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BRIEF REPORT

# Mortality in patients with dementia treateds with atypical antipsychotics (olanzapine, quetiapine, and ziprasidone)

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**KEYWORDS**
Atypical antipsychotic agents;
Quetiapine;
Olanzapine;
Ziprasidone;
Cardiovascular risk;
Cognitive defect dementia;
Mortality;
Adverse drug reaction

**Abstract**
*Introduction:* The atypical antipsychotics (AA) quetiapine, olanzapine, and ziprasidone are used to treat behavioural disorders associated with dementia. This indication does not appear on their technical sheet. The object of this study is to analyse the relationship of these treatments with mortality and other factors.
*Method:* Retrospective study from March 2005 to July 2007 of AA treatments requested as compassionate use. We collected information on mortality, age, history of heart disease or cerebrovascular disease, and duration and number of concomitant treatments per patient.
*Results:* Two hundred eighty-nine patients were studied. Mortality was 31.1%. A higher mortality rate was shown for patients with a history of heart disease and in those who used olanzapine. Quetiapine was the most commonly prescribed antipsychotic drug.
*Conclusions:* The use of AA in the elderly could have risks that outweigh the benefits. When prescribing these drugs for at-risk patients, one should consider their safety warnings and the individual case of each patient. According to our data, olanzapine seems to be associated with a higher risk than quetiapine and ziprasidone.

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**PALABRAS CLAVE**
Agentes antipsicóticos atípicos;
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Reacciones adversas a medicamentos

**Mortalidad en pacientes con demencia tratados con antipsicóticos atípicos (olanzapina, quetiapina y ziprasidona)**

**Resumen**
*Introducción:* Los antipsicóticos atípicos (AA) quetiapina, olanzapina y ziprasidona se utilizan para el tratamiento de trastornos conductuales asociados a demencia. Esta indicación no figura en su ficha técnica. El objetivo de este estudio es analizar la relación de estos tratamientos con la mortalidad y otros factores.
*Método:* Estudio retrospectivo desde marzo de 2005 hasta julio de 2007 de los tratamientos de AA solicitados como uso compasivo. Se registraron datos de mortalidad, edad, antecedentes de cardiopatía o de enfermedad cerebrovascular (ECV), duración y tratamiento por paciente.
*Resultados:* Los pacientes estudiados fueron 289. La mortalidad fue del 31,1%. Se constató mayor mortalidad en los pacientes con antecedentes de enfermedad cardiovascular y en los que usaron olanzapina. La quetiapina fue el antipsicótico más prescrito.
*Conclusiones:* La utilización de AA en ancianos puede tener riesgos que superen los beneficios. Cuando se prescriben en pacientes de riesgo deben considerarse las alertas sobre su seguridad y la individualidad de cada paciente. De acuerdo con nuestros datos, la olanzapina parece entrañar un mayor riesgo que la quetiapina y la ziprasidona.

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## Introduction

Behavioural disorders and psychotic states are frequent in patients with dementia.[1] Pharmacological treatment with antipsychotic drugs is usually the treatment of choice for these disorders.[2]

Atypical antipsychotics (AA) refer to those drugs that, because of their neuroleptic properties, present a different adverse effect profile from that of classic antipsychotics. They are a heterogeneous group of molecules that block dopaminergic and serotoninergic receptors in the central nervous system. This study analyses olanzapine, quetiapine, and ziprasidone.

In recent years, we have been witnesses to increasing concern about the safety of these drugs. In 2004, the Spanish Agency of Drugs published 2 alerts warning of the risk of death associated with cerebrovascular events, which led to greater caution being used when prescribing AAs. In 2005, the Food and Drug Administration also released a note warning of the risk of cerebrovascular events in elderly patients with dementia who were treated with these drugs.[4] This note was based on the analysis of 17 placebo-controlled clinical trials on elderly patients with dementia and receiving treatment with antipsychotics. Fifteen of these studies showed increased mortality in the group treated with AA. Analysis of the causes of death revealed a high number of cardiac events. Some authors have doubts about the long-term safety of AA use.[5,6]

Meanwhile, it is necessary to assess these drugs' effect on patients' behavioural control, considering the social importance of the problem.[7]

In 2005, the Spanish Ministry of Health made it mandatory to have AA prescriptions for patients older than 75 approved. Patients in these circumstances were attended by our hospital's neurological or psychiatric teams, and since compassionate use of the drugs was requested from the Spanish Ministry of Health for all patients, they were also attended in the pharmacy division. We developed the most comfortable system possible for the doctor and the patient, without neglecting personalised handling of each case. As a result, we created an information and informed consent model that minimised the time needed to fill it out, and established a circuit to prevent delays in treatment and time wasted by patients or family members. Since that time, we have assisted nearly 300 patients with dementia and associated behavioural disorders, and provided them with the proper pharmacological care in order to minimise potential problems related to the medication.

The purpose of this study is to analyse the relationship between these treatments and other factors such as age, sex, treatment duration, and the presence of cerebrovascular disease or heart disease.

## Method

### Study population and follow-up

The study cases were patients diagnosed with dementia-associated behavioural disorders and receiving treatment with the following AA: olanzapine, quetiapine, and ziprasidone. The reason for excluding the other AAs is because they are not prescribed in some cases or not flagged in the pharmacy division because they do not require filing a compassionate use request (risperidone is approved for this indication). The follow-up period was between March 2005 until July 2007. Data was gathered from the clinical histories and from the pharmacy's database (DIPEX programme). Due to the fact that some of the patients had been treated in centres other than the hospital, it is not

**Table 1** Age, sex, and death data

| | |
|---|---|
| Patients | 289 |
| Distribution by sex | 177 women (61.2%)<br>112 men (38.7%) |
| Age range | 52-101 years (mean, 82.7) |
| Deaths | 90 total: 50 women (55.5%) and 40 men (44.5%) |

**Table 2** Distribution of patient deaths by treatment

| Treatment | Death | | Total |
|---|---|---|---|
| | No | Yes | |
| Olanzapine | 22 | 21 (48.8%) | 43 |
| Quetiapine | 134 | 57 (29.8%) | 191 |
| Ziprasidone | 43 | 12 (21.8%) | 55 |
| Total | 199 | 90 (31.1%) | 289 |

possible to ascertain the exact date when treatment began for every patient recorded during 2005. Most did not provide data in their clinical histories, and it was not clear whether or not they had had the same treatment, or another treatment, at a previous time. Many of them had been receiving treatment, and because of the change in approval procedures for these drugs, they then began to be monitored at a hospital level, and were identified that way. Patients were classified into 3 groups, according to the time of exposure to treatment: group 1 had received treatment for less than a year, group 2 had received more than 1 year but less than 2, and group 3 had received treatment for 2 years or more.

### Clinical variables

We grouped data according to mortality, age, sex, prescribed treatment, history of heart disease or cerebrovascular disease (CVD), and treatment duration. To compensate for a possible skew due to not knowing on what date some patients began treatment, we established a variable to separate patients whose exact treatment duration could not be established and those for whom the treatment duration was completely documented.

### Grouping criteria: cerebrovascular/heart disease

Diagnosis mentioned in the clinical history is included in one of the following ICD-9 sections (6th ed)[9]:

- 410-414: ischaemic heart disease.
- 420-429: other types of heart disease.
- 430-438: cerebrovascular disease.

CVD was established as the diagnosis of one or more transitory or definitive cerebrovascular events, regardless of their seriousness or the clinical symptoms, either noted in the patient's clinical history, or where there was an explicit reference to a remote episode.

### Statistical analysis

#### Descriptive study

Qualitative variables are expressed as percentages and absolute frequencies. Numerical variables are indicated by the mean and the typical deviation where there is a normal distribution, or by the median and the interquartile range if the distribution is non-Gaussian. Normality tests used were the Kolmolgorov-Smirnov test with the Lilliefors correction and the Shapiro-Wilk test.

#### Bivariate analysis

The $\chi^2$ test was used to evaluate the possible existence of statistical association between the categorical variables that were studied. Values of $P<.05$ were considered statistically significant.

The analyses were performed using Statistical Package for Social Sciences (SPSS) software, version 15.0, Spanish language edition.

## Results

The treatments of 289 patients were studied (Tables 1 and 2).

Although higher male mortality was detected, we found no significant relationship between mortality and sex ($P=.18$). Neither could any relationship be determined between mortality and age ($P=.21$).

Ten point seven percent of the patients (31) abandoned treatment after the first dose was administered.

The treatment durations are listed in Table 3.

Of the 289 patients in the study, 43 (14.8%) had a previous history of cerebrovascular events. Twelve patients (27.9%) of those 43 died.

The statistical relationship between having suffered a CVD and a higher probability of death could not be determined ($P=.620$).

There were 90 cases with a history of heart disease, out of which 39 died (mortality rate, 43.3%).

Statistical analysis showed a significant relationship between suffering from heart disease and the risk of death ($P=.003$).

### Antipsychotic treatment and mortality

The distribution of the patients who died per treatment is shown in Table 2.

Mortality rates differed according to the drug that was used, with a higher mortality rate among patients treated with olanzapine.

To evaluate the possible influence the treatment could have on the mortality rate, we compared the 3 treatments among each other and performed statistical analysis of the data. The statistical study of mortality among patients treated with quetiapine compared to ziprasidone did not reveal any significant differences ($P=.243$). We did find differences, however, between those treated with

**Table 3** Treatment duration and mortality

| Patients | Duration of treatment | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Less than 1 year | | More than 1 year and less than 2 | | More than 2 years | | Total | |
| | Total | * | Total | * | Total | * | Total | * |
| Death | | | | | | | | |
| No | 70 | 35 | 42 | 17 | 87 | 14 | 199 | 66 |
| Yes | 55 | 18 | 21 | 9 | 14 | 3 | 90 | 30 |
| Percentage | (61) | (60) | (23.4) | (30) | (15.5) | (10) | (100) | |
| Total | 125 | 53 | 63 | 26 | 101 | 17 | 289 | 96 |
| Mortality | 44% | 34% | 33% | 34.6% | 13.8% | 17.6% | 31.1% | 31.2% |

*Excludes patients whose treatment duration is not defined.

olanzapine compared with quetiapine ($P$=.017) and olanzapine compared with ziprasidone ($P$=.005), which seems to indicate a higher mortality rate when olanzapine is used.

### Treatment duration and mortality

In most of the patients who died, death occurred during the first year of treatment; after 2 years, mortality decreased considerably (Table 3). Mortality was at its highest point in patients who did not complete 2 years of therapy, and we found a statistical relationship ($P$<.005) that seems to confirm a higher risk of death during the first steps of the treatment. Filtering by patients beginning treatment during the study period, for whom the treatment duration is known exactly, produced similar results.

## Discussion

Olanzapine, quetiapine, and ziprasidone are AA drugs used in patients with dementia who develop behavioural disorders, psychosis, and aggressiveness.

Our data suggest that behavioural and psychotic disorders associated with dementia are more frequent in women than in men, which coincides with that stated in other publications.[10-12] Nevertheless, we did record higher male mortality.

The clinical trials carried out in elderly patients with psychotic disorders associated with dementia show an increase in mortality compared with a placebo (3.5% vs 1.5%, respectively; $P$=.024) and nearly 3 times the risk of CVA (1.3% vs 0.4% respectively; $P$=.043).[2] This resulted in the Spanish Agency of Drugs and Healthcare Products for publishing an informative note in March 2004 that warned of the increase in mortality among patients with dementia and psychotic disorders who were treated with olanzapine.

A third of our patients died during the study period, without there being any relationship between mortality and age. However, the highest mortality occurred in the patient group treated with olanzapine, which coincides with the alert issued by the Spanish Agency of Drugs.

In the patient group with a history of CVD, mortality was similar to general mortality.

In heart disease patients, mortality was higher than the mean and the relationship was statistically significant.

More than 40% of patients did not complete a year of treatment. It is also significant that the drop-out rate at the beginning of treatment was so high (11% of patients did not return after receiving the first dose). We cannot draw any conclusions as to the exact cause, but death is an important factor, as we can deduce from the higher number of deaths in early stages of the treatment.

In a study performed by Gill et al,[6] it was shown that the use of AA was associated with a significant increase in mortality for elderly patients with dementia, and that this risk was noticeable after 1 month and continued over 6 months. Another study by Wang et al[13] found a higher risk of death during the first 180 days. This means that the risk of death associated with the use of antipsychotics develops quickly and can last for 6 months. In this respect, our study also suggests that mortality is higher in patients receiving a shorter treatment.

However, the low number of patients in this study could make it difficult to draw clear conclusions. Additionally, the fact that it was impossible to establish the motive for the doctor's choice of a certain AA is a factor that could have an influence on the results. Nevertheless, we can come to the general conclusion that the risk-benefit ratio for drugs used for behavioural disorders can be a matter of debate in some cases. We therefore recommend selecting the patients carefully and following up on treatment effectiveness and safety, particularly during the first steps of treatment.

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