

## Antipsychotics increase mortality in elderly patients with dementia

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

### Action

Prescribers should continue to follow the NICE-SCIE guideline on dementia.<sup>2</sup> This advises that we should **avoid** using any antipsychotics (second-generation 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.<sup>2</sup>

### What does this study suggest?

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 more likely to die than those taking placebo (hazard ratio 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. However, fewer patients were analysed at the later time points and so the results should be interpreted with caution.<sup>1</sup>

### So what?

This small trial adds to the ever-growing evidence suggesting that all antipsychotics are associated with an increased risk of

serious adverse reactions (in this case mortality) in elderly patients with dementia. Since publication of DART-AD, the MHRA has concluded that there is a clear increased risk of stroke and a small increased risk of death when any antipsychotic (i.e. conventional or second-generation) is used in elderly people with dementia (see *MeReC Rapid Review Blog No. 312*).<sup>3</sup> The NICE-SCIE guidance<sup>2</sup> on dementia recommends that antipsychotics should be used only in exceptional circumstances in such patients (see **Action** and the NICE guideline for more details). Risperidone is the only antipsychotic licensed for treating dementia-related behavioural disturbances, and then only for short-term use (up to six weeks) for persistent aggression in Alzheimer's dementia, unresponsive to non-drug approaches and where there is risk of harm to the patient or others. The MHRA has recently issued advice on assessing cerebrovascular and other risks before prescribing risperidone for such patients. In addition, **all** suspected side-effects that occur when risperidone is used to treat elderly patients with dementia should be reported via the yellow card system.<sup>3</sup>

In February 2009, the Department of Health published its National Dementia Strategy.<sup>4</sup> NICE has also recently published an audit tool to assist organisations in reviewing and monitoring practice against the NICE-SCIE guidance on dementia.<sup>2</sup>

For more details see *MeReC Rapid Review Blog No. 263*. You can find further information on the treatment of dementia on the CNS and mental health floor of NPCi.



*Any use of antipsychotics should include a full discussion with the patient and/or carers about the possible benefits and risks of treatment.*

### 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
2. NICE/SCIE. Dementia: Supporting people with dementia and their carers in health and social care. Clinical Guideline 42. November 2006
3. MHRA. Drug Safety Update. Vol 2, Issue 8. March 2009
4. DH. Living well with dementia: a National Dementia Strategy. February 2009

## NICE updates schizophrenia guideline

NICE has updated its clinical guideline on the management of schizophrenia.<sup>1</sup> With regard to choice of antipsychotic, NICE does not recommend use of any particular drug or group of drugs. It recommends that a joint decision should be made between the

service user (and carer if appropriate) and healthcare professional after considering side-effect profiles. In this respect, the patient decision aid<sup>2</sup> on the schizophrenia floor of NPCi may be helpful.

*This publication was correct at the time of preparation: May 2009*

The guideline includes important recommendations for the management of schizophrenia. **Panel 1** includes the key implementation priorities.<sup>1</sup> Treatment with antipsychotics should be considered as an explicit individual therapeutic trial, which includes four- to six-week treatment at optimal dosage. See the guideline for details on the monitoring required and the records that need to be kept, along with recommendations on other aspects of the management of schizophrenia.<sup>1</sup>

**Panel 1: NICE schizophrenia guideline — key implementation priorities<sup>1</sup>**

- GPs and primary care healthcare professionals should monitor the physical health of people with schizophrenia at least once a year.
- Offer cognitive behavioural therapy (CBT) to all people with schizophrenia, and offer family intervention to all families of people with schizophrenia who live with, or are in close contact with, the service user.
- Offer people with newly diagnosed schizophrenia oral antipsychotic medication. Provide information on the benefits and side-effect profiles of each drug. A joint decision on drug choice should be made between the healthcare professional and the service user (and carer if the service user agrees). Consider the relative potential of the individual antipsychotic drugs to cause extrapyramidal side effects, metabolic side effects and other side effects.
- Do not prescribe regular combined antipsychotics except for short periods (e.g. when changing medication).
- For people who do not respond adequately to pharmacological or psychological treatment: review diagnosis; consider non-adherence to medication regimen, when prescribed at an adequate dose for correct duration; review engagement with and use of psychological treatments, consider family intervention or CBT if not already undertaken; consider other reasons, such as comorbid substance misuse, concurrent use of other medications or physical illness.
- Offer clozapine to people with schizophrenia whose illness has not responded adequately to treatment despite sequential use of adequate doses of at least two antipsychotic drugs, at least one of which is a non-clozapine second-generation antipsychotic.

**Reasons behind NICE recommendations for antipsychotic choice**

The previous NICE guideline on schizophrenia (2002), recommended second-generation (atypical) antipsychotics as first-line treatment in some situations, primarily because they were thought to carry a lower potential for extrapyramidal side effects.<sup>3</sup> However, systematic reviews of the evidence from clinical trials and new evidence from pragmatic effectiveness trials (CATIE<sup>4</sup> and CUtLASS<sup>5</sup>) suggest that choosing the most appropriate antipsychotic for an individual may be more

important than the drug group. (Also see *MeReC Rapid Review Blog No. 264*).

Considering the lack of evidence to distinguish antipsychotics on efficacy grounds, and the uncertainty of health economic evidence, NICE were unable to make a recommendation for a preference of one antipsychotic over another. The exception is clozapine, for which there was robust evidence supporting the recommendations for its use in people who do not respond adequately to other antipsychotics.<sup>3</sup>

Although NICE identified evidence on relative side-effect profiles of antipsychotics from 138 evaluations, most trials were of short duration and were not designed to prospectively examine side effects. The trials were considered to offer little insight into the longer-term adverse effects of treatment, or whether or not there are any significant differences between antipsychotic drugs. Although recognising that the metabolic and neurologic side effects are not inconsistent with the summaries of product characteristics for each drug, the guideline provides no information on side effect profiles of individual antipsychotics to assist in deciding the most appropriate drug for an individual in this respect.<sup>3</sup> A patient decision aid<sup>2</sup> is available on the schizophrenia floor of NPCi, together with information on the management of this disorder. For more details see *MeReC Stop Press Blog No. 321*.

**References**

1. NICE. Schizophrenia: Core interventions in the treatment and management of schizophrenia in adults in primary and secondary care. Clinical guideline 82. March 2009
2. NPC. Schizophrenia: patient decision aid for antipsychotic drugs
3. National Collaborating Centre for Mental Health. Schizophrenia: Core interventions in the treatment and management of schizophrenia in primary and secondary care (update). National Clinical Practice Guideline No. 82. March 2009 (NICE full guideline)
4. NPC. Antipsychotics in schizophrenia: a message from CATIE. *MeReC Extra* July 2006;23:1
5. Jones PB, Barnes TRE, Davies L, et al. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study (CUtLASS 1). *Arch Gen Psychiatry* 2006;63:1079–87

**What's new from the National Prescribing Centre?**

This is a selection of some recent items that can be found on the NPC ([www.npc.co.uk](http://www.npc.co.uk)) and NPCi ([www.npci.org.uk](http://www.npci.org.uk)) websites.

**MeReC Blogs** [www.npci.org.uk/blog/](http://www.npci.org.uk/blog/)

The polypill – interesting DOO data, but no POOs yet  
Rosuvastatin produces a small absolute reduction in venous thromboembolism (VTE) in people at low baseline risk

Rosuvastatin has no CV benefits in patients undergoing haemodialysis

**New Medicines Blogs** [www.npci.org.uk/blog/](http://www.npci.org.uk/blog/)

Is clopidogrel ACTIVE for atrial fibrillation?  
Update on new treatments for chronic idiopathic thrombocytopenic purpura  
Prasugrel<sup>®</sup> (Efient<sup>®</sup>) in patients with STEMI

**Podcasts** [www.npci.org.uk/podcast/](http://www.npci.org.uk/podcast/)

The effects of Polycap in middle-aged individuals, rosuvastatin for venous thromboembolism, and rosuvastatin and cardiovascular events in patients undergoing haemodialysis

**MeReC Monthly** [www.npc.co.uk/ebt/merec.htm](http://www.npc.co.uk/ebt/merec.htm)

No. 13. April 2009; No. 14. May 2009

**MeReC Bulletin** [www.npc.co.uk/ebt/merec.htm](http://www.npc.co.uk/ebt/merec.htm)

Vol 19. No.4. April 2009. Recent safety issues with inhaled treatments for COPD

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