Medicines Evidence Commentary
commentary on important new evidence from Medicines Awareness Weekly

Alzheimer’s disease: risk of death or admission to nursing home from antipsychotics

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A US observational study has suggested that it is the symptoms of agitation and psychosis in people with Alzheimer’s disease that are associated with increased risks of admission to a nursing home and death, rather than antipsychotic medication. However, significant limitations of the study substantially limit the conclusions that can be drawn from it, and the study provides no reason to depart from the relevant NICE/SCIE guideline, MHRA advice and the Alzheimer’s Society’s best practice guide.

Overview and current advice

The harms and limited benefits of using first (typical) and second (atypical) generation antipsychotic drugs for treating dementia in people who exhibit challenging behaviours are well recognised. They have been the subject of several previous reviews and MHRA warnings and advice, collated in MeReC Rapid Review 847 and the May 2012 edition of Drug Safety Update.

In November 2009, the Department of Health’s report on the prescribing of anti-psychotic drugs to people with dementia suggested that up to a quarter of people with dementia were being prescribed antipsychotics. On average, for every 100 of such people about 20 find some benefit from antipsychotic treatment. However, each year an additional 1 out of 100 die prematurely, and a similar additional number suffer cerebrovascular adverse events (around half of which may be severe). The report stated that antipsychotics were too often used as a first-line response to behavioural difficulty in dementia, rather than as a considered second-line treatment when other non-pharmacological approaches have failed.

As discussed in the NICE key therapeutics topic document, data from the National dementia and antipsychotic prescribing audit suggest that there has been an encouraging overall reduction in the proportion of people with dementia being prescribed antipsychotics in the period 2006 to 2011. Nevertheless, although reductions in prescribing rates were seen in all English Strategic Health Authorities, there was still considerable variation in the percentage of people diagnosed with dementia prescribed an antipsychotic.

The NICE/SCIE guideline Dementia: supporting people with dementia and their carers in health and social care (NICE clinical guideline 42) gives recommendations on the care of people with all types of dementia. This includes managing behavioural and psychological symptoms of dementia. Non-cognitive symptoms and behaviour that challenges are included in the NICE quality standard on...
The NICE/SCIE guideline advises against the use of any antipsychotic for non-cognitive symptoms or challenging behaviour of dementia unless the person is severely distressed or there is an immediate risk of harm to them or others. Any use of antipsychotics should include a full discussion with the person and carers about the possible benefits and risks of treatment. The MHRA has advised that no antipsychotic (with the exception of risperidone in some circumstances) is licensed in the UK for treating behavioural and psychological symptoms of dementia. However, antipsychotics are often prescribed off-label for this purpose.

In September 2010, the Department of Health published an implementation plan for Living well with dementia: a national dementia strategy, reviewed in MeReC Rapid Review 3471. In July 2011, a best practice guide, Optimising treatment and care for people with behavioural and psychological symptoms of dementia, was produced by the Alzheimer's Society and endorsed by the Department of Health. These resources build on the NICE/SCIE guideline on dementia and include strategies to reduce inappropriate prescribing of antipsychotics. A NICE Pathway brings together all related NICE guidance and associated products on dementia in a set of interactive topic-based diagrams.

New evidence

A US observational study has explored the risk of death and admission to a nursing home associated with taking antipsychotics in people with probable Alzheimer's disease.

In this nested cohort study, participants (n=957) were drawn from those enrolled in 2 long-term Alzheimer's disease research programmes between 1983 and 2005. They were community-living and predominantly had mild or moderate Alzheimer's disease. As part of the research programmes, evaluations were repeated annually at clinic visit. In addition every 6 months between visits, a social worker contacted the person's caregiver to ascertain the person's status and medication use; an annual contact was made for those who stopped coming to clinic. The cohort excluded those with a history of schizophrenia, bipolar disorder or schizoaffective disorder, those who had undergone electroconvulsive therapy (ECT), had alcohol or drug abuse or dependency, had cancer or significant disease or an unstable medical condition.

Three Cox regression models were used to determine if exposure to antipsychotic medication (n=241, first generation antipsychotics n=138, second generation antipsychotics n=95, both n=8) was associated with death or admission to a nursing home, compared with those not exposed (n=716). Model 1 included antipsychotic exposure, age, education level, gender and MMSE score. Model 2 included the items in Model 1 plus incident stroke/transient ischaemic attack, hypertension, diabetes mellitus and heart disease, and whether or not extrapyramidal symptoms were present at baseline (as extrapyramidal symptoms can occur in people with Alzheimer's disease who have not been exposed to antipsychotics). Model 3 included the items in Models 1 and 2 plus aggression, agitation, psychosis, major depression and use of dementia medication (such as cholinesterase inhibitors).

Exposure to first generation antipsychotics was associated with a statistically significantly increased risk of admission to a nursing home in Model 1 (hazard ratio [HR] 2.21, 95% confidence interval [CI] 1.68 to 2.90, p<0.0001) and Model 2 (HR 2.27, 95% CI 1.71 to 3.01, p<0.0001). However, in Model 3 the association was not statistically significant (HR 1.30, 95% CI 0.95 to 1.79, p=0.10), whereas agitation (HR 1.35, 95% CI 1.01 to 1.79, p=0.04) and psychosis (HR 1.56, 95% CI 1.19 to 2.04, p=0.001) were both associated with admission to a statistically significant extent, although aggression was not (HR 1.26, 95% CI 0.95 to 1.69, p=0.11). Use of second generation antipsychotics was not associated with a statistically significantly increased risk in any model.

Level of education was associated with a statistically significantly increased risk of admission to a nursing home in each model, as was the presence of extrapyramidal symptoms at baseline, and development of heart disease (Models 2 and 3). MMSE score at baseline was associated with a lower risk of admission (similar in all models, for example, HR 0.95, 95% CI 0.93 to 0.97, p<0.0001), as was use of dementia medication (Model 3, HR 0.38, 95% CI 0.28 to 0.52, p<0.0001).

Use of first or second generation antipsychotics was not associated with an increased risk of death in any model, nor was aggression or agitation. However, psychosis was associated with a statistically significantly increased risk of death (Model 3, HR: 1.26, 95% CI 1.00 to 1.59, p=0.04).
The authors conclude that, after adjustment for covariates, it was the presence of psychiatric symptoms including psychosis and agitation, rather than antipsychotic exposure, that was associated with admission to a nursing home or death.

Commentary provided by the Medicines and Prescribing Centre

The behavioural and psychological problems associated with dementia can be distressing to people with the condition, their relatives and carers. Management of these problems can be very difficult and, in certain circumstances, there is no alternative but to use antipsychotic medication. This study is interesting but has several important limitations which substantially limit the conclusions that can be drawn from it.

Firstly, the original evidence for an increased risk of death associated with antipsychotics was drawn from 17 placebo-controlled clinical trials. Prospective controlled studies are accepted as providing the fairest test of interventions. Although observational studies, such as this one, can be very useful in identifying possible associations including adverse effects of medicines, they are prone to confounding, which limits the conclusions that can be drawn, and can show only association, not causation. Unlike in the setting of an RCT, in ‘real life’, treatment plans are chosen, changed, or actively not chosen in the light of individual patients’ risk factors, preferences and tolerability of or responses to other drugs. Thus observed differences in outcomes may be due to differences among the patients, not only the different treatments. The intention of the study authors was to explore what other factors might have been associated with an increased risk of admission to a nursing home or death, in addition to or instead of exposure to antipsychotics. However, this is necessarily both exploratory and selective. We do not know the effects of factors that were not selected for inclusion in the models. In addition, for example, although level of education was associated with a small but highly statistically significant increased risk of admission to a nursing home and to death, the authors do not discuss this.

Secondly, it is important to note that ‘no statistically significant difference’ does not necessarily mean there is truly no difference between the interventions, just that a difference has not been shown ‘beyond reasonable doubt’. Although this study included 957 people over 22 years, only about a quarter of them were exposed to antipsychotics at all, and no information is provided about the extent of exposure, for example in terms of person-years. The Department of Health report estimated the excess risk of death associated with antipsychotics as around 1 per 100 person-years: thus the study may not have had sufficient statistical power to detect true effects to a statistically significant extent.

Finally, the authors concede that if medication initiation and death both occurred within the 6 months between contacts, use of antipsychotics may not have been detected. Thus, such participants would have been classified as dying unexposed to antipsychotics, biasing the results and tending to reduce the observed hazard ratios.

In summary, this study provides no reason to depart from the NICE/SCIE guideline, MHRA advice and the Alzheimer’s Society’s best practice guide.

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References

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