

London, 4 August 2009  
Doc.Ref: EMEA/493730/2009

## EMEA 2010 Priorities for Drug Safety Research

### Safety aspects of antipsychotics in demented patients

Around six million people in Europe have dementia. Although some drugs may modify disease progression, the mainstay of therapy is in controlling the behavioural and psychological symptoms of dementia. Antipsychotics are prescribed to between 20-50% of patients in institutional care with presumably a smaller percentage receiving them in the community.

Antipsychotics are divided into conventional (or typical) antipsychotics and atypical antipsychotics based on their propensity to cause extrapyramidal signs and symptoms and tardive dyskinesia. All antipsychotics act via the dopamine D2 receptor but atypical antipsychotics affect a wider range of receptors in addition to the D2 receptor, such as serotonin receptors. Some attribute the difference in the side effect profile between typical and atypical antipsychotics to the modifying effect of serotonin and other receptors whilst others postulate that it is the length of time that the D2 receptor is occupied and the speed of dissociation that is most relevant.

In 2005 analyses of 17 placebo controlled trials found that there was a higher mortality rate in elderly people prescribed atypical antipsychotics for dementia. This led to warnings in Europe and elsewhere about the use of atypical antipsychotics in this population. However, evidence on whether this effect extended to the typical antipsychotics was not available largely because of the lack of randomised controlled clinical trials for these drugs, which were developed during the 1950s.

Concern that typical antipsychotics could have an equal or increased mortality rate led to a request under Article 5(3) of Regulation (EC) 726/2004 to seek the scientific opinion of the Committee for Medicinal Products for Human Use (CHMP) on the interpretation of the available evidence in relation to typical antipsychotics (see link below). The CHMP concluded that typical antipsychotics were associated with increased mortality when used in elderly people with dementia. Some evidence suggested that the risk of increased mortality was higher in typical compared with atypical antipsychotics but methodological limitations prevented firm conclusions. The CHMP also concluded that it was not possible to differentiate between different antipsychotics and that further research was needed.

The objective of further research is to investigate and quantify any increased risk of mortality in elderly patients with dementia treated with antipsychotic drugs. The research should generate data that will allow the comparison of different antipsychotic drugs with regard to their risk of serious cardiac and cardiovascular events and mortality in elderly demented patients. Identification of risk factors for increased mortality would allow those at highest risk to be protected.

[http://www.emea.europa.eu/pdfs/human/opinion/Conventional\\_Antipsychotics\\_Article5.3-CHMP\\_Opinion.pdf](http://www.emea.europa.eu/pdfs/human/opinion/Conventional_Antipsychotics_Article5.3-CHMP_Opinion.pdf)