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## Antipsychotics Increase Mortality Over Long Term in Alzheimer's Patients: DART-AD

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Medscape Medical News 2009. © 2009 Medscape

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January 13, 2009 — Results from a long-term study show an increased mortality in patients with Alzheimer's disease (AD) treated over time with antipsychotic medications, confirming concerns about the safety of these drugs in patients with dementia.

After 1, 2, and 3 years of follow-up, more patients who continued treatment on antipsychotic drugs died than those who had medication withdrawn at baseline.

Best-practice recommendations already counsel that antipsychotics should be used in AD only for patients with severe symptoms of aggression or distress and should not, except in exceptional circumstances, be used longer than 3 months, first author Clive Ballard, MD, from the Wolfson Center for Age-Related Diseases at King's College London, in the United Kingdom, told *Medscape Neurology & Neurosurgery*.

However, he points out, "in real life, in the clinic, the average length of prescribing is still 1 to 2 years, so I think what this is doing is reinforcing that those guidelines are correct, and it's important that we actually adhere to them."

The results, from long-term follow-up of the Dementia Antipsychotic Withdrawal Trial (DART-AD), are published online January 9 ahead of print in the February issue of *Lancet Neurology*. It was funded by the UK Alzheimer's Research Trust.

### Long-Term Concerns

Antipsychotics are widely used as the first-line pharmacological approach to treat neuropsychiatric symptoms in AD, the authors write, with randomized trials showing "significant but modest" improvement vs placebo over 6 to 12 weeks of treatment. However, there is also "clear evidence" of a significant increase in adverse events with treatment, they note, including parkinsonism, edema, chest infections, accelerated cognitive decline, and cerebrovascular events.

A recent meta-analysis of these short-term studies suggested there was also an increase in mortality with treatment, they write (Schneider LS et al. *JAMA* 2005;294:1934-1943). "On the basis of this information, the US Food and Drug Administration [FDA] published a warning about a significant increase in mortality risk with treatment with atypical antipsychotics in patients with AD," the authors write.

However, many patients are treated much longer than 6 to 12 weeks, they note, so information on longer-term

treatment is needed.

DART-AD was a trial in which patients with Alzheimer's disease residing in care facilities in the United Kingdom were randomized to either continue with the previously prescribed antipsychotic treatment for 12 months or switch to an oral placebo. The primary outcome was mortality at 12 months. An additional follow-up telephone assessment was done to establish whether patients were still alive at 24 months after enrollment of the last patient, giving a range of follow-up from 24 to 54 months. Cause of death was obtained from death certificates.

Patients were on a variety of antipsychotic drugs, including thioridazine, chlorpromazine, haloperidol, trifluoperazine, or risperidone. Of 165 patients randomized, 128 started on their randomized treatment, 64 continuing on antipsychotics and 64 switched to placebo.

A previous analysis from DART-AD, looking at the effect of treatment on behavior and cognition in patients treated during the double-blind phase up to 12 months, showed no benefit with antipsychotic treatment on behavior or cognition for patients who continued treatment, Dr. Ballard noted (Ballard C et al. *PLoS Med.* 2008;5:e76).

Now, they report that longer-term treatment with antipsychotics increases mortality in these patients. Across the whole study period, the overall risk of death was 42% lower in those treated with placebo vs those receiving antipsychotics. The difference was evident by 12 months but increased at 24 and 36 months

**Table. DART-AD: Survival With and Without Antipsychotic Treatment at 12, 24, and 36 Months**

Time Point (mo)	Continued Antipsychotic Treatment (%)	Placebo (%)
12	70	77
24	46	71
36	30	59

"The previous mortality concerns were around the 12-week trials, and over 12 weeks there's a similar relative risk of mortality of between 1.5 and 1.7, depending on which analysis you read," Dr. Ballard said. "But the point has been made that the absolute numbers of deaths are quite small because of the short period of treatment, so although the relative risk is high, the absolute number of people who die because of it is quite small."

These findings now make the point that, carried over a longer period, the relative risk remains the same but the absolute number of people affected becomes very substantial, he said. "At 3 years, for example, about one-third of people are still alive if they're on antipsychotics and almost two-thirds are if they're not on antipsychotics.

"Our data add further serious safety concerns about the long-term use of antipsychotics in this population, and clinicians should certainly try to replace antipsychotics with safer management approaches," the authors conclude.

For example, several studies have shown that psychological management can replace antipsychotic therapy without appreciable worsening of neuropsychiatric symptoms, they note. Although cholinesterase inhibitors do not seem to be an effective short-term treatment for agitation, there is some evidence that memantine or antidepressants such as citalopram might be safer and effective alternatives for some of these symptoms.

"Our opinion is that there is still an important but limited place for atypical antipsychotics in the treatment of severe neuropsychiatric manifestations, particularly aggression, of AD," they conclude. "However, accumulating safety concerns, including the substantial increase in long-term mortality, emphasize the urgent need to put an end to unnecessary and prolonged prescribing."

### Protecting Health and Dignity

A "Leading Edge" editorial from *Lancet Neurology* accompanying the article points out that the "mounting body" of evidence documenting the risks associated with antipsychotics in dementia led regulatory agencies in North America and Europe to issue warnings against the use of these drugs in these patients, and the FDA requires both atypical and typical antipsychotics to carry a black-box warning of the increased risk for mortality.

"Despite these warnings, antipsychotic drug use still seems to be widespread, particularly in care settings," the editorial states. About 30% to 60% of patients in these facilities receive antipsychotic drugs, at a cost of about £80 million annually in the United Kingdom alone.

However, the behavioral and psychological symptoms are challenging and distressing, and these medications may be the only option when the patient is a danger to themselves or others. Often, though, inadequate numbers of staff and a lack of training mean that antipsychotics may be used unnecessarily as a first option, the editorial adds.

"Evidence is scarce, but 1 randomized trial showed that when staff were trained to provide more individualized support to patients by tackling environmental, care practice, and attitudinal factors, the need for antipsychotics was significantly reduced," the editorial notes.

"The risks and benefits of prescribing antipsychotics to patients with dementia need to be carefully balanced, and these drugs should only be used if alternative strategies do not work," the editorial concludes. "To protect the health and dignity of people with dementia and reduce the use of antipsychotic drugs, approaches that make the needs of patients central to decisions about care should be promoted."

*The study was funded by the UK Alzheimer's Research Trust. Dr. Ballard reports that within the past 5 years he received honoraria from Novartis, Pfizer, Shire, Lundbeck, Myriad, Servier, and Arcadia; research grants from Novartis and Lundbeck; and honoraria and research grants from AstraZeneca and Janssen more than 5 years ago. None of the other authors report any conflict of interest.*

*Lancet Neurol.* Published online January 9, 2009.

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