

Questions and answers on the review of the use of conventional antipsychotic medicines in elderly patients with dementia

The European Medicines Agency (EMA) has completed a review of the evidence available on the safety of conventional antipsychotic medicines in elderly patients with dementia. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that there is some evidence that the use of these medicines can increase the risk of death in this group of patients. The review was carried out under an 'Article 5(3)' procedure¹.

What are antipsychotic medicines?

Antipsychotics are medicines that are used in patients with psychosis, a type of serious mental illness such as schizophrenia or mania. In addition, they are sometimes used in older patients with psychotic disorders (violent and disturbed behaviour) due to dementia or Alzheimer's disease.

Antipsychotic medicines are classified in two groups: 'conventional' (or typical) antipsychotics and 'atypical' antipsychotics.

Conventional antipsychotic medicines have been available since the 1950s. They mainly work by changing the balance of 'neurotransmitters' in the brain, in particular reducing the effects of the neurotransmitter dopamine. A neurotransmitter is a chemical that allows nerve cells to communicate with each other. Conventional antipsychotic medicines include chlorpromazine, fluphenazine, haloperidol, perphenazine, and sulpiride, among others. Chlorpromazine and haloperidol are the most commonly used conventional antipsychotics to treat dementia-related behavioural disturbances. The licensing status of these medicines is different in different member states.

Newer antipsychotic medicines are known as 'atypical' antipsychotics as they have a slightly different mode of action to that of the conventional antipsychotics. They include aripiprazole, clozapine, paliperidone, quetiapine, risperidone, olanzapine and sertindole.

Why were these medicines reviewed?

In 2005, a review of studies (placebo controlled clinical trials) carried out with atypical antipsychotic medicines in elderly patients with dementia showed that there was an approximate 1-2% increased risk of death, compared with no treatment. It was not possible to identify from these studies what was causing this increased risk. As a result, a warning against the use of these medicines in this group of patients was added to the prescribing information.

At that time, there were no similar trials looking into the safety of the conventional antipsychotics in the elderly. There were some indicators that use was switching from atypical to typical antipsychotics. Since then, observational studies (studies looking at the effects of medicines as they are used by patients) have provided some evidence that these older medicines could also increase the risk of death in elderly patients with dementia.

¹ Article 5(3) of Regulation (EC) 726/2004, opinion on any scientific matter concerning the evaluation of medicinal products for human use

Consequently, in October 2008, the United Kingdom's (UK's) medicines regulatory agency referred the matter to the CHMP to seek its scientific opinion on this evidence. The UK asked the CHMP to give its opinion on the following issues:

- whether there is an increased risk of death with conventional antipsychotics in elderly patients with dementia;
- whether any such increase is larger than that seen with atypical antipsychotics;
- whether any such increase applies to all medicines in the class;
- whether any further studies should be carried out.

Which data has the CHMP reviewed?

The CHMP has reviewed articles reporting on the use of conventional antipsychotics in elderly patients with dementia, as published in scientific journals up to the end of August 2008.

This involved nine studies showing a small increased risk of death in patients with dementia, including two large, key studies carried out in Canada² that involved a total of over 60,000 patients receiving conventional or atypical antipsychotics. In both studies, there was an increased risk of death. In contrast, however, there were three smaller studies, involving a total of about 3,600 patients, which did not show an increase.

What are the conclusions of the CHMP?

Based on the evaluation of the data and the scientific discussion within the Pharmacovigilance Working Party and within the Committee, the CHMP concluded that:

- As with atypical antipsychotics, conventional antipsychotics are likely to be associated with a small increase in the risk of death when used in elderly patients with dementia. However, there was insufficient evidence to give a firm estimate of the precise magnitude of the risk;
- although some of the studies showed a greater risk with conventional antipsychotics than atypical antipsychotics, there is not enough evidence to confirm this trend;
- there is not enough evidence to determine whether the risk differs from one medicine to another, so the risk is assumed to apply to all medicines in the class;
- it is not possible to identify the cause of the increased risk, or the mechanism through which antipsychotic medicines may have this effect. However, it is unlikely that further clinical studies will provide firm evidence on the underlying cause or help to determine whether the risk differs from one medicine to another.

The CHMP recommended that a warning should be included in the Product Information for all conventional antipsychotics on the increased risk of death when used in elderly patients with dementia.

What are the recommendations for prescribers, carers and families?

- Doctors whose dementia patients are presenting with psychotic symptoms or aggressive behaviour are reminded that they should follow national treatment guidelines for the management of these episodes and discuss the risks and benefits of treatments as appropriate.
- The evidence of the increased risk of mortality does not provide a basis for switching between atypical and conventional antipsychotics in these patients.

What will happen next?

The CHMP opinion will be communicated to the Member States, so that they can take appropriate action at national level.

² Schneeweiss S., Setoguchi S., Brookhart A., Dormuth C., Wang P.S. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *CAMJ* 2007; 176(5): 627-632; Gill S.S., Bronskill S.E., Normand S.T., Anderson G.M., Sykora K., Lam K., Bell C.M., Lee P.E., Fischer H.D., Herrman N., Gurwitz J.H., Rochon P.A. Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med.* 2007; 146: 775-786.