Mortality risk of antipsychotic treatment in people with dementia

There may be differences in mortality risk between individual antipsychotic agents used to treat people with dementia. Patients should be monitored for adverse events in the acute treatment period, and periodic attempts to discontinue medication should be made.

Overview: In the UK there are approximately 700,000 people living with dementia, and this number is set to double over the next 30 years (Knapp et al. 2007).

The Department of Health has made dementia a national health and social care priority. Living well with dementia: a national dementia strategy was published in February 2009. It set out a vision for transforming dementia services with the aim of achieving better awareness of dementia, early diagnosis and high quality treatment at whatever stage of the illness and in whatever setting.

The strategy was followed by the publication of a report addressing the over-prescription of antipsychotic medication for people with dementia. Implementation of the 11 recommendations contained within that report is an integral part of improving the care and experience of people with dementia and their carers.

Current advice: NICE/SCIE recommend that people with dementia who develop non-cognitive symptoms or behaviour that challenges should be offered a pharmacological intervention in the first instance only if they are severely distressed or there is an immediate risk of harm to the person or others.

People with dementia with Lewy bodies, Alzheimer's disease, vascular dementia or mixed dementias with mild-to-moderate non-cognitive symptoms should not be prescribed antipsychotic drugs because of the risk of severe adverse reactions, including death.

Drug treatment may be an option to control violence, aggression or extreme agitation, the aim being to reduce the risk of violence and harm. Healthcare professionals should aim for an optimal response in which agitation or aggression is reduced without sedation.

New evidence: A retrospective cohort study using national data from the US Department of Veterans Affairs (1999-2008) examined mortality risk in outpatients with dementia during the first 6 months of an antipsychotic treatment, focusing on the medications, risperidone, olanzapine, quetiapine and haloperidol (Kales et al. 2012).

The total sample included 33,604 patients aged 65 and older, and individual drug groups were compared for 180 day mortality rates. Results showed that haloperidol was consistently associated with the highest mortality rates. However, demographics of patients given haloperidol indicate that they were older and had more comorbidities, more days in hospital, and the highest concurrent delirium diagnoses compared to those given the other medications studied. Risk of mortality for patients on haloperidol was highest in the first 30 days. For the other medications studied mortality risk was higher in the first 120 days than for the subsequent period.
Quetiapine had the lowest risk of mortality. It was thought that this could be related to its side-effect profile, or perhaps explained by patient selection. Patients with milder dementia or behavioural problems may have received this drug instead of another because there is no rapid acting form of quetiapine, so it is less likely to be used in urgent situations.

The use of valproic acid and its derivatives as an alternative to antipsychotics to address the neuropsychiatric symptoms of dementia is not without risk. The mortality risk for valproic acid was higher than that for quetiapine, but no different to that for risperidone or olanzapine. In addition its use in the elderly may be linked to fracture, somnolence and thrombocytopenia.

The researchers conclude that there may be differences in mortality risk between individual antipsychotic agents and suggest several clinical implications of a greater mortality risk for atypical antipsychotics and valproic acid and its derivatives in the first 4 months of treatment than in subsequent months. They suggest that prescribing this medication should be guided by a risk-benefit approach. Patients should be monitored for adverse events in the acute treatment period, and periodic attempts to discontinue medication should be made.

**Commentary:** "This is an interesting and useful study. Its main value is in providing further (if indirect) evidence that the excess risk of mortality in those with dementia prescribed antipsychotic medication is certainly no lower in the older "typical" antipsychotics compared with newer "atypical" antipsychotics, and is probably in fact higher.

"The study design means that there is a high likelihood of confounding by indication and contraindication which means that the relative mortality data must be interpreted with some caution. There will be bias introduced if, for example, haloperidol is selectively used to control delirium in dementia, which may be a sign of severe physical illnesses that are in turn associated with higher mortality. The provision of comparative mortality data on those with dementia but not prescribed medication would have been of major value. These findings and limitations are echoed exactly in another US database analysis of mortality in nursing homes (Huybrechts et al. 2012).

"These data are unlikely to have a major effect on the management of behavioural disturbance in dementia in the UK since haloperidol and other "typical" drugs are seldom used. However, it may well affect practice for the treatment of delirium in general hospitals where haloperidol is still used. The higher mortality, which is concentrated in the first month of treatment, might make clinicians more likely to use "atypicals" such as risperidone. The best advice remains to avoid the use of any antipsychotic in dementia unless it is absolutely necessary and non-drug treatments, including treating the cause of the delirium, have been exhausted. The finding that valproate has the same mortality associated with it as olanzapine and risperidone is of interest and shows the need for well powered trials of any compound used to treat behavioural and psychological symptoms in dementia so that risks and benefits can be assessed. We cannot assume that drugs used in dementia act the same as the drugs prescribed in those without dementia. Things are different in dementia." - Professor Subrata Banerjee, Professor of Mental Health and Ageing, King’s College London.