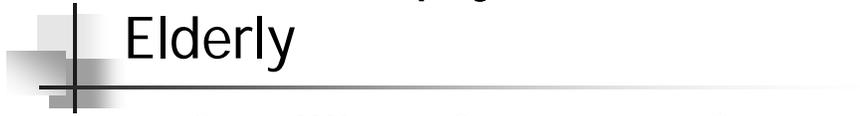




Anti-Psychotic Use in AD: Implications from CATIE-AD

Maria T. Caserta, MD, PhD
Former Director of Geriatric Psychiatry
USF
Professor and Director of Inpatient Psychiatry
UIC Medical School



Risk of Antipsychotics in the Elderly

- In October 2002, Health Canada and Janssen-Ortho (a manufacturer of atypical antipsychotics) issued a warning to Canadian clinicians of a possible link between risperidone use and cerebrovascular adverse events. This concern emerged from a clinical trial evaluating risperidone in the management of BPSD (**Brodsky H, Ames D, Snowden J, Woodward M, Kirwan J, Clarnette R, et al. A randomized placebo controlled trial of risperidone for the treatment of aggression, agitation, and psychosis in dementia. *J Clin Psychiatry* 2003;64:134-43.**
- Subsequent meta-analysis of the risperidone trials for this indication also showed more cerebrovascular adverse events among participants receiving risperidone (4%) than among participants receiving placebo (2%). (**Wooltorton E. Risperidone (Risperdal): increased rate of cerebrovascular events in dementia trials. *CMAJ* 2002;167:1269-70.**



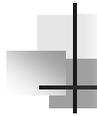
Risks of Antipsychotics

The US Food and Drug Administration issued a similar warning in April 2003. More recently, pooled data from clinical trials evaluating olanzapine for BPSD have shown that it may also be associated with an increased risk of cerebrovascular adverse events.

These data suggest around a threefold increase in the relative risk of cerebrovascular events among people taking risperidone or olanzapine.

Based on these data, the UK Committee on Safety of Medicines and the FDA issued a warning in March 2004 advising that risperidone and olanzapine should no longer be used to manage BPSD, and that patients already receiving these drugs for BPSD should be switched to other treatments.

These warnings have led to controversy among clinicians.



References

- Atypical antipsychotic drugs and stroke: Message from Professor Gordon Duff, Chairman, Committee on Safety of Medicines (CEM/CMO/2004/1). www.mca.gov.uk/ourwork/monitorsafequalmed/safetymessages/antipsystroke_9304.htm (accessed 15 Nov 2004).
- Mowat D, Fowlie D, MacEwan T. CSM warning on atypical psychotics and stroke may be detrimental for dementia. *BMJ* 2004;328:1262-b.
- Smith DA, Beier MT. Association between risperidone treatment and cerebrovascular adverse events: examining the evidence and postulating hypotheses for an underlying mechanism. *J Am Med Dir Assoc* 2004;5:129-32.

Reality

- Who in this audience has not used anti-psychotics, either conventional or atypical, in the management of patients with a diagnosis of dementia with behavioral symptoms, i.e., agitation, aggression towards caregivers, wandering at night, resistance to care, etc.?

Symptoms that Lead to NH Placement

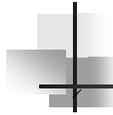
Which ones are the most common?

Reasons for NH Placement

- Behavioral and psychological symptoms of dementia
- Delusions or hallucinations appear in 30%–50%, and as many as 70% demonstrate agitated or aggressive behaviors.
- Caregiver stress
- Incontinence
- Caregiver death or illness

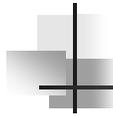
BPSD

- Although dementia is diagnosed by observing cognitive symptoms, non-cognitive abnormalities are also prevalent in dementia and were, in fact, described by Alois Alzheimer in his original description of what would become known as Alzheimer's disease. Behavioral and psychological symptoms of dementia (BPSD) include signs of disturbed perception, thought content, mood, or behavior.
- BPSD tend to occur in clusters, which have been grouped into the categories of aggression, psychomotor agitation, psychosis, apathy, and depression.



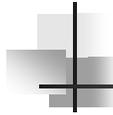
BPSD

- Conventional antipsychotics were often used for the management of BPSD, and at least 35 trials of varying quality have investigated their efficacy and safety in this condition. A meta-analysis of seven controlled trials of conventional antipsychotics in agitated dementia patients showed modest efficacy, with haloperidol and thioridazine producing benefits in 18 percent more patients than placebo.



BPSD

- A more recent Cochrane review of **haloperidol** for the treatment of agitation in patients with dementia found that aggression was reduced, but there were no improvements in agitation, behavioral symptoms as a whole, or in clinical global impression. Because tolerability is frequently reduced in the elderly and doses of conventional antipsychotics that are high enough to produce efficacy are associated with side effects such as parkinsonism, somnolence, tardive dyskinesia, and falls, the modest benefit of haloperidol treatment may not always be justified.

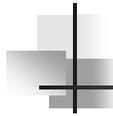


BPSD

One of the primary advantages of atypical antipsychotics over conventional antipsychotics for the treatment of BPSD, as well as other disorders, is their greater tolerability.

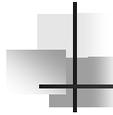
These drugs are associated with fewer extrapyramidal symptoms (EPS), which is especially important in the elderly due to their increased susceptibility to such reactions.

Effective dosages of atypicals in BPSD are generally lower than for schizophrenia, which is another factor that improves tolerability.



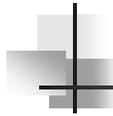
BPSD

- Risperidone was the first atypical antipsychotic shown to be effective in treating BPSD.
- Several controlled double-blind studies have demonstrated the efficacy and tolerability of low doses of risperidone in patients with BPSD.



Risperidone

- Three placebo-controlled studies resulted in a sample size large enough (1191 patients) to allow better estimates of effect size, especially in subpopulations.
- The patients in all three trials were aged 55 years or older, lived in an institution, and had been diagnosed using DSM-IV criteria with dementia of the Alzheimer's type, vascular dementia, or mixed dementia. At baseline, the median (MMSE) score was 6 (range, 0 to 23) showing that overall the patients tended to have moderate-to-severe cognitive decline.
- Patients in two of the trials had a wide range of BPSD, while the third trial focused specifically on patients with aggressive behavior. Measures included the BEHAVE-AD and CGI subscales .



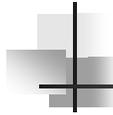
Risperidone

Risperidone was efficacious at all time points on all the outcome measures (CMAI total and subscales and BEHAVE-AD total and psychotic symptom scales). The positive effects were confirmed by significant improvements in CGI-Severity and CGI-Change Scales.

In general, risperidone showed efficacy

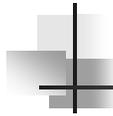
- **regardless of the type or severity of dementia**
- **presence of psychosis, or**
- **presence of somnolence.**

In studies comparing risperidone with haloperidol, risperidone was at least as effective in improving BPSD overall. In a head-to-head crossover trial, risperidone was superior to haloperidol in the treatment of BPSD.



Olanzapine

- Two double-blind studies have tested the effect of olanzapine on BPSD in patients with dementia. (Table 1 in Aupperle, P **AJADOD**, v.21 March/April 2006).
- The first, a six-week study of institutionalized patients with Alzheimer's disease and psychotic or behavioral symptoms, found that olanzapine in doses of 5 or 10 mg/d resulted in significant improvements in the Core Total of the NPI.
- Furthermore, a post hoc analysis of these patients found a significant attenuation in the emergence of psychosis over the short term compared with placebo. (6 week study)



Other Antipsychotics

- Quetiapine
 - Two short, open-label pilot studies with quetiapine in AD patients found improvements in behavioral symptoms without significant adverse events.
 - A larger short term, open-label study in 151 psychotic elderly patients demonstrated good tolerability as well as improvement in psychotic symptoms and clinical global impressions.
 - A 52-week open-label study in 184 elderly patients with psychotic disorders (72 percent due to general medical conditions such as AD) found significant improvements in psychotic symptoms and CGI.

Other Antipsychotics

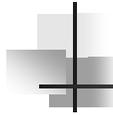
- Aripiprazole
- The efficacy of aripiprazole was evaluated in patients with psychosis related to AD. This double-blind placebo-controlled trial showed no difference between aripiprazole and placebo on the NPI psychosis subscale, but on the BPRS Psychosis and BPRS Core subscales aripiprazole showed significantly greater improvements from baseline.

Catie AD study

The National Institute of Mental Health (NIMH) Clinical Antipsychotic Trials of Intervention Effectiveness— Alzheimer's Disease (CATIE-AD) project was designed to

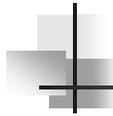
compare the effectiveness of antipsychotic medications and placebo in patients with Alzheimer's disease and psychosis or agitated/aggressive behavior .

In contrast to typical efficacy trials, CATIE-AD included outpatients in usual care settings and assessed treatment effectiveness on several clinical outcome measures over a 9-month intervention period.



Catie-AD

- **Clinical Symptom Responses to Atypical Antipsychotic Medications in Alzheimer's Disease: Phase 1 Outcomes From the CATIE-AD Effectiveness Trial**
- David L. Sultzer, M.D. Sonia M. Davis, Dr.P.H. Pierre N. Tariot, M.D, Karen S. Dagerman, M.S, Barry D. Lebowitz, Ph.D., Constantine G. Lyketsos, M.D., M.H.S., Robert A. Rosenheck, M.D. John K. Hsiao, M.D., Jeffrey A. Lieberman, M.D. Lon S. Schneider, M.D. and CATIE-AD Study Group
- *Am J Psychiatry 165:7, July 2008*



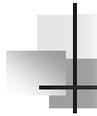
Design of Catie-AD Trial

- The CATIE-AD research design
- Forty-two clinical sites enrolled 421 patients, who were randomly assigned initially to masked treatment with olanzapine, quetiapine, risperidone, or placebo in a 2:2:2:3 ratio. The treating physician could adjust the dose, as indicated clinically, over the 36 weeks of the trial. At any time after the first 2 weeks of treatment, the clinician could discontinue the initially assigned (phase 1) medication for insufficient efficacy, adverse effects, or other reason. At that point, phase 1 ended and the patient could enter phase 2 and be assigned randomly to masked treatment with an atypical antipsychotic medication that had not been assigned in phase 1 or with citalopram. Patients could also go directly to an open-choice treatment.



Catie-AD

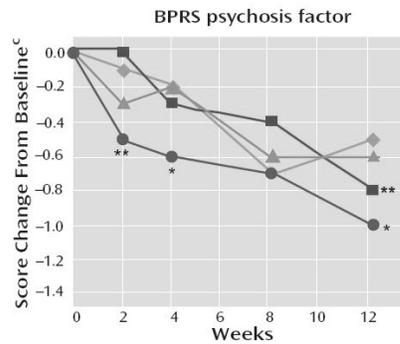
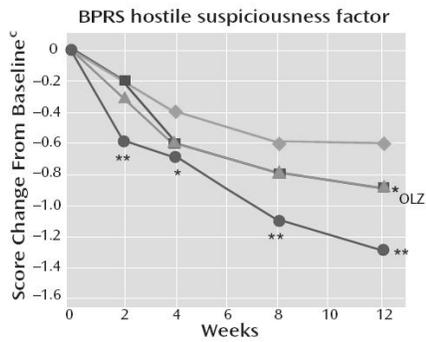
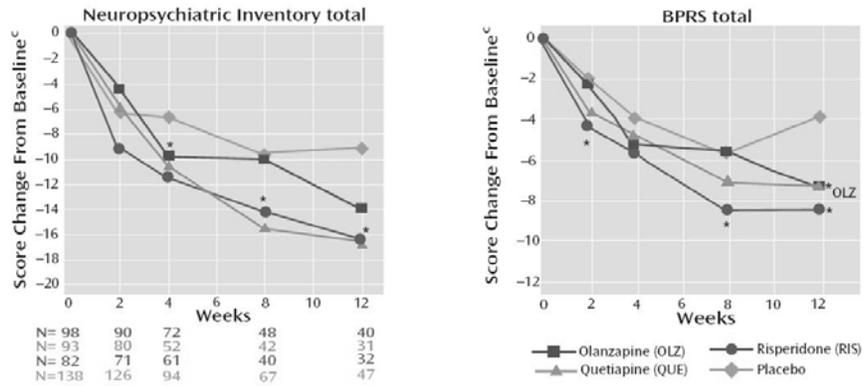
- To participate in the trial, patients met DSM-IV criteria for dementia of the Alzheimer's type or met NINCDS-ADRDA criteria for probable AD, after a thorough history, physical and cognitive examination, and laboratory assessment were completed. Enrolled patients were outpatients living at home or in an assisted-living facility, had a knowledgeable informant, and were ambulatory. **Patients in skilled nursing homes were not included.**
- Mini-Mental State Exam (MMSE) score was 5 to 26. Entry criteria required that delusions, hallucinations, agitation, or aggression had occurred nearly every day over the previous week or intermittently over 4 weeks. Symptoms had to have been rated at least moderate in severity on the (BPRS) conceptual disorganization, suspiciousness, or hallucinatory behavior item, or had occurred at least weekly with moderate severity or greater on the delusion, hallucination, agitation, or aberrant motor behavior item of the (NPI) .

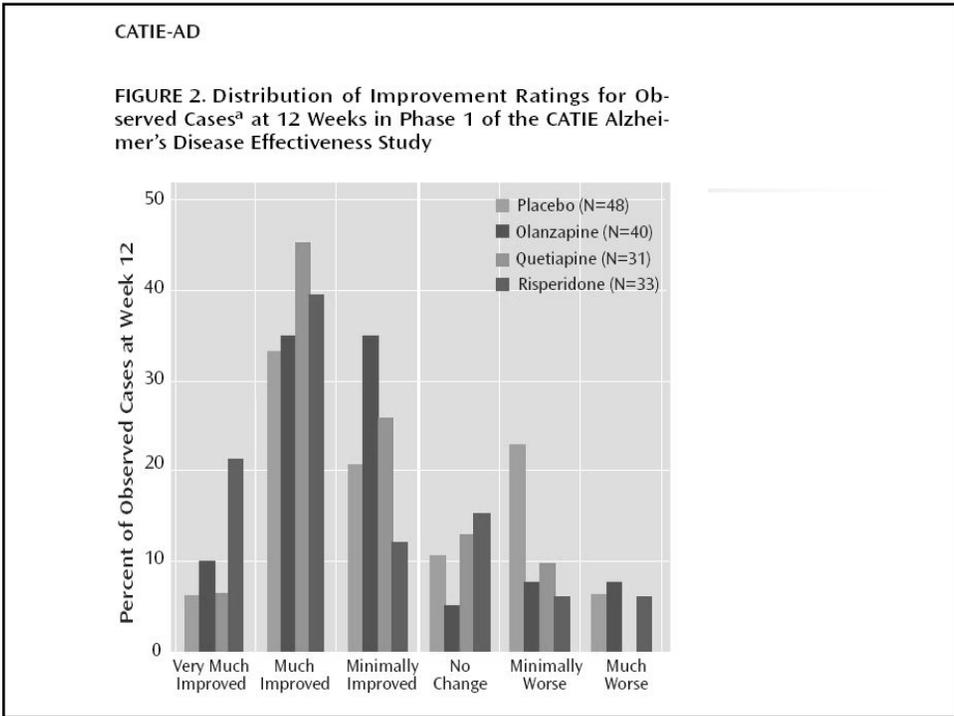
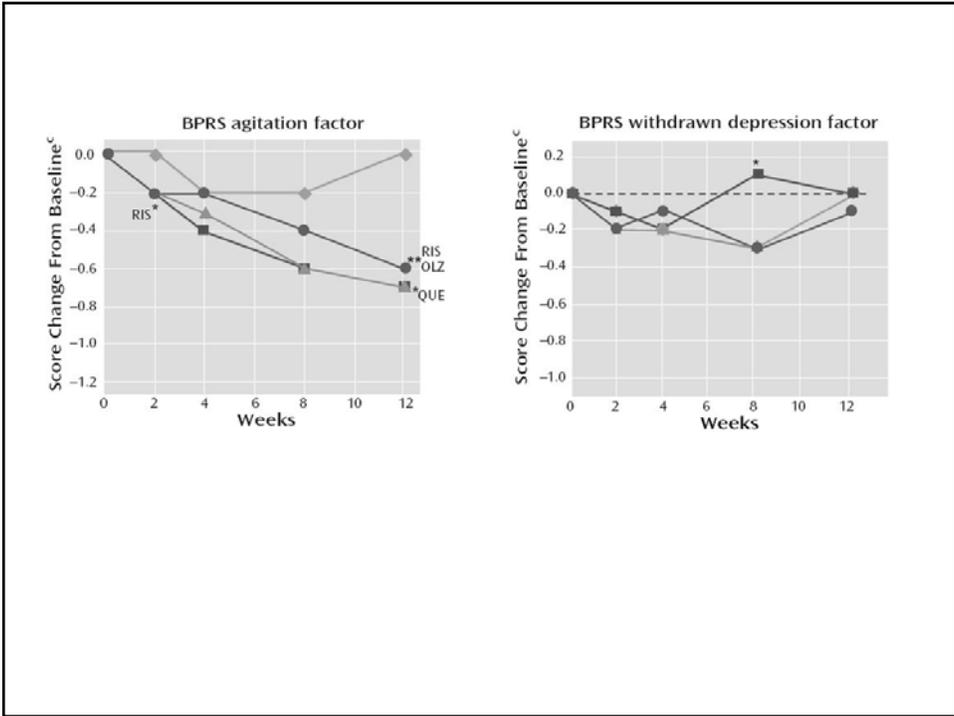


CATIE-AD

- Medications were prepared in low-dose and high-dose capsules that contained either olanzapine (2.5mg or 5mg), quetiapine (25mg or 50mg), risperidone (0.5mg or 1mg), or placebo.
- Mean age of participants was 77.9 (SD 7.5) years; 56% were female; 21% were non-white.
- Overall, 77–85% of patients discontinued the Phase 1 medication treatment prior to the end of the 36-week study period. The median duration of Phase 1 treatment was 7.1 weeks and did not differ significantly across the treatment groups

FIGURE 1. Change in Clinical Symptoms for Observed Cases^a in Phase 1 of the CATIE Alzheimer's Disease Effectiveness Study^b

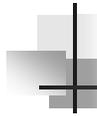






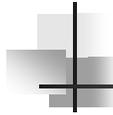
Catie-AD

- Beneficial effects of olanzapine and risperidone were apparent on the NPI total score, a summary measure of psychiatric and behavioral symptoms.
- The magnitude of mean global score improvements with active medication compared to placebo was usually small.
- The BPRS factor scores provide a view of antipsychotic treatment effects on distinct symptoms. Patients treated with risperidone or olanzapine showed improvement on the BPRS Hostile Suspiciousness factor, which assesses hostility, aggression, mistrust, and uncooperativeness. **This subscale had the highest mean score at baseline among noncognitive measures, and the mean score improved by more than 50% in the risperidone group in those continuing Phase 1 treatment at week 12.**



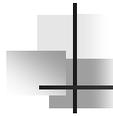
CATIE-AD

- Beneficial effects were **not** apparent on measures of functional abilities, quality of life, or caregiving time needed. Thus, improved clinical symptoms with antipsychotic treatment did not translate to functional benefits or improved quality of life in the context of the CATIE-AD effectiveness design.
- This may be due to additional factors that contribute to functional disability and poor life quality, such as progression of dementia, caregiver interactions, environmental factors, and perhaps adverse effects of the drugs. Nonetheless, improved psychiatric and behavioral symptoms may be clinically meaningful for individual patients without impacting function.



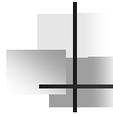
Conclusions

- On measures of depression or cognition, the magnitude of changes was small and there were no differences across treatments except for increased scores in the olanzapine group on the BPRS withdrawn depression factor at the last observation in phase 1.
- Taken together, these findings suggest that antipsychotic medication may have differential effects on specific symptoms in Alzheimer's disease.
- Better understanding of specific effects can help clinicians to select optimal pharmacotherapy.

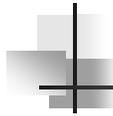


Conclusions

- Several clinical outcome measures in CATIE-AD indicate that patients may benefit symptomatically from treatment with atypical antipsychotic medications.
- As applied to clinical practice, these findings support an individualized approach, where the value of an individual patient's symptomatic improvement needs to be assessed in the context of that person's particular clinical circumstances.

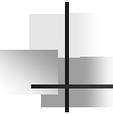


More to worry about



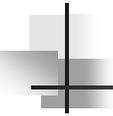
DART-AD Study

- **The dementia antipsychotic withdrawal trial (DART-AD): Long-term follow-up of a randomised placebo-controlled trial.**
- **Lancet Neurology 2009 Feb 8: 152.**
- **Ballard C, Hanney ML, Theodoulou M, Douglas S, McShane R, Kossakowski K, Gill R, Juszcak E, Yu LM, Jacoby R; DART-AD investigators**



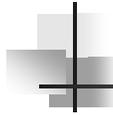
DART-AD

- **Conclusion:** There is an increased long-term risk of mortality in patients with AD who are prescribed antipsychotic medication; these results further highlight the need to seek less harmful alternatives for the long-term treatment of neuropsychiatric symptoms in these patients



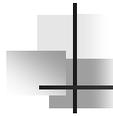
DART-AD

- To assess whether continued treatment with antipsychotics in people with AD is associated with an increased risk of mortality.
- **METHODS:** Between October, 2001, and December, 2004, patients with AD who resided in care facilities in the UK were enrolled into a randomised, placebo-controlled, parallel, two-group treatment discontinuation trial. Participants were randomly assigned to continue with their antipsychotic treatment (thioridazine, chlorpromazine, haloperidol, trifluoperazine, or risperidone) for 12 months or to switch their medication to an oral placebo. The primary outcome was mortality at 12 months. An additional follow-up telephone assessment was done to establish whether each participant was still alive 24 months after the enrollment of the last participant (range 24-54 months). Causes of death were obtained from death certificates.



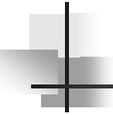
DART-AD

- FINDINGS: 165 patients were randomised (83 to continue antipsychotic treatment and 82 to placebo), of whom 128 (78%) started treatment (64 continued with their treatment and 64 received placebo).
- **There was a reduction in survival in the patients who continued to receive antipsychotics compared with those who received placebo.**

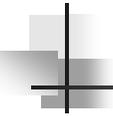


DART-AD

- Cumulative probability of survival during the 12 months was 70% (95% CI 58-80%) in the continue treatment group versus 77% (64-85%) in the placebo group.
- Kaplan-Meier estimates of mortality for the whole study period showed a **significantly increased risk of mortality** for patients who were allocated to continue antipsychotic treatment compared with those allocated to placebo (mITT log rank $p=0.03$; ITT $p=0.02$). The hazard ratio for the mITT group was 0.58 (95% CI 0.35 to 0.95) and 0.58 (0.36 to 0.92) for the ITT population.
- The more pronounced differences between groups during periods of follow up longer than 12 months were evident at specific timepoints (**24-month survival 46% vs 71%; 36-month survival 30% vs 59%**).



What else is there?



Other treatments

- Small scale studies of treatment with drugs other than antipsychotics have produced equivocal results. Trazodone, anti-convulsant mood stabilizers, SSRIs, benzodiazepines, and cognitive enhancers may reduce symptoms of agitation and aggression in a proportion of patients with dementia, although the overall results are inconsistent. The available data are limited by small numbers of subjects or shortcomings in study design, and a number of these drugs have their own adverse effects.
- None of these drugs has been approved by the FDA for treatment of behavioral symptoms of dementia.