Evidence-based Pharmacology for Aggression and Psychosis in Dementia

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I have no Conflicts of Interest for this presentation.

The Evidence

Atypical antipsychotics for aggression and psychosis in Alzheimer's disease.

The Cochrane Database of Systematic Reviews

Date of Most Recent Update 24-May-2006

The Evidence

Sixteen placebo-controlled trials have been completed with atypical antipsychotics although only nine had sufficient data to contribute to a meta-analysis and only six have been published in peer reviewed journals.

The Evidence

1. There was a significant improvement in aggression with risperidone and olanzapine treatment compared to placebo.
2. There was a significant improvement in psychosis among risperidone treated patients.

The Evidence

3. Risperidone and olanzapine treated patients had a significantly higher incidence of serious adverse cerebrovascular events, extrapyramidal side effects, and other important adverse outcomes.
4. There was a significant increase in drop-outs in risperidone (2mg) and olanzapine (5-10mg) treated patients.

RCT for Atypical Antipsychotics

- **Risperidone**
  - Brodaty H, Ames D, Snowdon J, et al. J Clin Psychiatry 2003;64:134-143.
  - Katz IR, Jeste DV, Mintzer JE, et al. J Clin Psychiatry 1999;60:107-115.

RCT for Atypical Antipsychotics

- **Olanzapine**
  - De Deyn PP, Carrasco MM, Deberdt W, et al. Int J Geriatr Psychiatry 2004;19:115-126.
  - Street JS, Clark S, Gannon KS, et al. Arch Gen Psychiatry 2000;57:968-976.
- **Quetiapine**
  - Ballard C, Margallo-Lana M, Juszczak E, et al. BMJ 2005: 874-:originally published online 18 Feb 2005;doi:10.1136/bmj.38369.459988.8F

RCT for Atypical Antipsychotics

- **Aripiprazole**
  - DeDeyn PP, et al. J Clin Psychopharm 2005;25(5):463-7.
- **Ziprasidone**
  - No published controlled, double blind studies involving elderly patients with AD
- **Clozapine**
  - No published controlled, double blind studies involving elderly patients with AD

RCT for Atypical Antipsychotics

- **Quetiapine**
  - Ballard C, Margallo-Lana M, Juszczak E, et al. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomized double blind placebo controlled trial. BMJ 2005: 874-:originally published online 18 Feb 2005;doi:10.1136/bmj.38369.459988.8F

RCT for Atypical Antipsychotics

- Quetiapine: Ballard et al.
  - A 26 week, double-blind, randomized, placebo-controlled study conducted at multiple sites in Newcastle, England.
  - Participants: 93 NH residents with Alzheimer's disease, dementia, and clinically significant agitation.
    - Cohen-Mansfield Agitation Inventory total score >39.
    - Diagnosis of possible or probable Alzheimer's disease.
    - Age > 60
    - Clinically significant agitation for at least 6 weeks.
    - No use of antipsychotics or cholinesterase inhibitors for at least 4 weeks.

RCT for Atypical Antipsychotics

- Quetiapine: Ballard, et al.
  - Exclusionary criteria:
    - Advanced, severe or unstable disease that might interfere with efficacy.
    - Severe, unstable or poorly controlled medical conditions.
    - Bradycardia, sick sinus syndrome, conduction delay.
    - Uncontrolled peptic ulcer disease.
    - Clinically significant urinary obstruction.

RCT for Atypical Antipsychotics

- Quetiapine: Ballard, et al.
  - Primary measures:
    - CMAI - Baseline, 6 weeks, 26 weeks
    - Severe Impairment Battery (SIB) – Baseline, 6 weeks, 12 weeks, 26 weeks
  - Randomization:
    - Quetiapine, Rivastigmine, or Placebo

RCT for Atypical Antipsychotics

- Quetiapine: Ballard, et al.
  - Target doses:

    Week 12
    - Quetiapine 25-50 mg twice a day
    - Rivastigmine 3-6 mg twice a day

    Week 12-26
    - Quetiapine 50 mg twice a day
    - Rivastigmine >/= 9 mg daily

RCT for Atypical Antipsychotics

- Quetiapine: Ballard, et al.
  - CMAI
    - No significant difference between treatments in Δ CMAI between baseline and 6 weeks and baseline and 26 weeks.
  - SIB
    - Patients who received quetiapine experienced, on average, an estimated mean difference in Δ SIB greater than placebo at 6 weeks (P=0.009) and 26 weeks (P=0.001), indicating a significantly greater deterioration in the quetiapine group.

RCT for Atypical Antipsychotics

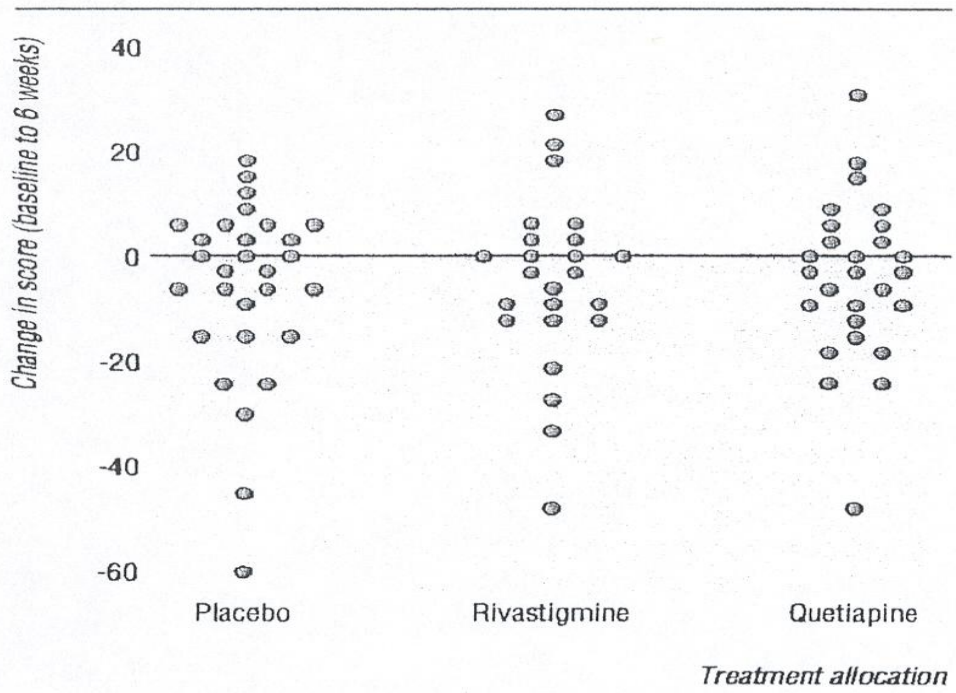


Fig 2 Change in score on Cohen-Mansfield agitation inventory (baseline to six weeks) by treatment group

RCT for Atypical Antipsychotics

- Quetiapine: Ballard, et al.
  - Conclusions:
    - Quetiapine and rivastigmine seemed of no benefit in patients with dementia and agitation in institutionalized care, and quetiapine was associated with greater cognitive decline than placebo. The results suggest that quetiapine should not be used as an alternative treatment to risperidone or olanzapine in people with dementia.

RCT for Atypical Antipsychotics

- **Olanzapine**
  - De Deyn PP, Carasco M, Deberdt W, et al. Olanzapine versus placebo in the treatment of psychosis with or without associated behavioral disturbances in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2004;19:115-126

RCT for Atypical Antipsychotics

- Olanzapine: De Deyn et al.
  - A 10 week, double-blind, randomized, placebo-controlled study conducted at multiple sites in multiple countries
  - Participants: 652 NH residents in Europe, Australia, Israel, Lebanon, and South Africa with clinically significant psychotic symptoms due to Alzheimer's disease.
    - Diagnosis of possible or probable Alzheimer's disease
    - Age > 39
    - At least moderately severe delusions or hallucinations
    - Clinically significant symptoms for at least 4 weeks
    - Required pharmacological intervention
    - Can be taking cholinesterase inhibitor

RCT for Atypical Antipsychotics

- Olanzapine: De Deyn et al.
  - Exclusionary criteria:
    - Diagnosis of a current primary mood disorder or other Axis I disorder with onset prior to diagnosis of AD.
    - MMSE score < 5
    - Medication with primary central nervous system activity
    - Stable use of benzodiazepines and antidepressants were permitted
    - Up to 4 mg/d of lorazepam equivalents were permitted as a rescue medication for chronic users but not within 8 hours of an assessment. No increases in dose after 8 weeks.

RCT for Atypical Antipsychotics

- Olanzapine: De Deyn et al.
  - Primary measures:
    - Sum of individual items of “Hallucinations” and “Delusions” of Neuropsychiatric Inventory/NH version
    - Clinical Global Impression of Change scale
    - Baseline, week 1, week 2, then bi-weekly until week 10
  - Randomization:
    - 14 day placebo lead-in
    - Fixed dose olanzapine – 1 mg/d, 2.5 mg/d, 5 mg/d, 7.5 mg/d, or placebo
    - Titrated up every 7 days

RCT for Atypical Antipsychotics

- Olanzapine: De Deyn et al.
  - NPI/NH psychosis total
    - No significant difference between treatments in Δ NPI/NH psychosis total at the 10 week endpoint.
  - CGI-S
    - No significant difference between treatments in Δ CGI-S at the 10 week endpoint.

RCT for Atypical Antipsychotics

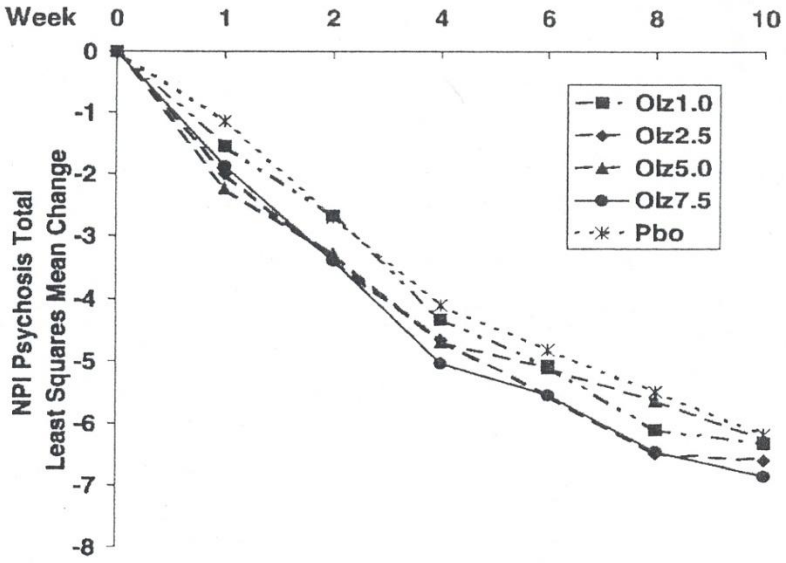


Figure 1. Visitwise changes (least squares mean, mixed-model repeated measures analysis of variance) in mean NPI/NH Psychosis Total (sum of *Delusions* and *Hallucinations* item scores). No significant treatment effects were seen in pairwise comparisons at the 10 week endpoint

Int J Geriatr Psychiatry 2004; **19**: 115–126.

RCT for Atypical Antipsychotics

- Olanzapine: De Deyn et al.
  - NPI/NH Agitation/Aggression
    - The patients appeared to benefit most from treatment with olanzapine on this dimension, relative to the placebo group in the 7.5 mg/d group (P=0.002).
  - NPI/NH Delusion
    - The patients appeared to benefit most from treatment with olanzapine on this dimension, relative to the placebo group in the 7.5 mg/d group (P=0.002).

RCT for Atypical Antipsychotics

- Olanzapine: De Deyn et al.
  - Safety
    - Treatment with olanzapine was generally well tolerated and no adverse effects occurred with an incidence greater than 8% in any group.
    - 3 events were significantly greater in the olanzapine group versus placebo:
      - Weight gain
      - Anorexia
      - Urinary incontinence
    - No worsening of cognition from baseline noted in any group.

RCT for Atypical Antipsychotics

- **Olanzapine**
  - Street JS, Clark S, Gannon KS, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer's disease in nursing care facilities. Arch Gen Psychiatry 2000;57:968-976.

RCT for Atypical Antipsychotics

- Olanzapine: Street, et al.
  - A 6 week, double-blind, randomized, placebo-controlled study of 206 subjects conducted at 28 sites in the US.
  - Participants: 206 elderly US nursing home residents with AD who exhibited psychotic and/or behavioral symptoms who scored 3 or higher on any of the Agitation/Aggression, Hallucinations, or Delusions items of the NPI/NH.
    - **Diagnosis of possible or probable Alzheimer's disease**
    - **Clinically significant agitation after a single-blind placebo lead in.**

RCT for Atypical Antipsychotics

- Olanzapine: Street, et al.
  - Exclusionary criteria:
    - History of DSM-IV Axis I disorder
    - Any neurological condition other than AD that could contribute to psychosis or dementia
    - MMSE > 24
    - Bedridden status
    - Use of concomittant medications with primarily central nervous system activity.
    - Benzodiazepines were allowed as rescue medication up to 4 mg/d lorazepam equivalents for a total of 21 days during active treatment.

RCT for Atypical Antipsychotics

- Olanzapine: Street, et al.
  - Primary measures
    - NPI/NH items for Agitation/Aggression, Hallucinations, and Delusions summed as a Core Total
    - Baseline, weekly for 6 weeks
  - Randomization
    - 3-14 day single blind washout placebo lead-in period
    - Fixed dose olanzapine: 5 mg/d, 10 mg/d, 15 mg/d, or placebo

RCT for Atypical Antipsychotics

- Olanzapine: Street, et al.
  - Core Total NPI/NH measures at endpoint
    - The 5 mg/d (P<0.001) and 10 mg/d (P=0.006) olanzapine groups experienced significantly greater improvement than the placebo group.
    - The 15 mg/d olanzapine group was not statistically superior to placebo (P=0.24).
  - Core Total "response" rates (≥ 50% reduction)
    - Olz 5 mg/d – 65.5%; P=0.05
    - Olz 10 mg/d – 57.1%; P=0.04
    - Olz 15 mg/d – 43.1%; P=0.53
    - Placebo - 35.6%

RCT for Atypical Antipsychotics

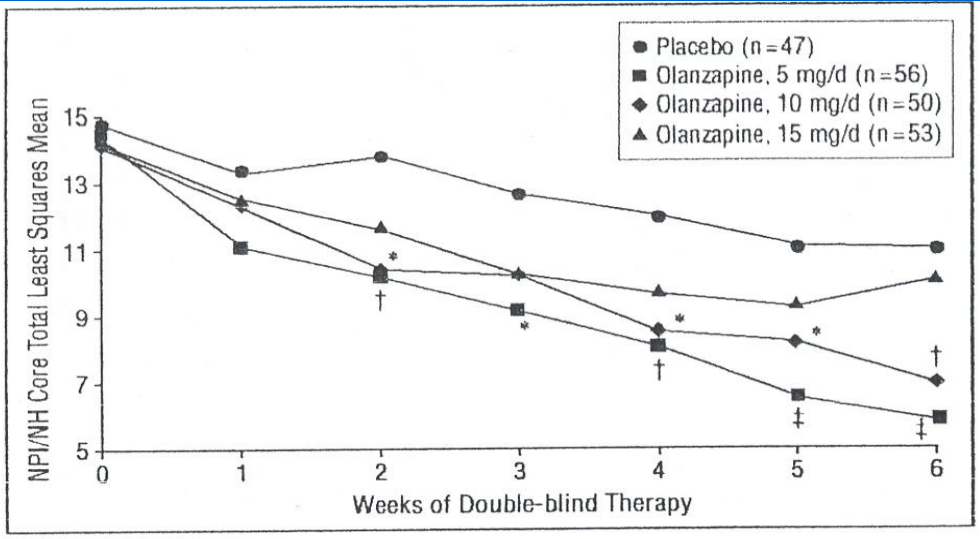


Figure 2. *Visitwise results for the Neuropsychiatric Inventory–Nursing Home version (NPI/NH) Core Total score. The NPI/NH Core Total (sum of the Agitation/Aggression, Hallucinations, and Delusions items) scores across the 6-week study period for placebo and olanzapine groups (5, 10, and 15 mg/d). Patients treated with 5 mg/d of olanzapine showed a significantly greater improvement compared with placebo at week 2, which was maintained throughout the study. Patients treated with 10 mg/d of olanzapine showed a significantly greater improvement at week 2, which was maintained at weeks 4 to 6. Asterisk indicates* $P<.05$ *vs placebo; dagger,* $P<.01$ *vs placebo; and double dagger,* $P<.001$ *vs placebo.*

RCT for Atypical Antipsychotics

- Olanzapine: Street, et al.
  - Safety
    - All olanzapine-emergent events were similar compared with placebo except somnolence and abnormal gait (stooped posture, unsteady gait, leaning, ambulation dysfunction).
      - Risk of somnolence vs placebo
        - Olz 5 mg/d 4.9
        - Olz 10 mg/d 5.2
        - Olz 15 mg/d 8.2

RCT for Atypical Antipsychotics

- **Risperidone**
  - Brodaty H, Ames D, Snowdon J, et al. A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. J Clin Psychiatry 2003;64:134-143.

RCT for Atypical Antipsychotics

- Risperidone: Brodaty et al.
  - A 12 week, double-blind, randomized, placebo-controlled study conducted at multiple sites in Australia and New Zealand.
  - Participants: 384 NH residents with Alzheimer's disease, vascular dementia, or mixed dementia
    - Age >54
    - Functional Assessment Staging Test score ≥4
    - MMSE score ≤ 23
    - CMAI score ≥ 4 on one item or 3 on two items
    - At least one month of residence at NH

RCT for Atypical Antipsychotics

- Risperidone: Brodaty et al.
  - Exclusionary criteria:
    - Nondementia conditions that diminish cognition
    - Major depression within 6 months
    - Nondementia causes of psychosis
    - Tardive dyskinesia
    - Clinically uncontrolled organic disease
    - Use of a depot neuroleptic w/in 2 treatment cycles
    - History of risperidone failure after 4 weeks
    - Short acting benzodiazepines were allowed for treatment of insomnia if the dosage was stable for at least 3 months.

RCT for Atypical Antipsychotics

- Risperidone: Brodaty et al.
  - Primary measures:
    - Cohen-Mansfield Agitation Inventory total aggression score
    - Selection, baseline, week 4, week 8, week 12 or endpoint
  - Randomization:
    - Maximum 7 day, single-blind placebo washout
    - Risperidone 0.25 mg bid or placebo. Flexible dosing.
    - Titrated no faster than 0.25 mg bid qod

RCT for Atypical Antipsychotics

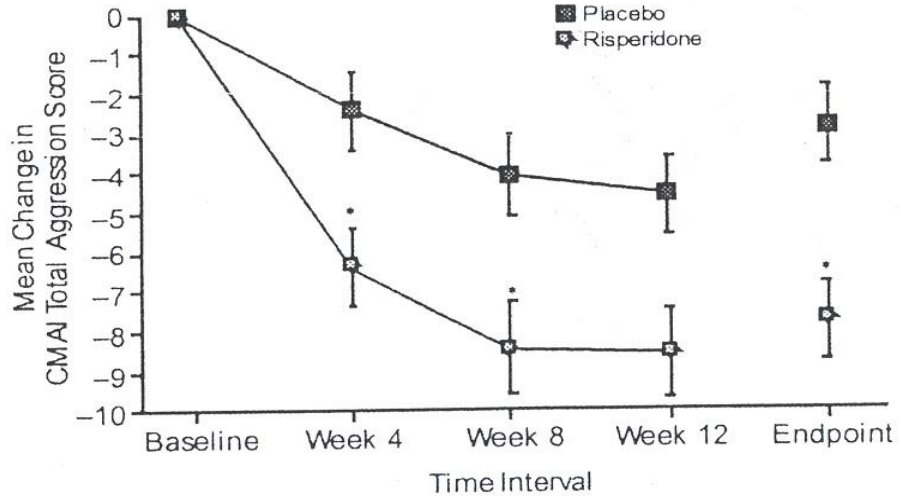
- Risperidone: Brodaty et al
  - Results:
    - 345 patients randomly assigned
    - Demographic and baseline clinical and outcome data not statistically different between groups.
    - Proportion of patients completing the 12 week trial was not statistically different between the groups (~70%).
    - Treatment with benzodiazepines was initiated in significantly more patients in the placebo group (66.5%) than the risperidone group (56.3%;p=.029).
    - Mean dose of risperidone was 0.95 mg

RCT for Atypical Antipsychotics

- Risperidone: Brodaty et al
  - CMAI total aggression subscale
    - Mean changes indicated significantly greater improvement in the risperidone group than in the placebo group ($p<.01$) at all but the week 12 evaluation where the difference approached statistical significance ($p=.058$).

RCT for Atypical Antipsychotics

Figure 2. Change (mean and SE) in Total Aggression Subscale Score of the CMAI Over Time (intent-to-treat patients at included sites)



Placebo:	N = 153	N = 138	N = 123	N = 112	N = 152
Risperidone:	N = 151	N = 141	N = 132	N = 119	N = 149

*p < .01 vs. placebo.
Abbreviation: CMAI = Cohen-Mansfield Agitation Inventory.

RCT for Atypical Antipsychotics

- Risperidone: Brodaty et al:
  - Safety
    - Somnolence (36.5% vs 25.5%) and UTI (23.4% vs 14.7%) were more common in the risperidone group than the placebo group.
    - There was no significant difference in total Extrapyramidal Symptom Rating Scale score between groups at endpoint. The initiation of anti-EPS medication was similar in the 2 treatment groups – 1.8%

RCT for Atypical Antipsychotics

- **Risperidone**
  - Katz IR, Jeste DV, Mintzer J, et al. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. J Clin Psychiatry 1999;60:107-115.

RCT for Atypical Antipsychotics

- Risperidone: Katz et al.
  - A 12 week, double-blind, randomized, placebo-controlled study conducted at 40 sites in the US
  - Participants: 625 NH residents with Alzheimer's disease, vascular dementia, or mixed dementia.
    - Aged 55 years or older
    - Functional Assessment Staging scale score ≥ 4
    - MMSE score ≤ 23
    - Behavioral Pathology in Alzheimer's disease score ≥ 8

RCT for Atypical Antipsychotics

- Risperidone: Katz et al.
  - Exclusionary criteria:
    - Untreated reversible causes of dementia
    - Medical or neurological condition that decreased cognition
    - AIDS or substance-induced persisting dementia
    - Non-dementia psychiatric cause of psychosis
    - Lorazepam could be given in doses up tp 3 mg/day for up to 4 days in any 7 day period.
    - Chloral hydrate was allowed for insomnia
    - Benztropine was allowed for Parkinsonian symptoms.

RCT for Atypical Antipsychotics

- Risperidone: Katz et al.
  - Primary measures:
    - BEHAVE-AD
    - Selection, baseline, weeks 1-4, 6, 8, 10, and 12
  - Randomization:
    - Single-blind placebo washout period of 3 to 7 days
    - Fixed dose risperidone 0.5 mg/d, 1.0 mg/d, 2.0 mg/d or placebo
    - Titrated up by 0.5 mg/d every 2 days.

RCT for Atypical Antipsychotics

- Risperidone: Katz et al.
  - Results
    - 625 patients randomly assigned to treatment at 40 sites
    - Demographics and illness characteristics at baseline not statistically different between groups.
    - Proportion of patients completing the 12 week trial was not statistically different between groups (~70%)
    - 42% of the risperidone 2 mg/d group discontinued treatment prematurely
    - No significant difference in benzodiazepine use in any treatment group.
    - Antiparkinsonian medication use: 9% plb, 7% rsp 0.5, 6% rsp 1.0, 13% rsp 2.0.

RCT for Atypical Antipsychotics

- Risperidone: Katz et al.
  - BEHAVE-AD scores
    - Categorical responses defined by a 50% or more reduction in BEHAVE-AD scores occurred in more patients receiving 1 mg/d (45%; p=.02) and 2 mg/d (50%; p=.002) than placebo (33%).

RCT for Atypical Antipsychotics

- Risperidone: Katz et al.
  - Safety
    - Dose related increases were noted in the risperidone group for somnolence, extrapyramidal symptoms, and peripheral edema.
    - The severity of parkinsonism did not differ significantly between patients receiving 0.5 or 1 mg/d of risperidone and placebo patients. However, differences between 2 mg/d of risperidone and placebo were significant.

RCT for Atypical Antipsychotics

- **Aripiprazole**
  - DeDeyn P, Jeste DV, Swanink R, et al. Aripiprazole for the treatment of psychosis in patients with Alzheimer's disease. J Clin Psychopharm 2005;25:463-467.

RCT for Atypical Antipsychotics

- Aripiprazole: DeDeyn et al.
  - A 10 week, double-blind, randomized, placebo-controlled study conducted at multiple sites.
  - Participants: 208 noninstitutionalized men and women living in assisted living facilities or adult communities, or with a caregiver.
    - Symptoms of delusions or hallucinations present at least intermittently for 1 month or longer.
    - MMSE score 6-24
    - NPI score ≥ 6 for delusions or hallucinations
    - Lorazepam ≤ 4 mg/d was permitted
    - Antidepressants and cognitive enhancers were allowed at stable doses.

RCT for Atypical Antipsychotics

- Aripiprazole, DeDeyn et al.
  - Exclusionary criteria
    - Nondementia cause of psychosis
    - Use of carbamazepine, valproate, lithium, sleeping agents other than zolpidem, all psychotropics except antidepressants, all other benzodiazepines.

RCT for Atypical Antipsychotics

- Aripiprazole: DeDeyn et al.
  - Primary measures:
    - Mean change from baseline to end of study in the caregiver-assessed NPI Psychosis subscale score.
    - Secondary measure: Clinical Global Impression Severity of Illness (CGI-S) and CGI-Improvement (CGI-I).
  - Randomization:
    - Minimum 7 days washout for previous psychotropic medications
    - Aripiprazole 2 mg/d or placebo
    - Titration to 5 mg/d, 10 mg/d, and 15 mg/d at maximum of 2 week intervals.

RCT for Atypical Antipsychotics

- Aripiprazole: DeDeyn et al.
  - NPI/Psychosis total
    - No significant difference between treatments in Δ NPI/Psychosis total at the 10 week endpoint.
  - CGI-S and CGI-I
    - No significant difference between treatments in Δ CGI-S or CGI-I at the 10 week endpoint.

RCT for Atypical Antipsychotics

- Aripiprazole: DeDeyn et al.
  - Safety
    - Aripiprazole was well tolerated.
    - Only somnolence was >5% more common on the aripiprazole group.
    - No worsening of cognition from baseline was noted in any group.

Risks of Atypical Antipsychotics

- Schneider LS, Dagerman KS, Insel MS. Risk of death with atypical antipsychotic drug treatment for dementia. Meta-analysis of randomized placebo-controlled trials. JAMA 205;294:1934-43.

Risks of Atypical Antipsychotics

- Death: Schneider et al.
  - 15 Placebo-controlled RCT's
    - 3 aripiprazole
    - 5 olanzapine (1 olz + rsp)
    - 5 risperidone (1 rsp + olz)
    - 3 quetiapine
  - 3353 patients randomized to drug
  - 1175 randomized to placebo

Risks of Atypical Antipsychotics

- Death: Schneider et al.
  - 87% Alzheimer's disease
  - Mean age 81.2 years
  - 70% women
  - 27% had vascular or mixed dementia

Risks of Atypical Antipsychotics

- Death: Schneider et al.
  - 118 deaths in the atypical antipsychotic drug groups
  - 40 deaths in the placebo groups
  - Overall odds ratio for deaths in patients treated with atypical antipsychotic drugs compared with placebo was 1.54.
  - Sensitivity analyses did not show evidence for differential risks for individual drugs.

Risks of Atypical Antipsychotics

- Death: Schneider et al.
  - “A fair speculation is that in frail, often medically ill, elderly patients with dementia a wide range of classes of drugs (antidepressants, sedatives, hypnotics, anxiolytics, mood stabilizers, anticonvulsants, and cardiovascular or antihypertensive drugs) similarly could be associated with this level of risk.”

Risks of Atypical Antipsychotics

- Death: Schneider et al.
  - 2 trials included haloperidol
    - 243 patients received haloperidol – 15 died
    - 239 patients received placebo – 9 died
    - Overall odds ratio for deaths in patients treated with haloperidol compared with placebo was 1.68.

Risks of Atypical Antipsychotics

- Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 2005;353:2335-41.

Risks of Atypical Antipsychotics

- Death: Wang, et al.
  - A retrospective cohort study involving 22,890 patients 65 years of age or older who had drug insurance benefits in PA and who began receiving a conventional or atypical antipsychotic medication between 1994 and 2003.

Risks of Atypical Antipsychotics

- Death, Wang, et al.
  - Analyses of mortality rates and Cox proportional-hazards models were used to compare the risk of death within 180 days, less than 40 days, 40 to 79 days, and 80 to 180 days after the initiation of therapy with an antipsychotic medication.

Risks of Atypical Antipsychotics

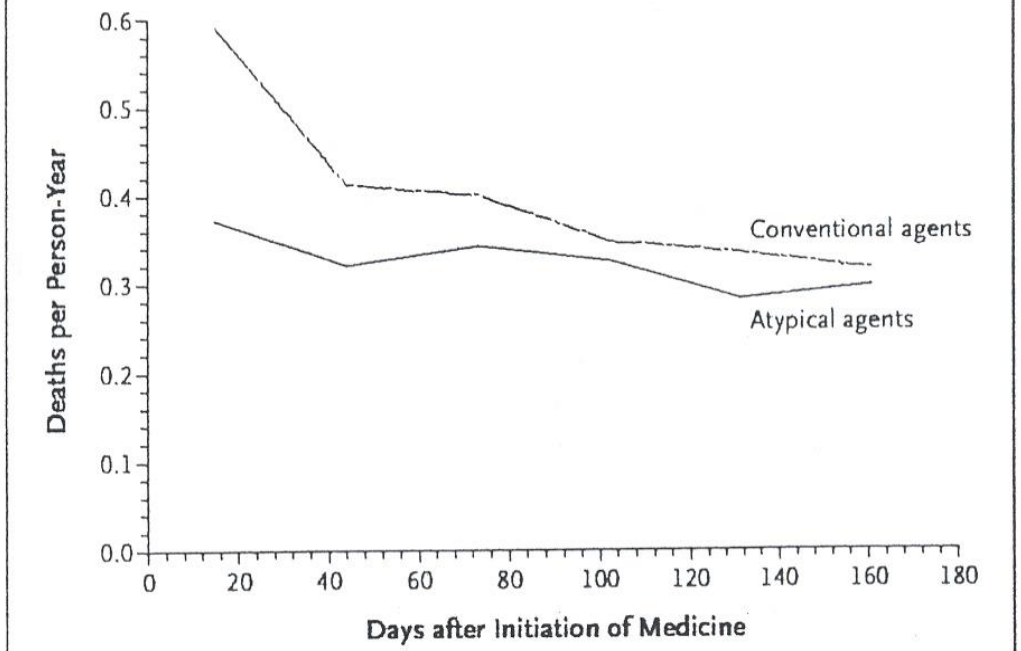


Figure 1. **Rates of Death after the Initiation of Conventional and Atypical Antipsychotic Medications.**

The rate of death before 10 days was not calculated, owing to insufficient data.

Risks of Atypical Antipsychotics

- **Death: Wang, et al.: Relative Risk of Death with Conventional vs Atypical APM**

Model	Hazard Ratio
Unadjusted analysis	1.51
Adjusted analysis	
Any conventional APM	1.37
Low dose APM	1.14
High dose APM	1.73
Adjusted analysis of death	
< 40 days after initiation	1.56
40-79 days after initiation	1.37
80-180 days after initiation	1.27
Adjusted analysis of patient subgroups	
With dementia	1.29
Without dementia	1.45
In a nursing home	1.26
Not in a nursing home	1.42

Risks of Atypical Antipsychotics

- Death. Wang, et al.
  - If confirmed, these results suggest that conventional antipsychotic agents are at least as likely as atypical agents to increase the risk of death among elderly persons and that conventional drugs should not be used to replace atypical agents in the treatment of psychotic or agitated states in the elderly.

Risks of Atypical Antipsychotics

- Schneeweiss S, Setoguchi S, Brookhart A, et al. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. CMAJ 2007;176(5):627-32.

Risks of Atypical Antipsychotics

- Death. Schneeweiss, et al.
  - A retrospective cohort study involving 37,241 patients 65 years of age or older who reside in British Columbia and who began receiving a conventional or atypical antipsychotic medication between Jan,1996 and Dec, 2004 and were free of cancer.

Risks of Atypical Antipsychotics

- Death. Schneeweiss, et al.
  - Analyses of mortality rates and Cox proportional-hazards models were used to compare the risk of death within 180 days, less than 40 days, 40 to 79 days, and 80 to 180 days after the initiation of therapy with an antipsychotic medication.

Risks of Atypical Antipsychotics

- **Death: Schneeweiss, et al.: Relative Risk of Death with Conventional vs Atypical APM**

Model	Hazard Ratio
Unadjusted analysis	1.47
Adjusted analysis	
Any conventional APM	1.32
Low dose APM	1.23
High dose APM	1.67
Adjusted analysis of death	
< 40 days after initiation	1.60
40-79 days after initiation	1.31
80-180 days after initiation	1.18
Adjusted analysis of patient subgroups	
With dementia	1.26
Without dementia	1.30
In a nursing home	1.25
Not in a nursing home	1.35

Risks of Atypical Antipsychotics

- Death. Schneeweiss, et al.
  - Together with the earlier findings, the results from our study strongly suggest that Health Canada and the FDA should include conventional antipsychotic medications in their public health advisories, which currently warn only of the increased risk of death associated with the use of atypical antipsychotic medications in elderly patients with dementia.

Risks of Atypical Antipsychotics

- Ray WA, Chung CP, Murray KT, et al. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med 2009;360:225-35.

Risks of Atypical Antipsychotics

- Death. Wayne, et al.
  - A retrospective cohort study involving 90,307 patients 30-74 years of age who reside in Tennessee and who began receiving a conventional or atypical antipsychotic medication between Jan,1990 and Dec, 2005 and were free of high risk from death by noncardiac causes.

Risks of Atypical Antipsychotics

- Death. Wayne, et al.
  - Analyses of mortality rates and Poisson regression models were used to compare the risk of death after the initiation of therapy with an antipsychotic medication.

Risks of Atypical Antipsychotics

- **Death: Wayne, et al.: Adjusted Incidence-Rate Ratios for Sudden Cardiac Death, According to use or nonuse of Antipsychotic Drugs**

User Status	Hazard Ratio
Nonuser	1.00
Former User	1.13 (ns)
Current User	
Conventional Agent	
Any	1.99
Haloperidol	1.61
Thioridazine	3.19
Atypical Agent	
Any	2.26
Clozapine	3.67
Olanzapine	2.04
Quetiapine	1.88
Risperidone	2.91

Psychotropic Risks

- Huybrechts KF, Rothman KJ, Silliman RA, et al. Risk of death and hospital admission for major medical events after initiation of psychotropic medications in older adults admitted to nursing homes. CMAJ 2011.DOI:10.1503/cmaj.101406

Psychotropic Risks

- Death: Huybrechts, et al.
  - A retrospective cohort study involving 1942 patients 65 years of age or older who were admitted to a nursing home in British Columbia and who began receiving a conventional or atypical antipsychotic medication, an antidepressant, or a benzodiazepine between 1996 and 2006.

Psychotropic Risks

- Death. Huybrechts, et al.
  - Proportional hazards models were used to compare rates of death and rates of hospital admissions for medical events within 180 days after treatment initiation with a psychotropic drug.

Psychotropic Risks

- Death, Huybrechts, et al
  - Propensity score models contained all of the potential confounders except those that were known to be strongly related to the exposure and thought to be unrelated to the outcome.
  - High dimensional propensity scores were then utilized in an effort to further reduce residual confounding

Psychotropic Risks

- **Death: Huybrechts, et al.: Relative Risk of Death with Psychotropic vs Atypical APM**

Model	Hazard Ratio
Conventional vs. Atypical	
Unadjusted analysis	1.37
Age, sex, calendar year	1.47
Propensity score	1.47
High dimensional propensity score	1.67
Antidepressant vs. Atypical	
Unadjusted analysis	1.25
Age, sex, and year	1.34
Propensity score	1.20
High dimensional propensity score	1.20
Benzodiazepines vs. Atypical	
Unadjusted analysis	1.37
Age, sex, and year	1.52
Propensity score	1.28
High dimensional propensity score	1.20

RCT for Benzodiazepines

- Cumming RG, LeConteur DG. Benzodiazepine and risk of hip fractures in older people. CNS Drugs 2003:17;825-37.

RCT for Benzodiazepines

- Hip fractures. Cumming and LeConteur
  - A detailed review of 11 epidemiological studies of the relationship between the use of benzodiazepines and the risk of hip fracture.

RCT for Benzodiazepines

- Hip fractures. Cumming and LeConteur
  - Findings
    - Eleven primary studies were identified from a literature search.
      - 4 hospital based case-control
      - 6 population based case-control
      - 1 cohort study
    - Inconsistent findings were noted and were explained by the differences in study design.

RCT for Benzodiazepines

- Hip fractures. Cumming and LeConteur
  - Findings
    - When the hospital case-control studies were excluded, then the research evidence was very consistent: use of benzodiazepines increased the risk of hip fracture by about 60%.
    - Risk of hip fracture was similar regardless of the half life of the benzodiazepine studied.
    - Higher doses were associated with higher risk

The Evidence

Valproate preparations for agitation in dementia.

The Cochrane Database of Systematic Reviews

Date of Most Recent Update Oct 2008

Valproate

- Hermann N, Lanctor KL, Rothenberg LS, et al. A placebo-controlled trial of valproate for agitation and aggression in Alzheimer's disease. Dementia and Geriatric Cognitive Disorders 2007;23:116-9.

- Porsteinsson AP, Tariot PN, Erb R, et al. Placebo controlled study of divalproex sodium for agitation in dementia. Am J Geriatr Psychiatry 2001;9(1):58-66.

- Sival RC, Haffmans PMJ, Jansen PA, et al. Sodium valproate in the treatment of aggressive behavior in patients with dementia – a randomised placebo controlled clinical trial. Int J Psychiatry 2002;17(6):579-85.

- Tariot PN, Schneider LS, Mintzer JE, et al. Safety and tolerability of divalproex sodium in the treatment of signs and symptoms of mania in elderly patients with dementia: results of a double blind placebo controlled trial. Curr Ther Rev 2001;62(1):51-67.

- Tariot PN, Raman R, Jakimovich L, et al. Divalproex sodium in nursing home residents with possible or probable Alzheimer disease complicated by agitation: a randomized controlled trial. Am Ger Psychiatry 2005;13:942-9.

Study	Population	Mean Age	% Female	Intervention
Porteinsson 2001	Mulitcentric Instutionalized Mixed dementias	85.0	61.0%	**VPA (N=28)** **Placebo (N=28)** **Mean dose 826mg/d** **6 weeks**
Sival 2002	Institutionalized Mixed dementias	80.4	59.5%	**VPA (N=42)** **Placebo (N=42)** **480mg/d** **3 weeks**
Tariot 2001	Multicentric Institutionalized Mixed dementias	83.3	64.0%	**VPA (N=87)** **Placebo (N=87)** **20mg/kg** **6 weeks**
Tariot 2002	Multicentric Institutionalized Alzheimer's dementia	84.0	68.6%	**VPA (N=48)** **Placebo (N=48)** **750mg/d** **6 weeks**
Herrmann 2007	Multicentric Institutionalized Alzheimer's dementia	85.6	42.8%	**VPA (N=14)** **Placebo (N=13)** **1500mg/d** **6 weeks**

Valproate

- The updated review corroborates the earlier findings that valproate preparations are ineffective in treating agitation among demented patients, and that valproate therapy is associated with an unacceptable rate of adverse effects. On the basis of current evidence, valproate therapy cannot be recommended for management of agitation in dementia.

Antidepressants

- Nine studies 692 individuals
  - 4 SSRI vs Placebo
  - 3 SSRI vs Conventional antipsychotics
  - 1 SSRI vs Atypical antipsychotics
  - 1 Trazodone vs Placebo
- Sertraline and citalopram were associated with a modest reduction in symptoms of agitation and psychosis.

SSRI vs Placebo

- Auchus AP, Bissey-Black C. Pilot study of haloperidol, fluoxetine, and placebo for agitation in Alzheimer's disease. J Neuropsychiatry Clin Neurosci 1997;9(4):591-93.
- Finkel SI, Mintzer E, Dysken M, et al. A randomized, placebo-controlled study of the efficacy and safety of sertraline in the treatment of the behavioral manifestations of Alzheimer's disease in outpatients treated with donepezil. Int J Ger Psychiatry 2004;19(1):9-18.
- Nyth AL, Gottfries CG. The clinical efficacy of emotional disturbances in dementia disorders. Br J Psychiatry 1990:157;894-901.
- Olafsson K, Jorgensen S, Jensen HV, et al. Fluvoxamine in the treatment of demented elderly patients: a double-blind, placebo-controlled study. Acta Psychiatrica Scand 1992;85:453-456.
- Pollock B, Mulsant BH, Rosen J, et al. Comparison of citalopram, perphenazine, and placebo for the acute treatment of psychosis and behavioral disturbances in hospitalized, demented patients. Am J Psychiatry 2002;159(3):460-5.

Study	Population	Outcomes	Bias	Intervention
Auchus 1997	Outpatients Mixed dementias	CMAI BEHAVE-AD	Low	**FLX 20 mg (N=5)** **HAL 3 mg (N=5)** **Placebo (N=5)** **6 weeks**
Finkel 2004	Outpatients Mixed dementias	NPI CGI BEHAVE-AD CMAI	Unclear	**SRT 25-200 mg (N=124)** **Placebo (N=120)** **12 weeks**
Nyth 1990	Outpatients Mixed dementias	CGI GBS	Unclear	**CIT 30 mg (N=49)** **Placebo (N=49)** **4 weeks**
Olaffson 1992	Multicentric Institutionalized Mixed dementias	GBS	Mod	**FLV 50-150 mg (N=22)** **Placebo (N=24)** **6 weeks**
Pollock 2002	Multicentric Institutionalized Mixed dementias	NBRS	Low	**CIT 20 mg (N=31)** **PER .1 mg/kg (N=33)** **Placebo (N=21)** **17 days**

Antidepressants

- The SSRI's sertraline and citalopram were associated with a reduction in symptoms of agitation when compared to placebo in two studies. One study of trazodone compared to placebo showed no difference in outcome. Both SSRI's and trazodone appear to be tolerated reasonably well when compared to placebo, typical antipsychotics, and atypical antipsychotics.

Final Recommendations

- Nonpharmacologic interventions such as optimal pain management, medical stabilization, stimulus control, socialization, adequate sleep, and exercise should be first attempted.

Final Recommendations

- At the present time atypical antipsychotics remain the best supported treatment for severe symptoms of agitation or psychosis where such behaviors are refractory to non-pharmacological interventions or when patient safety is jeopardized.

Final Recommendations

- The best evidence supports the use of risperidone as the first line pharmacotherapy for psychosis in dementia.
- The best evidence supports the use of either risperidone (0.5 mg – 2.0 mg) or olanzapine (5 mg – 10 mg) as first line pharmacotherapy for agitation in dementia.

Final Recommendations

- If clinical improvement is not observed with atypical antipsychotic drugs, they should be discontinued.
- If improvements occur, a gradual dose reduction should be attempted by 12 weeks.

Final Recommendations

- There is evidence that conventional antipsychotics, antidepressants, and benzodiazepines confer even higher risk of death and should not be considered a substitute treatment for an atypical antipsychotic based on safety considerations.
- There is evidence that benzodiazepines increase the risk of hip fractures in the elderly and should not be considered a lower risk alternative to atypical antipsychotics.

Final Recommendations

- Valproate cannot be recommended for management of agitation in dementia.
- Sertraline at 50-200 mg and citalopram at 20-30 mg can be considered as alternatives or adjuncts to risperidone and olanzapine for the treatment of agitation in dementia.

The End

Thank you!