

## Antipsychotics increase mortality in patients with Alzheimer's disease

**Extended follow-up of the DART-AD<sup>1</sup> trial found that patients with Alzheimer's disease who continued antipsychotic medication for behavioural or psychiatric problems were twice as likely to die as those switched to placebo.**

### Action

Prescribers should continue to follow the NICE-SCIE guideline on dementia. This advises that we should **avoid** using any antipsychotics (atypical or conventional) for non-cognitive symptoms or challenging behaviour of dementia unless the patient 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 patient and/or carers about the possible benefits and risks of treatment.

### What was DART-AD?

DART-AD was a 12-month randomised controlled trial [RCT] in 165 patients with Alzheimer's disease. Patients were randomised to either continue their antipsychotic medication (mainly risperidone or haloperidol) or to stop treatment and receive placebo instead. The cumulative probability of survival during the 12-month trial was 70% (95% confidence interval [CI] 58% to 80%) in those who continued treatment compared with 77% (95% CI 64% to 85%) in those who switched to placebo. During extended follow-up (up to 54 months), people who took antipsychotics were almost twice as likely to die as those taking placebo (hazard ratio [HR] for survival 0.58; 95% CI 0.35 to 0.95). The difference in mortality was more pronounced after

the 12-month randomised phase of the trial, with a cumulative survival of 46% vs. 71% at 24 months, 30% vs. 59% at 36 months, and 26% vs. 53% at 42 months for the continued treatment vs. placebo groups, respectively. However, fewer patients were analysed at the later time points and these results should be interpreted with caution.<sup>1</sup>

### So what?

This study adds to the ever-growing evidence suggesting that all antipsychotics, regardless of their type, are associated with an increased risk of serious adverse reactions in elderly patients with dementia. In some ways this study is more helpful than earlier studies as it involved withdrawing antipsychotic medication from those who have behavioural problems. This helps address earlier concerns that the behavioural problems themselves were responsible for the increased rate of adverse events seen.

For more details on this study and background information, see *MeReC Rapid Review Blog No. 263*.

### References

1. 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 Neurology* 2009;8:151-7

## Further evidence to support individualised antipsychotic drug treatment for schizophrenia

**A recent meta-analysis<sup>1</sup> concludes that all antipsychotic drugs differ in their efficacy and adverse effects and they are not a homogeneous group. This supports an individualised approach to treatment.**

### Action

This meta-analysis alone does not provide us with good quality evidence to guide our practice in this area. Better quality and more pragmatic studies such as CATIE and CUTLASS are more useful. However, it adds support to the view that the initial choice of antipsychotic should be determined on an individual basis, taking into account patient preference, the relative efficacy of each drug, the likelihood of adverse effects and cost of treatment. Trials of two or more drugs are likely to be needed and switching will be necessary in most people before the most suitable treatment can be identified. This meta-

analysis supports the view that first-generation agents, such as perphenazine, should be considered as well as second-generation agents in patients with schizophrenia. Many first-generation drugs are as effective as second-generation ones, they are similarly tolerated, and they are generally far less costly. The NICE clinical guideline on schizophrenia is currently being updated, with publication anticipated in March 2009.

### What was this study?

This large meta-analysis of patients with schizophrenia (150 RCTs, n=21,533) compared

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the efficacy and adverse effects of nine second-generation antipsychotic drugs with first-generation drugs (haloperidol in 95 of these studies). For a detailed discussion of the results and limitations of this meta-analysis, see *MeReC Rapid Review Blog No. 264*.

**So what?**

In summary, both first- and second-generation antipsychotic classes are very broad and include some distinctly different agents. There appears to be little to choose in terms of efficacy between first- and second-generation agents, and differences in

the overall tolerability of the different types of antipsychotic may be far smaller than was previously thought. Second-generation antipsychotics are generally associated with fewer parkinsonian-like extrapyramidal side effects and most are associated with some degree of weight gain, but otherwise they are a heterogeneous group and have distinct side-effect profiles.

**References**

1. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 2009;373:31–41

## Antiepileptic product information to be updated

**All antiepileptic medicines have recently been found to be associated with a small risk of suicidal thoughts and behaviour (incidence increased by about 2 additional patients per 1000). The European Medicines Agency (EMA) has recommended that the product information for these agents is updated to warn of this.**

**Action**

Healthcare professionals should continue to follow MHRA advice and NICE guidance on epilepsy. Patients taking antiepileptics (and their carers) should be advised to seek medical advice if they develop any mood changes, distressing thoughts or feelings about suicide or self-harm at any point during treatment. Such

patients should be referred for appropriate treatment if necessary and advised against stopping or switching treatment without talking to a healthcare professional first.

For more details see *MeReC Rapid Review Blog No. 268*.

## All non-analgesics similarly effective for neuropathic pain

**A Canadian Health Technology Assessment report<sup>1</sup> concludes that, in patients with neuropathic pain, there is no statistically significant difference in clinical response rates between tricyclic antidepressants, anticonvulsants and serotonin-norepinephrine reuptake inhibitors (SNRIs).**

**Action**

There appears to be no evidence to distinguish between tricyclic antidepressants, anticonvulsants and SNRIs on the basis of safety or effectiveness. Therefore, as with all medicines where this is the case, choice should be based on both individual patient preference and cost. As they are likely to be the least costly, the meta-analysis suggests that tricyclic antidepressants should be the first-line treatment option in patients whose neuropathic pain is not controlled using simple analgesia. A NICE guideline on neuropathic pain is due to be published in March 2010.

to 46.3%) for anticonvulsants. The adjusted and pro-rated rate for full response with tricyclic antidepressants was 46.0% (95% CI 32.8% to 59.2%).

The dropout rates due to adverse drug reactions were similar between the three drug classes: 12.3% for anticonvulsants, 12.0% for SNRIs and 11.7% for tricyclic antidepressants.

For more details of this study, including its limitations, see *MeReC Rapid Review Blog No. 266*.

**What does this study claim?**

This meta-analysis (28 RCTs) assessed the clinical response rates in adults diagnosed with neuropathic pain who were taking tricyclic antidepressants (e.g. amitriptyline), SNRIs (duloxetine<sup>▼</sup>, venlafaxine) or anticonvulsants (gabapentin, pregabalin<sup>▼</sup>) compared with placebo.

**So what?**

This meta-analysis shows that there is little to choose between the pain response rates and adverse effect dropout rates of SNRIs, anticonvulsants and tricyclic antidepressants. Because the evidence to support the use of treatments for neuropathic pain is generally limited, treatment should be tailored to the individual's circumstances, taking into account any contraindications, co-morbidities etc. It is difficult to predict how a person will respond and trials of several drugs may be necessary to obtain optimal pain relief and minimise adverse effects. However, tricyclic antidepressants are a good first choice treatment for neuropathic pain and they are likely to be more cost-effective than SNRIs or anticonvulsants.

From indirect comparisons, as the 95% confidence intervals all overlapped, no significant difference was seen between the three drug classes in terms of partial or full response when these were adjusted against placebo rates. A partial response (30% reduction in pain on a visual analogue scale) [adjusted] was seen in 49.7% (95% CI 43.4% to 56.0%) of patients taking an SNRI, 54.4% (95% CI 49.9% to 59.0%) of patients taking an anticonvulsant, and 59.4% (95% CI 42.4% to 76.5%) of patients taking a tricyclic antidepressant. For full response (50% reduction in pain on a visual analogue scale) the adjusted rate was 38.3% (95% CI 33.1% to 43.5%) for SNRIs and 42.3% (95% CI 38.3%

**References**

1. Canadian Agency for Drugs and Technologies in Health. Anticonvulsants, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants in management of neuropathic pain: A meta-analysis and economic evaluation. *Technology Report 116*. December 2008

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