug. However, it cannot be excluded that at least part of the deaths attributed to the underlying principal disorder, i.e. to dementia, in death certificates were actually due to an undesired effect of the prescribed antipsychotic.

One major finding of our study was the observed increase in the risk of death in conventional versus atypical antipsychotic drug users. In nursing home residents, conventional antipsychotic drugs have been reported to increase the occurrence of ventricular arrhythmias and cardiac arrest with respect to atypical antipsychotics [26]. Conversely, atypical antipsychotic drugs have been reported to be associated with an increase of venous thromboembolisms in the elderly, whereas contradictory results were reported by studies investigating the occurrence of stroke in relation to antipsychotic drug use [11, 12]. Thus, due to this conflicting evidence, there is no clear explanation for the mortality risk associated with conventional antipsychotics in our study. However, this finding is consistently reported in most of the mortality studies [13, 15–17].

The limitations of the current study are mainly related to the observational design, and the fact that we used administrative data. Although a randomized controlled clinical trial might be more appropriate to address the research questions, the large sample size and long observation period necessary make such a study difficult to perform. The largest published study on this topic, which compared atypical antipsychotics with placebo in persons with BPSD, observed 421 patients for up to 36 weeks [7]. Thirteen deaths occurred in the entire cohort, which is too small a number to assess the potential influence of the medications on mortality. Thus, although bias may occur, observation studies such as ours have the advantage of collecting data from very large cohorts of elderly persons for adequate lengths of time.

Another potential limitation is that we defined our study population of Alzheimer's disease patients based on AChEI use. This may cause a selection bias, where some cases of dementia are not included in our cohort if they were not diagnosed with Alzheimer's disease by a physician and thus were not receiving AChEI treatment. However, it is highly unlikely that we have many false positive cases of Alzheimer's disease in our sample, because in Italy, AChEIs are prescribed by the health service only for persons with mild to moderate Alzheimer disease, and these prescriptions are only made by physicians expert in dementia disorders, such as neurologists, psychiatrists, and geriatricians, in certified special units [20]. Further, the guidelines recommend AChEI treatment for all newly diagnosed Alzheimer's disease patients. Thus, it is likely that most of the persons prescribed AChEIs had Alzheimer's disease. Further, even if our study included a small number of false positive dementia cases, there is no valid reason to assume that there was a differential distribution between the 3 groups (nonusers of antipsychotic drugs, users of conventional or atypical drugs). Therefore, the relevant comparison between mortality of patients using antipsychotic drugs within this sample is unlikely to be affected by the exclusion of Alzheimer's disease patients who were not diagnosed and therefore not taking AChEIs, or by the inclusion of cases that were not true Alzheimer's disease.

Another limitation of our study was the use of administrative data. All our analyses were based on drug prescriptions rather than actual use of antipsychotic drugs. We cannot be certain that every person prescribed an antipsychotic was exposed to the prescribed drug. However, we had similar results when we restricted the analysis to the 6 months following the first prescription to maximize the probability of exposure in persons prescribed an antipsychotic drug.

In conclusion, in this study we observed a higher mortality in persons with dementia who were prescribed an antipsychotic drug. This mortality increase might be partly attributed to the conditions and symptoms that prompted the prescription of these drugs. The death risk increase was higher for persons prescribed a conventional rather than an atypical antipsychotic. From a clinical point of view, our results support the recommendations of guidelines [2, 3] suggesting the use of antipsychotic drugs as a second-choice intervention after trying to change the environment and life conditions of the patients. However, when drugs become unavoidable, the use of conventional antipsychotics might be associated with a higher risk of death with respect to the use of atypical drugs.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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