Informed Choices: Benefits vs. Risks with Dementia Medications and Natural Products

Alzheimer’s Society – Family Education
October 22nd, 2013

Shawn Bugden BSc (Pharm), MSc, PharmD
Associate Professor
Faculty of Pharmacy
University of Manitoba
Evidence-Based Medicine

Shared Decision Making

Cholinesterase Inhibitors
- Efficacy
- Side Effects
- Guidelines
- Discontinuation

Behavioral & Psychological Symptoms of Dementia

Anti-psychotic Medications
- Efficacy
- Risks
- Shared Decisions

Natural Products
- Ginkgo
- Coconut Oil
Evidence-Based Medicine Defined

“Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients”

Dr. David Sackett

BMJ 1996 312:71-2
Evidence
Efficacy
Effectiveness
Economics
Efficiency
Ethics
Equity
The Three E’s

- **Evidence-Based Medicine** – review of best available evidence to evaluate the efficacy and effectiveness of interventions – avoid wasting resources on ineffective or inappropriate treatments

- **Economics** - seeks efficient use of resources from the standpoint of population health – with scarce resources an economic approach seeks to optimize health benefits to the general population

- **Ethics** – focus on fairness in allocating resources to meet health needs – when resources are scarce – ethical approach seeks a fair distribution among competing health needs

Evidence Based-Medicine Paradigm

- Professional Judgement
- Experience

Best Evidence

Clinical Expertise

EBM

Patient Values

- Clinical Trials
- Systematic Reviews

- Religious & Moral Beliefs
- Preferences and Rights
Concordance?

- **Compliance**: The process of prescribing and medicine-taking based on partnership.

- **Adherence**: It is an agreement reached after negotiation between a patient and a healthcare professional that respects the beliefs and wishes of the patient in determining whether, when and how medicines are to be taken.

- **Concordance**: Differs from compliance, as compliance suggests the patient should simply follow the doctor’s orders.
When possible persons with dementia should be kept informed and included in decisions related to daily life

> 90% of people with dementia wanted to be more involved in decision making

67-95% of people with Alzheimer’s Disease are cared for at home

**Medication management** known contributor to caregiver workload and stress

Prince M. Psychiatry 2007;6:488.
The Balance

Benefit

Safety

Costs
Hierarchy of Evidence

- Meta-analysis of RCTs
- Individual RCT
- Observational Studies (Patient Important Outcomes)
- Basic Research (Test tube, animal/human physiology)
- Clinical Experience (Non-systematic clinical observation)
Alzheimer’s Medications
Mechanism
# Alzheimer’s Medications

<table>
<thead>
<tr>
<th></th>
<th>Rivastigmine</th>
<th>Donepezil</th>
<th>Galantamine</th>
<th>Memantine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand Name</strong></td>
<td>Exelon</td>
<td>Aricept</td>
<td>Reminyl</td>
<td>Ebixa</td>
</tr>
<tr>
<td></td>
<td>Exelon Patch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Half Life</strong></td>
<td>1h capsule</td>
<td>70h</td>
<td>7h</td>
<td>60-100 h</td>
</tr>
<tr>
<td></td>
<td>3h patch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Approved Indications</strong></td>
<td>Alzheimer's Disease</td>
<td>Alzheimer's Disease</td>
<td>Alzheimer's Disease</td>
<td>Alzheimer's Disease</td>
</tr>
<tr>
<td></td>
<td>Alzheimer's Disease</td>
<td>Alzheimer's Disease</td>
<td>Alzheimer's Disease</td>
<td>Alzheimer's Disease</td>
</tr>
<tr>
<td><strong>Starting Dose</strong></td>
<td>1.5mg TWICE Daily</td>
<td>5mg/day</td>
<td>8mg /24 hour</td>
<td>5mg/day</td>
</tr>
<tr>
<td><strong>Target Dose</strong></td>
<td>6mg TWICE daily</td>
<td>10mg day</td>
<td>12mg TWICE daily</td>
<td>20mg day</td>
</tr>
</tbody>
</table>
Alzheimer’s Disease Outcomes

- Measurement of rate of patient decline rather than improvement or prevention of events

- Greater focus on patient testing and functional assessment
  - Mini-Mental Exam
  - Functional Assessment
    - AD Functional Assessment and Change Scale (ADFACS)
  - Quality of Life Measurements
<table>
<thead>
<tr>
<th>Activity</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORIENTATION</strong> – one point for each answer</td>
<td></td>
</tr>
<tr>
<td>Ask: “What is the: (year)(season)(date)(day)(month)?”</td>
<td></td>
</tr>
<tr>
<td>Ask: “Where are we: (state)(county)(town)(hospital)(floor)?”</td>
<td></td>
</tr>
<tr>
<td><strong>REGISTRATION</strong> – score 1,2,3 points according to how many are repeated</td>
<td></td>
</tr>
<tr>
<td>Name three objects: Give the patient one second to say each.</td>
<td></td>
</tr>
<tr>
<td>Ask the patient to: repeat all three after you have said them.</td>
<td></td>
</tr>
<tr>
<td>Repeat them until the patient learns all three.</td>
<td></td>
</tr>
<tr>
<td><strong>ATTENTION AND CALCULATION</strong> – one point for each correct subtraction</td>
<td></td>
</tr>
<tr>
<td>Ask the patient to: begin from 100 and count backwards by 7.</td>
<td></td>
</tr>
<tr>
<td>Stop after 5 answers. (93, 86, 79, 72, 65)</td>
<td></td>
</tr>
<tr>
<td><strong>RECALL</strong> – one point for each correct answer</td>
<td></td>
</tr>
<tr>
<td>Ask the patient to: name the three objects from above.</td>
<td></td>
</tr>
</tbody>
</table>
LANGUAGE

Ask the patient to: identify and name a pencil and a watch. (2 points)

Ask the patient to: repeat the phrase “No ifs, ands, or buts.” (1 point)

Ask the patient to: “Take a paper in your right hand, fold it in half, and put it on the floor “ (1 point for each task completed properly)

Ask the patient to: read and obey the following: “Close your eyes.” (1 point)

Ask the patient to: write a sentence. (1 point)

Ask the patient to: copy a complex diagram of two interlocking pentagons. (1 point)

TOTAL (0–30): ___
Functional Assessment

- Alzheimers Disease Functional Assessment and Change Scale
- 54 Point Scale
- 24 Points
  - 6 items assess Activities of Daily Living (0 to 4 points per item)

### Activities of Daily Living
- Toileting
- Feeding
- Dressing
- Grooming
- Bathing
- Walking

30 Points
- 10 items assess Instrumental Daily Activities (0 to 3 points per item)

Higher Score = Greater Impairment

<table>
<thead>
<tr>
<th>Instrumental Daily Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of Telephone</td>
</tr>
<tr>
<td>Household Tasks</td>
</tr>
<tr>
<td>Using Household Appliances</td>
</tr>
<tr>
<td>Managing Money</td>
</tr>
<tr>
<td>Shopping</td>
</tr>
<tr>
<td>Food Preparation</td>
</tr>
<tr>
<td>Ability to Get Around</td>
</tr>
<tr>
<td>Hobbies and Leisure</td>
</tr>
<tr>
<td>Handling Mail</td>
</tr>
<tr>
<td>Grasp of Situations/Explanations</td>
</tr>
</tbody>
</table>
Impact of Treatment

- Both placebo and treatment groups +’ve change = greater impairment
- Statistical Significance
- Clinical Significance

Levels of Evidence

- Meta-analysis systematic reviews
  - Quality rating
- Randomised controlled trials
  - Quality rating
- Observational studies
  - Quality rating
- Non-analytic studies
- Expert opinion

Evidence table → Considered judgment → Graded recommendation
Consensus Guidelines - Benefits

- Impact for most patients is modest and temporary with not everyone responding to therapy
- Cognitive responders (4 or more points on Alzheimer’s Disease Assessment Scale)

- Number Needed to Treat (NNT)
  10 95% CI (9 to 15)

Hogan DB et al. CMAJ 2008;179:1019.
### Cholinesterase Inhibitors
#### Common Side Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Nausea</th>
<th>Diarrhea</th>
<th>Headache</th>
<th>Insomnia</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>11%</td>
<td>10%</td>
<td>10%</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Galantamine</td>
<td>17%</td>
<td>10%</td>
<td>8%</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>37%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(oral)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hogan DB et al. CMAJ 2008;179:1019.
Consensus Guidelines
– Side Effects

- Urinary incontinence, insomnia, increased use of hypnotics
- Anorexia, nausea, vomiting, diarrhea
- Weight loss

- Number Needed to Harm (NNH)
  12 95% CI (10 to 18)

* 2012 Consensus – no new drugs approved since last consensus 2006/8

Hogan DB et al. CMAJ 2008;179:1019.
Problem with Dropouts

- Drop rates > 20%
- 1-year drop rates in trials (26.9 – 48.1%)
- Last observation carried forward
- Exaggerates the benefit of dementia therapy
Problem with Dropouts

- Drop rates even higher in community
- 65% of patients taking suboptimal doses
- Adherence to therapy low
- Average duration therapy 4-5 months

Targeted Therapy
"NO!
Try not!
DO or DO NOT,
There is no try."
Your options according to Yoda.

- Do.
- Do not.
- Try.

Source: GraphJam.com
Deliberate Discontinuation

- Adequate trial at reasonable dose
- Assessment of personal benefit and risk
- Impact on targeted symptoms
- Appropriate taper and review
Consensus Guidelines - Discontinuation

- Patient/proxy decides to stop based on benefit/risk
- Non-adherence
- Cognitive/functional decline is greater than prior to treatment
- Intolerable side effects
- Dementia progresses to point where no further clinically meaningful benefit is possible

Hogan DB et al. CMAJ 2008;179:1019.
Alzheimer’s Medications Mechanism
Reference List of Drugs with Anticholinergic Effects

Aricept (donepezil) and Exelon (rivastigmine) are reversible inhibitors of the enzyme acetylcholinesterase. Because of their mechanism of action, anticholinergic medications can interfere with the activity of Aricept and Exelon. The following is a list of drugs with anticholinergic effects with emphasis on those with moderate to high activity. This list has been reviewed by DQAC and SFC and will be used for assessing Aricept and Exelon requests. Coverage cannot be approved if a patient is using a drug on this list concurrently with Aricept or Exelon.

**Antidepressants with moderate to high anticholinergic effects**
- amitriptyline (Elavil)
- clomipramine (Anafranil)
- doxepin (Sinequan)
- imipramine (Tofranil)
- nortriptyline (Aventyl)
- protriptyline (Triptil)
- trimipramine (Surmontil)

**Antiparkinsonian**
- benztropine mesylate (Cogentin)
- biperiden HCl (Akineton)*
- ethopropazine (Parsitan)
- orphenadrine (Disipal)
- procyclidine (Kemadrin)
- trihexyphenidyl (Novo-Hexidyl, Apo-Trihex)

**Antiemetics/Antivertigo with moderate to high anticholinergic effects**
- dimenhydrinate (Gravol)
- meclizine (Antivert)
- promethazine (Phenergan)*
- scopolamine (Transderm V)

**Antipsycotics with moderate to high anticholinergic effects**
- chlorpromazine (Largactil)
- clozapine (Clozaril)
- flupenthixol (Fluanxol)
- loxapine (Loxapac)
- mesoridazine (Serentil)
- methotrimeprazine (Nozinan)
- olanzapine (Zyprexa)
- pericyazine (Neuleptil)
- pimozide (Orap)
- thioproperazine (Majeptil)*
- thioridazine (Mellaril)
- zuclopenthixol (Clopixol)

**Antihistamines/Antipruritics with moderate to high anticholinergic effects**
- chlorpheniramine (Chlor-Triplon)*
- cyproheptadine (Periactin)*
- diphenhydramine (Benadryl)*
- trimeprazine (Panectyl)

**Miscellaneous**
- cyclobenzaprine (Flexeril) - moderate
- diphenoxylate/atropine (Lomotil) – moderate
- disopyramide (Norpace) – moderate

**Antispasiotics**
- dicyclomine (Formulex, Bentylol)
- flavoxate (Urispas)
- glycopyrrolate (Robinul)
- hyoscyne butylbromide (Buscopan)
- hyoscyamine/atropine/hyoscyne/
  - phenobarbital (Donnatal)
- oxybutynin (Ditropan)
- pinaverium bromide (Dicetel)*
- propantheline bromide (Pro-Banthine, Propanthel)
- tolterodine l-tartrate (Detrol)
Please complete all sections to allow this request to be processed.

1. Drug requested (check one):  [ ] Aricept  or  [ ] Exelon  or  [ ] Reminyl

2. This patient is (check one):  [ ] not currently taking the requested medication (new patient)
   [ ] currently taking the requested medication (existing patient) or renewal
   [ ] switching from one cholinesterase inhibitor to another

3. Diagnosed with probable Alzheimer disease as per DSM-IV criteria.  Yes  [ ]  No  [ ]

4. Recent+ MMSE score*  _____________  date  _____________

5. FAQ score*  _____________  date  _____________

6. Drugs with anticholinergic activity++ are to be discontinued at least 14 days before the MMSE and FAQ are administered and are not to be used concurrently with Aricept, Exelon or Reminyl.
   List all medications the patient is currently taking or attach a list.
   [ ] this patient is not taking other medications

   ______________________________________  ______________________________________
   ______________________________________  ______________________________________
   ______________________________________  ______________________________________
   ______________________________________  ______________________________________
   ______________________________________  ______________________________________
   ______________________________________  ______________________________________
Evaluation of Local Practice

Acetylcholinesterase Use in X Region

# of Residents

- PCH A
- PCH B
- PCH C
- PCH D
- PCH E
- PCH F

Legend:
- Inhibitors & Anticholinergics
- Inhibitors
Evaluation of Local Practice

Concurrent Anticholinergic Use with Acetylcholinesterase Inhibitors

- PCH A
- PCH B
- PCH C
- PCH D
- PCH E
- PCH F
- Overall

Percentage Concurrent Use of Anticholinergics

0% 10% 20% 30%
## Memantine

N-methyl-D-aspartate (NDMA) Receptor Antagonist

### Starting Dose
5mg once daily am

### Maintenance Dose
10mg twice daily

### Warnings
- Avoid in hypersensitivity
- Avoid in severe renal impairment
- Caution cardiovascular disease, seizures
- Monitor ophthalmic condition
- Do not combine with amantadine, ketamine or dextromethorphan

### Adverse Effects
- Dizziness 7%
- Constipation 6%
- Confusion 6%
- Headache 6%
- Hypertension 3%
Behavioral & Psychological Symptoms of Dementia (BPSD)

- Aggression
  - Physical aggression
  - Verbal Aggression
  - Aggressive resistance to care
- Agitation
  - Pacing
  - Repetitive actions
  - Dressing/undressing
  - Restless/anxious
- Apathy
  -Withdrawn
  - Lacks interest
  - Amotivation
- Depression
  - Sad
  - Tearful
  - Hopeless
  - Guilty
  - Anxious
  - Irritable/screaming
  - Suicidal
- Mania
  - Euphoria
  - Pressured speech
  - Irritable
- Psychosis
  - Hallucinations
  - Delusions
  - Misidentification
  - Suspicious

McShane, R. International Psychogeriatrics. 12-S1:147-153.
Story Outline

- WHAT
  - What are Antipsychotics?
- WHERE
  - Where Are They Being Used?
- WHO
  - Who Should Be Using Them?
    - Do They Work
    - Are They Safe
- WHEN
  - When Should They Be Used?
- WHY
  - Why We All Have a Role?
What Are Antipsychotics

- Typical (1\textsuperscript{st} Generation)
  - Haloperidol
  - Loxapine
  - Methotrimemeprazine

- Atypical (2\textsuperscript{nd} Generation)
  - Risperidone
  - Olanzapine
  - Quetiapine
**Risperidone in Dementia**

Total BEHAVE-AD

<table>
<thead>
<tr>
<th>Dose of Risperidone</th>
<th>Mean Improvement from Baseline*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo n=161</td>
<td>4.2</td>
</tr>
<tr>
<td>0.5 mg n=146</td>
<td>4.8</td>
</tr>
<tr>
<td>1.0 mg n=148</td>
<td>6.5†</td>
</tr>
<tr>
<td>2.0 mg n=162</td>
<td>6.4†</td>
</tr>
</tbody>
</table>

*At end point.
†P=0.002 vs placebo.
†P=0.001 vs placebo.

Hierarchy of Evidence

- Meta-analysis of RCTs
- Individual RCT
- Observational Studies (Patient Important Outcomes)
- Basic Research (Test tube, animal/human physiology)
- Clinical Experience (Non-systematic clinical observation)
**Cochrane Review: Efficacy of Risperidone**

**BEHAVE-AD**

- **Behavior Pathology in Alzheimer's Disease**
- **Rating Scale**
  - 25 items on a 4-point scale of increasing severity
  - 7 clusters of behavior
  - Aggressive Subscore
    - 3 symptoms subscores
      - Verbal outbursts
      - Physical threats, violence or both
      - Other agitation

**Risperidone 1mg/day vs placebo**

- **-0.84 95% CI (-1.28 to -0.40)**

**Ballard, C. et al. 2006. Cochrane Database of Systematic Reviews CD003476.**

---

**Risperidone in Dementia**

**Total BEHAVE-AD**

- **Mean Improvement from Baseline**
- **Placebo n=161**
- **0.5 mg n=146**
- **1.0 mg n=148**
- **2.0 mg n=162**

- **Placebo**
  - 4.2
- **0.5 mg**
  - 4.8
- **1.0 mg**
  - 6.5
- **2.0 mg**
  - 6.4

*At end point. 
†P=.002 vs placebo. 
P=.001 vs placebo.

BEHAVIORAL PATHOLOGY IN ALZHEIMER’S DISEASE (BEHAVE-AD)

Assessment is based on information obtained from caregiver or other informants regarding behavior over the last 2 weeks. Choose the highest applicable severity rating for each item, then tally the score for each type of symptom.

Paranoid and Delusional Ideation

“People are stealing things” delusion:

0. not present
1. delusion that people are hiding objects
2. delusion that people are coming into the home and hiding or stealing objects
3. talking and listening to people coming into the home

0 1 2 3
BEHAVE-AD

- Behavior Pathology in Alzheimer’s Disease Rating Scale
- 25 items on 4 point scale of increasing severity
- 7 clusters of behavior

- Aggressive Subscore – 3 symptoms subscores
  - Verbal outbursts
  - Physical threats, violence or both
  - Other agitation

Risperidone 1mg/day vs placebo
-0.84 95% CI (-1.28 to -0.40)

# Cohen-Mansfield Agitation Inventory

A seven point rating scale for assessing the frequency with which people show certain behaviours. Rate each descriptor from 1-7. The scale takes 10-15mins to complete.

1 = never  
2 = less than once per week  
3 = 1-2 per week  
4 = several times per week  
5 = 1-2 per day  
6 = several times per day  
7 = several times per hour

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Pace, aimless wandering</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Inappropriate dress or disrobing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Spitting (include at meals)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Cursing or verbal aggression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Constant unwarranted request for attention or help</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Repetitive sentence or questions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Hitting (include self)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Kicking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>Grabbing onto people</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>Pushing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>Throwing things</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CMAI Total Aggressiveness

- Cohen-Mansfield Agitation Inventory
- 29 types of agitated behaviour – pacing, verbal aggression ...
- 7 point scale for frequency (1 = never, 7 = several times per hour)
- Total aggression cluster score

Risperidone 1mg/day vs placebo
-1.17 95% CI (-2.02 to -0.32)

Cohen-Mansfield Agitation Inventory

Antipsychotics in Dementia

- **Typical Antipsychotics**
  - No difference in efficacy
  - Limited study
  - Higher EPS symptoms
  - Concern over side effects – atypicals favored

- **Atypical Antipsychotics**
  - Off Label Use
  - > 80% of antipsychotics in older adults are atypicals
  - 40% placebo response rate
  - 40% patients with dementia taking antipsychotic drugs


Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease

Lon S. Schneider, M.D., Pierre N. Tariot, M.D., Karen S. Dagerman, M.S., Sonia M. Davis, M.D., Ph.D., John K. Hsiao, M.D., M. Saleem Iqmail, M.D., Barry D. Lebowitz, Ph.D., Constantine G. Lyketsos, M.D., M.H.S., J. Michael Ryan, M.D., T. Scott Stroup, M.D., David I. Sultzer, M.D., Daniel W. Weintraub, M.D., and Jeffrey A. Lieberman, M.D., for CATIE-AD Study Group

ABSTRACT

BACKGROUND
Second-generation (atypical) antipsychotic drugs are widely used to treat psychosis, aggression, and agitation in patients with Alzheimer's disease, but their benefits are uncertain and concerns about safety have emerged. We assessed the effectiveness of atypical antipsychotic drugs in outpatients with Alzheimer's disease.

METHODS
In this 42-site, double-blind, placebo-controlled trial, 421 outpatients with Alzheimer's disease and psychosis, aggression, or agitation were randomly assigned to receive olanzapine (mean dose, 8.1 mg per day), quetiapine (mean dose, 5.3 mg per day), risperidone (mean dose, 1.4 mg per day), or placebo. Doses were adjusted as needed, and patients were followed for up to 36 weeks. The main outcomes were the time from initial treatment to the discontinuation of treatment for any reason and the number of patients with at least minimal improvement on the Clinical Global Impressions of Change (CGIC) scale at 12 weeks.

RESULTS
There were no significant differences among treatments with regard to the time to the discontinuation of treatment for any reason: olanzapine (median, 8.1 weeks), quetiapine (median, 5.3 weeks), risperidone (median, 7.4 weeks), and placebo (median, 8.0 weeks) (P = 0.52). The median time to the discontinuation of treatment due to adverse events was shorter for olanzapine (22.1 weeks) and risperidone (26.7 weeks) compared with quetiapine (9.1 weeks) and placebo (8.0 weeks) (P = 0.002). The time to the discontinuation of treatment due to adverse events or intolerability favored placebo. Overall, 24% of patients who received olanzapine, 16% of patients who received quetiapine, 15% of patients who received risperidone, and 7% of patients who received placebo discontinued their assigned treatment owing to intolerability (P = 0.009). No significant differences were noted among the groups with regard to improvement on the CGIC scale. Improvement was observed in 12% of patients assigned to olanzapine, 26% of patients assigned to quetiapine, 29% of patients assigned to risperidone, and 21% of patients assigned to placebo (P = 0.22).

CONCLUSIONS
Adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease. (ClinicalTrials.gov number, NCT00115548.)
CATIE-AD

521 Patients screened

100 Excluded
   50 Did not meet inclusion criteria
   14 Declined to participate
   36 Were excluded for other reasons

421 Underwent randomization in phase 1

100 Assigned to olanzapine
   1 Did not take drug

94 Assigned to quetiapine
   0 Did not take drug

85 Assigned to risperidone
   1 Did not take drug

142 Assigned to placebo
   3 Did not take drug
Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer’s Disease

RCT

Double-blind, placebo-controlled

N=421

Four Arms

- Placebo
- Olanzapine 2.5 or 5mg
- Risperidone 0.5 or 1mg
- Quetiapine 25mg or 50mg
Outpatients – Alzheimer’s Disease with established psychosis aggression or agitation

Doses adjusted as needed – followed for 36 weeks

Primary outcome – time from initial treatment until discontinuation
CATIE-AD

Median Time (weeks)

Treatment Arm

Olanzapine  8.1
Quetiapine  5.3
Risperidone  7.4
Placebo  8

CATIE-AD Time to Discontinuation

Overall discontinuation rates range from 77-85%.

Clinical Global Impression of Change (CGI-C)
- 7 point scale
- No significant difference (P=0.22)

Conclusion – no large clinical benefit of treatment vs. placebo

CATIE-AD

- Average dosage per day
  - Olanzapine 5.5mg
  - Risperidone 1 mg
  - Quetiapine 56.5mg

- Median time to discontinuation due to lack of efficacy
  - Olanzapine 22.1 weeks
  - Risperidone 26.7 weeks
  - Quetiapine 9.1 weeks
  - Placebo 9.0 weeks

- Discontinuation Adverse Effects / Intolerability
  - Olanzapine 24%
  - Risperidone 18%
  - Quetiapine 16%
  - Placebo 5%

The Balance

- Benefit
- Safety
- Costs
New anti-psychotic drugs may double heart risk
Study: Meds for schizophrenia, bipolar disorder up chance of cardiac death

The Associated Press
updated 4:03 p.m. CT, Wed., Jan. 14, 2009

NEW YORK - Newer anti-psychotic drugs are no safer than older ones for the risk of suddenly dying from a heart problem, says a study that finds they roughly double that hazard.
Other Adverse Effects

- Meta-analysis of RCTs
  - Stroke  1.9% vs 0.9% in placebo
    - 1% Absolute Risk Increase
    - OR 2.1 95% CI 1.2 to 3.8
    - Not all studies have found a significant increase risk of stroke
- Falls - Increased Risk
- Drowsiness
- Cognitive Decline

Hierarchy of Evidence

- Meta-analysis of RCTs
- Individual RCT
- Observational Studies (Patient Important Outcomes)
- Basic Research (Test tube, animal/human physiology)
- Clinical Experience (Non-systematic clinical observation)
Death

- ICES – Institute for Clinical Evaluative Sciences
  - Retrospective data base analysis
  - Community adjusted HR 1.31 (95% CI 1.02 to 1.70)
  - Nursing Home adjusted HR 1.55 (95% CI 1.15 to 2.07)
  - 30 days – persist to 180 days

- Pooled Analysis of RCTs
  - 15 trials – 3353 patients
  - OR 1.54 (95% CI 1.06 to 2.23)
  - ARR 1%
  - Haloperidol just as bad

Safety – Sudden Cardiac Death

- Cohort Study of Medicaid Patients
  - Age 30 to 74 (mean age 45.7 years)
  - 65.2% women
  - 93,300 users antipsychotics matched controls 186,600
  - Block repolarizing K channels, prolong QT interval

- Rate Ratio – Sudden Cardiac Death
  - Typicals 1.99 (95% CI 1.68 to 2.34)
  - Atypicals 2.26 (95% CI 1.88 to 2.72)
  - Atypical vs Typical 1.14 (95% CI 0.93 to 1.39)

Safety – Sudden Cardiac Death – Dose Response

Figure 1. Adjusted Incidence-Rate Ratios for Sudden Cardiac Death among Current Users of Antipsychotic Drugs, According to Type of Drug and Dose.

Doses are shown as chlorpromazine equivalents: low dose, <100 mg; moderate dose, 100 to 299 mg; high dose, 300 mg or more. The reference category is nonusers of antipsychotic drugs. P values are for a dose–response relationship. I bars indicate 95% confidence intervals.

Safety – In Perspective

- 3 Deaths per year for every 1000 patients

- Clozapine agranulocytosis 6.8 cases per year for every 1000 patients

- Clozapine deaths was 0.2 per year for every 1000 patients

Safety – In Perspective

- Age – risperidone QT prolongation
  - 3% of patients – mean age 40
  - 6% of patients – mean age 78

- Risk vs Benefit

DART-AD

- Two Arms
  - Stop Antipsychotic, Switch to Placebo
  - Continue Antipsychotic
- Patient on Antipsychotics > 3 months
- Age – 85 years
- MMSE = 11
- Survival at 2 years
  - 71% vs 46%
  - NNT=4 (for 2 years)

DART-AD

Where Are They Being Used?

Figure 1

Annual number of antipsychotic prescriptions dispensed in Manitoba between 1996 and 2006

Where Are They Being Used?

Figure 2
Annual number of patients filling a prescription for an antipsychotic agent between 1996 and 2006

Figure 3
Annual total costs of first-generation versus second-generation antipsychotics between 1996 and 2006

Behavioral & Psychological Symptoms of Dementia (BPSD)

Aggression
- Physical aggression
- Verbal Aggression
- Aggressive resistance to care

Apathy
- Withdrawn
- Lacks interest
- Amotivation

Agitation
- Pacing
- Repetitive actions
- Dressing/undressing
- Restless/anxious

Sad
- Tearful
- Hopeless
- Guilty

Mania
- Euphoria
- Pressured speech
- Irritable

Psychosis
- Hallucinations
- Delusions
- Misidentification
- Suspicious

Depression
- Anxious
- Irritable/screaming
- Suicidal

McShane, R. International Psychogeriatrics. 12 -S1:147-153.
<table>
<thead>
<tr>
<th>Common BPSD Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>agitation*</td>
</tr>
<tr>
<td>apathy</td>
</tr>
<tr>
<td>aggression* (verbal/physical)</td>
</tr>
<tr>
<td>calling out, screaming</td>
</tr>
<tr>
<td>hostility</td>
</tr>
<tr>
<td>sexual dis-inhibition</td>
</tr>
<tr>
<td>resistive</td>
</tr>
<tr>
<td>wandering</td>
</tr>
<tr>
<td>vocalizations</td>
</tr>
<tr>
<td>hoarding</td>
</tr>
<tr>
<td>nocturnal restlessness</td>
</tr>
<tr>
<td>emotional lability</td>
</tr>
<tr>
<td>paranoid behaviours</td>
</tr>
<tr>
<td>psychosis* (hallucinations/delusions)</td>
</tr>
<tr>
<td>intrusiveness</td>
</tr>
<tr>
<td>repetitive behaviours</td>
</tr>
</tbody>
</table>

* symptoms with some evidence of benefit for antipsychotics

Adapted from RxFiles – October 2011
When?
Table 2. Common Triggering Factors in BPSD

<table>
<thead>
<tr>
<th><strong>Psychosocial</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Distress</td>
</tr>
<tr>
<td>Fear of Danger</td>
</tr>
<tr>
<td>Misinterpretation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Environmental</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Bad Company&quot;</td>
</tr>
<tr>
<td>Boredom</td>
</tr>
<tr>
<td>Confusing Surroundings</td>
</tr>
<tr>
<td>Noise</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Medical</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>B12/Folic Acid Deficiency</td>
</tr>
<tr>
<td>Hunger/Thirst</td>
</tr>
<tr>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>Hypo-thyroidism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Medications (Drug Induced Delirium)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics</td>
</tr>
<tr>
<td>Benzodiazepines</td>
</tr>
</tbody>
</table>
Nonpharmacological Interventions

- Unmet Needs Interventions
  - Behavior communicating unmet need
  - E.g. Pain, lack of socialization

- Learning and Behavioral Interventions
  - Undesirable behaviors inadvertently reinforced

- Environmental Vulnerability and Reduced Stress Threshold Interventions
  - Mismatch between environment and ability to cope
  - E.g. Agitated by too much noise

- 3 RCTs and 6 Single Case Designs – potential but further rigorous study required

Other Medications

- Cholinesterase Inhibitors and Memantine
- Trazadone
- SSRIs
- Anticonvulsants (Carbamazepine, Divalproex)
- Benzodiazepines

- Poor quality studies
- Small sample sizes
- No placebo control
- Heterogeneous enrolment criteria
- All off-label use

Balanced Decisions

- Antipsychotics associated with a NNH of 100 95% CI (53 to 1000) (1 death for every 100 patients treated for 10-12 weeks)

- Benefits are (at best) modest – not always statistically significant and clinical significance questionable (NNT 4 to 12)

- However – BPSD a significant and important problem

Balanced Decisions

- Avoid if possible but not always possible
- Avoid higher dosages
- When needed – assess for tolerability and efficacy in 3 to 7 days
- Reassess for taper and/or discontinuation every 3 months
Balanced Decisions

- Other medications – less studied – also modest efficacy

- Individual risk benefit assessment with informed consent

- Non-pharmacological methods should be embraced but require further rigorous evaluation

- Exercise

- Public research agenda

Other Agents

- **Metal protein attenuating compounds** (chelation – ex clioquinol) – no evidence beneficial – safety?

- **Statins** – prevention – no good evidence that they reduce the risk

- **Vitamin E** – no convincing evidence of benefit

- **Estrogen supplements** – may be harmful

- **ASA, NonSteroids Anti-inflammatory Drugs (NSAIDS)** in treatment – not proven, not recommended.

Scott HD et al. Cochrane Database of Systematic Reviews 2001
Jaturapatporn D et al. Cochrane Database of Systematic Reviews 2012
Farina N et al. Cochrane Database of Systematic Reviews 2012
Sampson EL et al. Cochrane Database of Systematic Reviews 2012
Ginkgo biloba

Ginkgo biloba

- Allergies
- Bleeding risks
There is A Dragon In My Garage
Pharmacology is a story not evidence
Pharmacology is low level evidence
Anecdote is not evidence
Risks?
Benefits?
How To Make A Dragon

- Acute example
- Alzheimer’s progressive but good days/periods and bad days/periods

![Natural Course of Disease](image.png)
How To Make A Dragon

Natural Course of Disease

Starting in the Middle

Figure 3.1. Hypothetical Natural History of Sarah's Arthritis Pain

Figure 3.3. Natural History Masquerading as a CAM Analgesic Effect
How To Make A Dragon

- Placebo effect of 30-40% response

![Graph showing the placebo effect plus decreasing pain over time.](Figure 3.4. The Placebo Effect Added to a Natural History Effect)
Coconut Oil

- University of South Florida Trial
- Economics of Trials
- 65 patients
- $250,000 grant from private foundation
- Results expected in a year