How safe are antipsychotics in dementia?

Around 800,000 people in the UK have dementia, about 80% of whom will have behavioural changes or psychological symptoms in the course of the illness.1 Such features lower quality of life for both patients and carers, and often result in transfer to residential care and higher costs.2-5 Currently, no drugs are licensed in the UK specifically for behavioural changes and psychological symptoms in patients with dementia. Nevertheless, antipsychotic medications have been used in people with dementia, both for psychotic symptoms and also for less specific problems such as agitation and aggression. There have been long-standing concerns about the inappropriate use of these drugs in such settings.6 In 2004, following worries over an increased likelihood of stroke with risperidone and olanzapine, the former UK Committee on Safety of Medicines (CSM) advised that these drugs “should not be used for the treatment of behavioural symptoms of dementia”.7 However, this led to reports of unsuitable interpretation of the guidance, with groups of patients having their medication withdrawn inappropriately or being switched to other, potentially more harmful, drugs.6 Here we assess the safety of antipsychotic medication in people with dementia.

What clinical features?

Alzheimer’s disease is the commonest type of dementia (being the underlying problem in around 60% of those affected), followed by vascular dementia (20–25%) and dementia with Lewy bodies (10–15%).1,8 Many patients with such conditions develop behavioural and psychological symptoms of dementia (BPSD), also known as neuropsychiatric symptoms, which have been defined as “signs and symptoms of disturbed perception, thought content, mood or behaviour that frequently occur in patients with dementia”.9 The symptoms can include anxiety, depressed mood, hallucinations and delusions, as well as behavioural symptoms such as aggression, screaming, restlessness, agitation, wandering, culturally inappropriate behaviours, sexual disinhibition, hoarding and cursing.9 Psychotic symptoms (e.g. delusions and hallucinations) occur in 30–50% of all patients with dementia,10 and in about 80% of patients with dementia with Lewy bodies.11

Treatment options

Guidelines from the National Institute for Health and Clinical Excellence (NICE) advise that people with dementia who develop non-cognitive symptoms (e.g. neuropsychiatric symptoms) that cause them significant distress or who develop challenging behaviour should be offered a comprehensive assessment at an early opportunity to establish the factors likely to generate, aggravate or improve the problem.12 For each patient, an individually tailored care plan should be developed, recorded in the notes and reviewed regularly.12 The generally recommended practice for such symptoms of dementia is first to try non-drug methods (e.g. behavioural and psychological interventions, occupational activities, environmental approaches), unless the patient is severely distressed or there is an immediate risk of harm to themselves or others.8,12 However, published studies of such methods have not provided convincing evidence of either benefit or lack of benefit.8,12

The NICE guidelines recommend that people with dementia with mild-to-moderate non-cognitive symptoms should not be prescribed antipsychotic drugs. Also, those with severe non-cognitive symptoms (i.e. psychosis and/or agitation behaviour causing significant distress) should only be offered treatment with an antipsychotic drug if specific conditions have been met (e.g. after assessment of cerebrovascular risk factors and changes in cognition; after target symptoms have been identified, quantified and documented; after comorbid conditions have been considered).12 The guidelines also advise that healthcare professionals who use medication in the management of people with dementia who are violent, aggressive or extremely agitated should be trained in the correct use of drugs for behavioural control (e.g. antipsychotics) and be able to assess the risks of such use.12
How safe are antipsychotics in dementia?

**Conventional antipsychotic drugs**

**Clinical efficacy**

Traditionally, conventional (first-generation, typical) antipsychotic drugs such as chlorpromazine and haloperidol have been used to treat patients with behavioural problems associated with dementia. In 2003, we concluded that “there is little convincing evidence from published randomised controlled studies to support the widespread use of [conventional] antipsychotic drugs” for such problems.

**Unwanted effects**

Conventional antipsychotic drugs are antagonists of dopamine D₂ receptors and blockade of these receptors in the nigrostriatal pathway in the CNS leads to extrapyramidal unwanted effects (e.g. parkinsonism, akathisia, acute dystonia, tardive dyskinesia). In turn, such effects may lead to falls due to problems with balance, and weight loss due to problems with eating and swallowing.

Older patients are particularly at risk of developing tardive dyskinesia, which may be irreversible (even if therapy is stopped) and unresponsive to treatment. Patients with dementia with Lewy bodies are particularly susceptible to severe antipsychotic sensitivity reactions, which may be life-threatening.

Other unwanted effects of conventional antipsychotics include drowsiness; hypotension (which increases the likelihood of falls); interference with temperature regulation; antimuscarinic effects (e.g. dry mouth, blurred vision, urinary retention, constipation); ECG changes with reports of sudden death; and, rarely, neuroleptic malignant syndrome. Research has suggested that conventional antipsychotics might exacerbate cognitive decline, possibly due to effects on dopaminergic, cholinergic and histaminic pathways; however, no causal effect has been established.

**Atypical antipsychotic drugs**

**Clinical efficacy**

One systematic review looked at the role of atypical (second-generation) antipsychotics in the management of patients with behavioural and psychological symptoms of dementia. It included four double-blind randomised controlled trials of risperidone (three vs. placebo, one vs. haloperidol) and one of olanzapine (vs. placebo), involving a total of 1,570 patients (around 76% with Alzheimer’s disease). The reviewers concluded that “limited evidence supports the perception of improved efficacy and adverse event profiles [with atypical antipsychotics] compared with typical antipsychotic drugs”.

Another systematic review, including 16 randomised placebo-controlled trials (lasting between 6 and 26 weeks) and a total of 5,324 patients, assessed the effectiveness of atypical antipsychotics for the treatment of aggression, agitation or psychosis in people with Alzheimer’s disease. Data were pooled only from the nine trials considered to have sufficient data to contribute to a meta-analysis. The primary outcome measure in most of the studies was change in the overall behavioural symptom rating scale used in the particular study. The reviewers found that there was a significant reduction in aggression with risperidone and olanzapine compared to placebo (p=0.007 and p=0.03, respectively) and in psychosis with risperidone (vs. placebo, p=0.01). They also concluded there were insufficient data to undertake a meaningful evaluation of the efficacy of any of the other atypical antipsychotics.

A third systematic review, including 15 randomised placebo-controlled double-blind parallel-group trials and a total of 5,110 patients, assessed the evidence for efficacy and adverse effects of atypical antipsychotics for people with dementia. Pooled data for the individual drugs found evidence for symptomatic efficacy with aripiprazole and risperidone, but not for olanzapine. There was judged to be a lack of evidence for or against quetiapine.

**Concerns about cerebrovascular events**

In 2002, Health Canada (Canada’s federal department of health) and the pharmaceutical company Janssen-Ortho jointly published a warning about the use of risperidone for patients with behavioural and psychological symptoms of dementia, following a study that identified an increased rate of “cerebrovascular adverse events” with the drug (9% of patients taking risperidone vs. 1.8% taking placebo). Similarly, in 2004, the UK CSM advised “that risperidone and olanzapine should not be used for the treatment of behavioural symptoms of dementia”.

The CSM decision

The CSM based its decision on a summary of clinical data on cerebrovascular adverse events from four randomised controlled trials of risperidone (0.5–2mg daily) involving a total of 1,779 patients with dementia; this summary was produced by the Medicines and Healthcare products Regulatory Agency (MHRA). Cerebrovascular adverse events were defined as all adverse events classified by the World Health Organization as cerebrovascular disorder (i.e. stroke, transient ischaemic attack, cerebrovascular disorder, cerebrovascular accident, cerebral infarct, cerebral ischaemia and cerebrovascular disturbance). The trials lasted 8–12 weeks, so were relatively short-term. There were a total of 33 cerebrovascular adverse events with risperidone and 8 with placebo. The overall odds ratio (OR) for events in the four studies was calculated as 3.32 (95% CI 1.43–7.70). This translates as 1 treatment-related cerebrovascular adverse event for every 37 patients treated with risperidone for 8–12 weeks. There was no evidence of higher all-cause mortality in patients taking risperidone as compared to placebo within the study period.
Based on this analysis, the CSM warned clinicians that the risk of stroke in elderly patients with dementia was approximately three times higher with risperidone than with placebo, and that a pooled analysis of the olanzapine data showed a similar increased risk of stroke, and a twofold increase in all-cause mortality. The increased risk was not confined to those patients with underlying vascular disease. The CSM stated that the size of the risk is sufficient to outweigh likely benefits in the treatment of patients with behavioural disturbances associated with dementia. Therefore, it advised that risperidone and olanzapine should not be used in the treatment of patients with such symptoms. It also pointed out that olanzapine was not licensed for the management of patients with acute psychoses. However, the CSM stated that risperidone could be used on a short-term basis, under specialist advice, in the management of elderly patients with acute psychotic conditions as well as dementia. Clinicians were advised to consider cerebrovascular risk factors before prescribing, and that patients with dementia who were currently being treated with an atypical antipsychotic drug should have their treatment reviewed. On the basis of the data considered by the CSM, action was then taken throughout the European Union by regulatory authorities to warn about the potential for risperidone and olanzapine to increase the likelihood of cerebrovascular adverse events. At the time, it was felt that there was not sufficient evidence for or against an increased risk from clinical trials to include other atypical or conventional antipsychotics in this advice. In 2005, the US Food and Drug Administration advised that atypical antipsychotics were not approved for the treatment of such symptoms.

Further guidance

More recently, the European Pharmacovigilance Working Party has considered data from an MHRA-initiated epidemiological study using the General Practice Research Database, along with two other epidemiological studies published between 2004 and 2005 that addressed the issue of the risk of stroke in older patients associated with conventional and atypical antipsychotics. The Working Party provides recommendations to the Committee for Medicinal Products for Human Use on all matters relating directly or indirectly to pharmacovigilance. On the observational data it considered, the Working Party concluded that the likelihood of cerebrovascular events associated with conventional antipsychotics was not significantly different from that with olanzapine and risperidone. It also pointed out the inclusion of warnings about a possible increased risk of cerebrovascular adverse events in patients with dementia in the SPCs [summaries of product characteristics] for all conventional and atypical antipsychotics.

Recent safety evidence on atypicals

Since the guidance issued by regulatory authorities, new evidence has emerged regarding the safety of antipsychotic drugs in patients with dementia.

Observational studies

A retrospective cohort study of 22,890 older patients (mean age 83 years) newly commenced on antipsychotics (9,142 on conventional, 13,748 on atypical), but not necessarily for dementia, suggested that risk of death associated with treatment with conventional antipsychotics compared to atypicals changed over time, and that conventional drugs carried a higher risk of death than atypical medications at all time intervals studied. The relative risk (and 95% CI) associated with conventional drugs compared to atypicals at 40 days after treatment was started was 1.56 (1.37–1.78); at 40–79 days 1.37 (1.19–1.59); and at 80–180 days 1.27 (1.14–1.41).

Another retrospective cohort study, involving 27,259 matched pairs of older adults with dementia (mean age around 83 years), looked at the association between treatment with antipsychotics (either conventional or atypical) and all-cause mortality in older patients with dementia, living either in the community or long-term care. The results suggested that new use of antipsychotics was associated with a significant increase in the risk of death at 30 days compared to non-use (community-dwelling cohort: adjusted hazard ratio [HR] 1.31, 95% CI 1.02–1.70; long-term care cohort: adjusted HR 1.55, 95% CI 1.02–1.70). Also, compared with atypical antipsychotics, conventional antipsychotics were associated with a higher risk for death at 30 days (community-dwelling cohort: adjusted HR 1.55, 95% CI 1.19–2.02; long-term care cohort: adjusted HR 1.26, 95% CI 1.04–1.53), and 180 days (community-dwelling cohort: HR 1.23, 95% CI 1.00–1.50; long-term care cohort: adjusted HR 1.27, 95% CI 1.09–1.48). The researchers listed several limitations of the study, including the following: information on causes of death was not available; many patients did not continue their treatment beyond 1 month; and unmeasured confounders could have affected associations.

Randomised controlled evidence

A 36-week double-blind randomised controlled trial has compared olanzapine, quetiapine, risperidone and placebo, in the treatment of 421 community-dwelling patients (mean age around 78 years) with Alzheimer’s disease and psychosis, agitation or aggression sufficiently severe and persistent to warrant drug therapy in the opinion of the treating clinician. The primary outcome measure was the time from initial treatment to discontinuation of treatment for any reason. The secondary outcome measure was attainment of any improvement on the Clinical Global Impression of Change (CGIC) scale at 12 weeks. The trial was designed as a pragmatic study, in which treating clinicians were permitted to change the dosages of medication as they deemed necessary, or discontinue medication if it was poorly tolerated or ineffective.

There were no significant differences between groups with regard to the time to discontinuation of treatment for any reason (median around 5–8 weeks), and around half the patients were taken off their study drugs within 8 weeks. Discontinuation due to lack of efficacy occurred sooner with placebo (9.0 weeks) and quetiapine (9.1 weeks) than with risperidone (26.7 weeks, vs. placebo p<0.01) and olanzapine (22.1 weeks, vs. placebo p<0.001). The rate of discontinuation due to intolerability was higher with risperidone (18% of patients, p=0.006), olanzapine...
reviews, there was a twofold increased likelihood of such placebo.\textsuperscript{41} Three trials were of aripiprazole, five of olanzapine, three of quetiapine and five of risperidone. Atypical antipsychotics were associated with an increased risk of serious adverse cerebrovascular events (including stroke) among patients given risperidone compared to placebo.\textsuperscript{42} The number (and rate) of deaths in the various groups was 1 (1%) in the olanzapine group, 1 (1%) in the risperidone group and 1 (1%) in the placebo group (\textit{p}=0.92, overall comparison). The number (rate) of deaths in the various groups was 1 (1%) in the olanzapine group, 3 (3%) with quetiapine, 1 (1%) with risperidone and 3 (2%) with placebo (\textit{p}=0.68, overall comparison). However, it is unlikely that the trial was powered to detect statistically significant differences in stroke or death.

Pooled data
A systematic review assessed the evidence for increased mortality from atypical antipsychotic drug treatment for people with dementia, pooling data from 15 trials (nine unpublished) that included a total of 3,353 patients randomised to a study drug and 1,757 randomised to placebo.\textsuperscript{41} Three trials were of aripiprazole, five of olanzapine, three of quetiapine and five of risperidone. Atypical antipsychotics were associated with an increased risk of death (118 deaths vs. 40 deaths with placebo, OR 1.54, 95% CI 1.06\textendash;2.23; \textit{p}=0.02). The death and dropout rates were similar in the published and unpublished trials. The results for the individual drugs were broadly similar, indicating that the increased mortality risk is likely to be a class effect, rather than being restricted to any one individual drug. There was no difference in risk in terms of diagnosis or severity of illness.

In one of the systematic reviews discussed above, risperidone was associated with an almost fourfold increased likelihood of serious adverse cerebrovascular events (including stroke) among patients given risperidone compared to placebo; 37 events in the 1,175 patients on risperidone and 8 in the 779 on placebo (3.15\% vs. 1.03\%, OR 3.64, 95\% CI 1.72\textendash;7.69; \textit{p}=0.0007); relevant data for olanzapine were not available to the reviewers.\textsuperscript{20} In another of the reviews, there was a twofold increased likelihood of such an event with the atypical antipsychotics overall; 63 events in the 3,327 patients on a drug and 16 in the 1,728 on placebo (1.9\% vs. 0.9\% with placebo, OR 2.13, 95\% CI 1.20\textendash;3.75; \textit{p}=0.009), and just over a threefold increased risk with risperidone (3.1\% vs. 1.0\% with placebo, OR 3.43, 95\% CI 1.60\textendash;7.32; \textit{p}=0.001).\textsuperscript{21}

Practical implications
Non-drug approaches should be considered first in a patient with behavioural and psychological symptoms of dementia, unless the individual is severely distressed or there is an immediate risk of harm to themselves or others. Where possible, carers should be involved in creating an individualised treatment plan. If treatment with an antipsychotic is being considered, the clinician should talk with the patient and carers about the rationale for its use and the possible risks and benefits involved. Medication should be chosen on an individual basis, taking into account symptoms, interactions with other medications, previous response to medications and any accompanying medical conditions and cerebrovascular risk factors. A decision to start an antipsychotic drug should be adequately documented, with the factors considered in making the decision also clearly recorded.\textsuperscript{6}

If used, antipsychotic therapy should be instigated at a low dose, and adjusted according to clinical response.\textsuperscript{8} The patient should be monitored for extrapyramidal effects, over-sedation and effects on cognition. Blood pressure, blood glucose, weight and central obesity should also be monitored. Individual symptoms often peak at one stage in the illness and may then decline. Evidence suggests that antipsychotic medication can be withdrawn if the patient has been symptom-free for at least 3 months, so it is important that the prescription is reviewed regularly.\textsuperscript{6} Where treatment is to be withdrawn, it is prudent to do this gradually. In some patients, it may be necessary to continue antipsychotic medication long term; the reasons for this should be clearly documented.\textsuperscript{6}

Conclusion
Behavioural and psychological symptoms are common and distressing features of dementia. The recommended practice for treating a patient with such symptoms is to try non-drug methods first, unless the person is severely distressed or there is an immediate risk of harm to themselves or others. In those with severe non-cognitive symptoms (psychosis and/or agitation) treating antipsychotic medication may be appropriate, but only after specific conditions have been met (e.g. target symptoms identified, comorbid conditions considered). Published evidence suggests that conventional and atypical antipsychotic drugs are similarly effective, but have different unwanted effects profiles.

The potential benefit of antipsychotic drug therapy might be outweighed by the significant cerebrovascular risk it carries. The risk of having an adverse cerebrovascular event (such as stroke) is increased more than threefold with risperidone or olanzapine, and advice from the UK Committee for the National Institute for Health and Clinical Excellence (NICE) and the National Institute for Clinical Excellence (NICE) is that this should not be used for the management of dementia. There may be a potential role in Parkinson's disease, but this should be restricted to patients with very severe symptoms, and the benefits are likely to be outweighed by the significant risk of cerebrovascular events. It is important that the prescription is reviewed regularly.
on Safety of Medicines is that these drugs should not be used for the treatment of patients with behavioural symptoms of dementia. The risk of such an event is also more than doubled in patients with dementia taking any atypical antipsychotic drug. So, it is possible that this is a class effect, although this possibility needs confirming. Observational evidence strongly suggests the risk is similarly increased by [M = meta-analysis, R = randomised controlled trial]

How safe are antipsychotics in dementia?

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