

# New warnings on the use of antipsychotic agents in the elderly with dementia

AVP Mackay

Board Member, Medicines and Healthcare Products Regulatory Agency, UK

Published online March 2009

Correspondence to AVP Mackay,  
Tigh-an-Rudha, Ardrishaig,  
Argyll PA30 8ER, UK

tel. +44 (0)1546 60 3272  
e-mail angus.mackay@nhs.net

**ABSTRACT** The use of antipsychotic drugs is common in the care of the elderly with dementia and associated behavioural problems, but until recently none of these agents had marketing authorisation for this indication. Medicines regulators have recognised this off-label use and issued warnings about the special risks posed to the elderly. The increased risk of stroke has been reflected in product information for five years, but recent attention has shifted to mortality risk. Initially confined to new-generation atypical antipsychotics in which an approximately 1.6–1.7-fold increase in mortality has been demonstrated, recent evidence points to a risk of at least similar magnitude with older-generation typical agents, prompting warnings by UK and US medicines regulators about an increased risk of death associated with the entire class, atypical and typical.

**DECLARATION OF INTERESTS** The author has had no involvement in any of the regulatory decisions reviewed.

It has been estimated that more than 90% of patients with dementia have an associated behavioural disturbance.<sup>1</sup> Despite a limited evidence base,<sup>2</sup> the use of antipsychotic agents for the control of difficult behaviour in the elderly with dementia is traditional, particularly for those with more advanced dementia and behavioural problems in long-term residential care. While current guidelines recommend that difficult behaviours are managed where possible by non-pharmacological techniques, failure to respond and/or inadequate staffing may prompt the prescription of an antipsychotic. Here, the clinician is faced with a problem. Until recently no antipsychotic agent was licensed in the UK specifically for dementia-related psychosis or behavioural disturbance in the elderly with dementia. In October 2008 risperidone (Risperdal), an atypical agent, was granted marketing authorisation for the narrow indication of persistent aggression in patients with moderate to severe Alzheimer's dementia, where the patient puts themselves or others at risk of harm, for periods of up to six weeks.

The use of antipsychotics for behavioural control in the elderly has prompted outrage in the media over the years, and within the last five years certain specific risks have prompted regulatory action on both sides of the Atlantic. Warnings about an increased risk of stroke have recently been joined by warnings of an increased risk of death from all classes of antipsychotic used in the elderly with dementia. This short review considers the evidence behind these regulatory decisions.

## RISKS

In 2004 the Committee on the Safety of Medicines advised the UK regulator, the Medicines and Healthcare Products Regulatory Agency (MHRA), of a clear increase in the risk of stroke with the use of risperidone or olanzapine in the elderly with dementia. A year later, a Europe-wide review concluded that this risk could not be excluded for other antipsychotic agents, whether typical

or atypical, and the product information for all antipsychotics was updated to include a class warning.<sup>3</sup>

In 2005 the US Food and Drugs Administration (FDA) issued a warning that the treatment of behavioural disorder with atypicals in the elderly with dementia is associated with an increased risk of death. This was based on 17 placebo-controlled trials (involving more than 5,000 patients), of which 15 showed a numerical increase of about 1.6–1.7-fold in mortality associated with four agents whose structures cover all three chemical classes of atypical. A pharmacological class effect was therefore inferred. In the same year, regulators in the UK and the rest of Europe came to similar conclusions, and product information was updated to include warnings on the increased risk of mortality, and in the case of risperidone an additional increased risk of death when co-prescribed with furosemide. Warnings were not extended to typical antipsychotics at that time in view of lack of evidence. Since then, concern has been felt over the possibility that prescribers would switch from atypical to typical antipsychotics in the elderly with dementia, in the absence of clear evidence of risk, despite the lack of evidence of absence of risk.

Some observational studies have since been published which, together, provide a clearer basis for a regulatory decision about first-generation typical drugs. In June 2008 the FDA issued an alert to healthcare professionals in the US. The UK Department of Health is currently reviewing the situation with regard to the prescription of antipsychotic medication for people with dementia of all ages. An important input to this will be the recent reviews conducted by the MHRA in the UK and the Commission on Medicinal Products for Human Use (CHMP) for the European Medicines Evaluation Agency (EMA) in late 2008. As a result of its own thorough assessment of the evidence, the UK presented to the EMA a request for a CHMP opinion on the risks of traditional antipsychotics when used in elderly people with dementia. The CHMP assessment report, for which the UK review was

the major ingredient, concluded that the increased mortality in elderly people with dementia is likely to be a class effect applying to all antipsychotic drugs.

## THE EVIDENCE

Two publications were identified as pivotal by the FDA; both described record-linkage, observational studies of large samples conducted in Canada. Schneeweiss et al.<sup>4</sup> examined a cohort of more than 37,000 elderly people, aged 65 or older, in British Columbia who had received a first prescription of an oral antipsychotic (either typical or atypical) over a nine-year period ending in 2004. Patients were identified by a Personal Health Number, and the outcome of interest was all-cause mortality over a 180-day period of drug exposure. Some 12% had a recorded diagnosis of dementia; 50% had other psychiatric diagnoses. The unadjusted mortality ratio for typical compared with atypical was 1.47 (95% CI 1.39–1.56), rising to 1.67 at higher doses. The authors concluded that patients prescribed a typical antipsychotic had a 32% greater dose-dependent risk of death within the first 180 days of treatment than patients taking an atypical drug. Placing this magnitude of risk in perspective, all measured health conditions except congestive cardiac failure and HIV infection conferred smaller adjusted mortality rate ratios in these analyses. An extensive list of potential confounders was drawn up in an attempt to control for possible predisposing factors other than antipsychotic medication, but it was not possible, for example, to exclude the possibility of a systematic preference by the prescribing physician for a typical agent in patients with a type or severity of dementia, or other medical condition, that might independently have increased the risk of death. Cause-specific mortality data were not available.

The other Canadian study, from Gill et al.,<sup>5</sup> used record-linkage data across four healthcare databases in Ontario to identify a cohort of more than 27,000 people aged 66 or older, all with a diagnosis of dementia, in the five-year period ending March 2002. Subjects receiving an antipsychotic had all begun use during that period and all-cause mortality was evaluated at intervals up to 180 days after first prescription. Groups receiving either a traditional or an atypical antipsychotic were analysed as matched pairs divided between those living in the community and those in long-term residential care. As early as 30 days into treatment, the death hazard ratio for those receiving atypical drugs compared with those on no antipsychotic were 1.3 (95% CI, 1.02–1.70) for those in the community and 1.6 (95% CI 1.15–2.07) for those in residential care. The hazard ratios for typical versus atypical agents were 1.6 (95% CI 1.19–2.02) for community subjects and 1.3 (95% CI 1.04–1.53) for residential subjects. Similar figures were observed at the later time points. Propensity score matching was used to balance groups on measured co-variables such as other medical diagnoses and use of other drugs, but this device could not take into account unknown or unmeasured confounders. Sensitivity analysis,

conducted to quantify the impact of hypothetical unmeasured confounders, showed that the atypical risk could be rendered statistically non-significant by the introduction of an unmeasured confounder 'moderately related to mortality', whereas the increased risk with typical agents would only have been influenced by a 'strong' confounder. As with the Schneeweiss study, there were no data on specific causes of death although, on the basis of a literature review, the authors suggested that these would most likely comprise cardiac deaths, aspiration pneumonia, venous thromboembolism, cerebrovascular events and initiating sequences such as falls. The authors conceded that interpretations other than a causal relationship with anti-psychotic medication are possible, such as preferential prescription depending on severity of dementia or the care setting.

The recent wave of observational studies consists of 12 publications including the two pivotal studies above. Of the ten other reports, seven concluded that an increased risk was associated with the use of typical antipsychotics. Hollis et al.<sup>6</sup> found haloperidol to be associated with highest risk among a group of atypical and typical agents, but the result was possibly confounded by medical illness. A subsequent analysis by Hollis and colleagues of part of that earlier study found that chlorpromazine, followed by haloperidol, were associated with the greatest risk relative to olanzapine in residents of residential homes.<sup>7</sup> Three small studies<sup>8–10</sup> found neither atypical nor conventional antipsychotics to be associated with increased mortality in the elderly population, but their interpretation is hampered by methodological problems including a sample with a low percentage of dementia sufferers, failure to study all-cause mortality<sup>8</sup> and uncertainty over actual antipsychotic exposure.<sup>9</sup> While in most of the studies considered by the regulators the outcome was all-cause mortality, Kales et al.<sup>11</sup> did examine specific causes of death and found no apparent association with cardiotoxic, vascular or immunological mechanisms, but rather with dementia-related causes, a conclusion at variance with the hypothetical suggestions from Gill and colleagues.<sup>5</sup>

Two studies have been published since the regulatory reviews. One points to cardiotoxicity as a cause of death on antipsychotics,<sup>12</sup> the other suggests an alarming reduction in long-term survival in an Alzheimer group receiving both typical and atypical antipsychotics.<sup>13</sup> Ray et al.<sup>12</sup> used Medicaid records of more than 40,000 adults (but not specifically elderly) in Tennessee and found that current users of either typical or atypical drugs had a two-fold increased risk of sudden cardiac death that was dose-dependent – rising to five-fold in those on thioridazine at high dose (300 mg or more) – a risk that disappeared in former users. Ballard et al.<sup>13</sup> have reported the first long-term prospective study of mortality risk in elderly patients receiving oral antipsychotics. A cohort of 165 Alzheimer patients in UK residential care facilities were randomised either to remain on an oral antipsychotic (mainly risperidone or haloperidol) or switch to matched placebo, and followed up for up to 54

months. One-year survival was 7% less in those remaining on antipsychotics, but the most striking findings emerged at later time points: for example 36-month survival was 59% in those randomised to placebo, and 30% in those on antipsychotics. The small sample size precluded any conclusions about excessively increased mortality due to cerebrovascular or cardiovascular causes. However, this study was well designed, executed and analysed and the results indicate a persistent risk of death associated with the chronic use of antipsychotics in the elderly with dementia. These findings have important implications for clinical practice and validate the earlier judgements of the regulatory authorities.

In contrast to the evidence for raised mortality risk with atypicals from randomised controlled trials, all studies upon which the US and European regulators have based their conclusions about the older drugs are observational and acknowledge the risk to interpretation from unknown and/or unmeasured confounders. Many of the methodological problems are common to all of these studies, including unmeasured bias due to unmeasured differences in illness burden such as the type and severity of the disorder for which an antipsychotic was being given. Some, but by no means all, studies were confined to elderly dementia sufferers. It is possible that there was an unknown imbalance of co-interventions that could have amplified the risk of death attributable to medication. There may have been preferential prescription of a typical agent for those patients more likely to die. In none of these studies or the UK or European reviews has any distinction been possible between the various types of dementia. Attention has been drawn to the special vulnerability of patients with Lewy body dementia to sudden death on antipsychotics by McKeith et al.<sup>14</sup> and unbalanced distribution of this, and multi-infarct dementia, could have affected the outcome. Other interpretative problems include the lack of control for dose of antipsychotic in most studies, and where it was, drug exposure was estimated merely from prescription fills. The pivotal studies used data from relatively short periods of exposure to antipsychotics. The UK interventional study,<sup>13</sup> published after the regulatory reviews, is highly noteworthy in the robustness of its design, lengthy follow-up and finding of an ongoing risk to life expectancy during prolonged exposure.

## CONCLUSIONS

Attribution of causality is always difficult with observational studies. To be fair, the authors generally, and certainly of the pivotal studies, were at pains to take account of known confounders and acknowledge the inherent difficulties with interpretation. The international

## REFERENCES

- 1 Ballard C, Oyebode F. Psychotic symptoms in patients with dementia. *Int J Geriatr* 1995; 142:202–11.
- 2 Ballard C, Howard R. Neuroleptic drugs in dementia; benefits and harm. *Nat Rev Neurosci* 2006; 7:492–500.
- 3 MHRA. *Safety warnings and messages for medicines: Atypical antipsychotic*

judgement on older, conventional, antipsychotics is cautious but clear: While taken individually, generalisation from each study is possibly unwarranted; taken together the evidence for an increased risk of death with traditional antipsychotics is sufficiently strong not to ignore.

While much of the evidence suggests an even greater risk of death with traditional antipsychotics over atypical agents, the regulatory view is that no such conclusion can be drawn due to methodological limitations, nor could any conclusion be drawn as to whether the risk differs between individual antipsychotics or between care settings. To quote from the CHMP opinion: 'Until and unless better evidence becomes available, it cannot be excluded that the increased risk applies to all products of the class. At present, there is no clear mechanistic basis for the observed increased risk of mortality, and further data would be needed to explore this.'<sup>15</sup> That would seem to be a balanced and defensible point of view at this time.

Further definition of the mortality risk with traditional agents, and of the underlying mechanism(s), may be difficult, however, due to ethical objections to large randomised trials, and the fact that commercial funding is unlikely for research into older drugs of generic status. All antipsychotics are currently subject to warnings about increased risks of stroke and death, and only risperidone has marketing authorisation in the UK for the tightly defined indication of short-term treatment of persistent aggression in dementia of Alzheimer type.

Recent Commission on Human Medicines advice on antipsychotics, and specifically the atypicals risperidone and olanzapine, for the treatment of behavioural disturbances associated with dementia is unequivocal. The risk/benefit balance should be carefully assessed in each case with consideration of the known increased mortality rate associated with antipsychotic treatment in the elderly. Olanzapine should not be used to treat behavioural problems, and risperidone should only be prescribed for aggression in dementia of Alzheimer type.

The recently published National Dementia Strategy for England<sup>16</sup> states the need to avoid inappropriate use of antipsychotics in people with dementia. Warning of mortality risk is now included in the prescribing information for conventional antipsychotics, but off-label use will doubtless continue. As ever, prescribing clinicians must judge the benefits and risks in each case, but these recent regulatory statements seem well founded and clearly increase the magnitude of the risk that must be taken into account.

*drugs and stroke*. 2004. Available from: <http://www.mhra.gov.uk>

- 4 Schneeweiss S, Setoguchi S, Brookhart A et al. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *Can Med Assoc J* 2007; 176(5):627–32.
- 5 Gill SS, Bronskill SE, Normand ST et al. Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med* 2007; 146:775–86.

- 6 Hollis J, Touyz S, Grayson D et al. Antipsychotic medication dispensing and associated odds ratios of death in elderly veterans and war widows, 2001. *Am J Psychiatry* 2006; 40:981–6.
- 7 Hollis J, Forrester L, Brodaty H et al. Risk of death associated with antipsychotic drug dispensing in residential aged care facilities. *Aust N Z J Psychiatry* 2007; 41:751–8.
- 8 Barak Y, Baruch L, Mazed D et al. Morbidity with antipsychotic medications in elderly psychiatric inpatients. *Am J Geriatr Psychiatry* 2007; 15:354–6.
- 9 Raivio M, Laurila J, Strandberg TE et al. Neither atypical nor conventional antipsychotics increase mortality or hospital admissions among elderly patients with dementia: a two-year prospective study. *Am J Geriatr Psychiatry* 2007; 15(5):416–24.
- 10 Suh G, Shah A. Effect of antipsychotics on mortality in elderly patients with dementia: a 1-year prospective study in a nursing home. *Int Psychogeriatr* 2005; 17(3): 429–41.
- 11 Kales HC, Valenstein M, Kim HM et al. Mortality risk in patients with dementia treated with antipsychotics versus other psychiatric medications. *Am J Psychiatry* 2007; 164:1568–76.
- 12 Ray WA, Chung CP, Murray KT et al. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med* 2009; 360(3):225–35.
- 13 Ballard C, Hanney ML, Theodoulou M et al. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. *Lancet Neurol* 2009; 8(2):151–7.
- 14 McKeith IG, Dickson DW, Lowe J et al. Diagnosis and management of dementia with Lewy bodies. *Neurology* 2005; 65:1863–72.
- 15 European Medicines Evaluation Agency. *Opinion of the Committee for Medicinal Products for Human Use pursuant to Article 5(3) of regulation (EC) no 726/2004, on conventional antipsychotics*. London: EMEA; 2008.
- 16 Department of Health. *Living well with dementia; a national dementia strategy*. London: DOH; 2009.

## Clinical opinions

# Experimental medicines in multiple sclerosis and compassionate use

JS Kelly

Editor, Clinical Section, *Journal of the Royal College of Physicians of Edinburgh, Edinburgh, UK*

**TITLE** Alemtuzumab vs. Interferon beta-1a in early multiple sclerosis

**AUTHORS** Coles AJ, Compston DAS, Selmaj KW et al.

**JOURNAL** *N Eng J Med* 2008; 359:1786–801.

**DECLARATION OF INTERESTS** The author has shares in pharmaceutical companies and has in the past received grants and fees from Fujisawa.

Published online March 2009

Correspondence to JS Kelly, Division of Neuroscience, University of Edinburgh, 1 George Square, Edinburgh EH8 9JZ, UK

tel. +44 (0)131 444 0512  
e-mail J.S.Kelly@ed.ac.uk

## SUMMARY

Although multiple sclerosis usually begins as a relapsing-remitting disease, for most patients it appears sooner or later to be a progressive neurological disorder. The relapsing phases are usually heralded by focal bursts of inflammation in the white matter of the spinal cord and brain, while during the progressive phase there is a slow, relentless axonal and neuronal loss. The focal bursts of inflammation not only result in demyelination, incomplete remyelination and gliosis but are believed to sensitise surviving axons to additional insults at a later date, and in essence shorten their life span. Thus although it is believed that the main cause of loss of mobility is the progressive disease, the main thrust of treatment is to abort or reduce the inflammatory relapses and, indirectly, disease progression. In any event, the only active drugs available at present are directed against the relapses. Although these drugs, interferons and glatiramer acetate, are strikingly effective in some patients, they at best reduce the relapse rate by only one third. Hereby lies the motivation of a number of trialists in this field to test compounds that are known to limit the activity of the immune system yet are certain to have serious or even extreme side effects.

In this paper Coles et al. report on a randomised, blinded phase 2 trial on 334 previously untreated patients with

early relapsing-remitting multiple sclerosis with a disease duration of three years or less. The 111 patients in one arm of the trial received subcutaneous injections of beta-1 interferon three times per week, and the 223 in the other an annual intravenous cycle of three or five days of alemtuzumab (12 or 24 mg daily) for 36 months. The trial of alemtuzumab was suspended in September 2005 after three patients developed immune thrombocytopenic purpura, one of whom died. Three more patients with this adverse reaction were identified later in 2005 and 2006 after the trial ended. One patient in the beta-1 interferon group developed asymptomatic, chronic immune thrombocytopenic purpura.

The results, however, were dramatic. As compared with beta-1 interferon, alemtuzumab reduced the risk of sustained disability or relapse by 71% and 74% respectively, and these effects were independent of dose. The number of patients needing to be treated with alemtuzumab instead of beta-1 interferon during a three-year period to avoid a disability event was 5.8 and, rather strikingly, 3.5 to avoid a relapse. These differences were mirrored by a significant difference in changes in brain volume between the two groups measured by T1-weighted magnetic resonance imaging at 12 and 36 months, with a reduction of 0.2% in brain volume in the patients receiving beta-1 interferon and an increase of 0.9% in those treated with alemtuzumab. The