Update and Review of the Pharmacological Treatment of Alzheimer’s Disease and Other Dementias

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Presentation Outline

• Introduction
• Pathophysiology
• Differential Diagnoses of Dementia
• Treatment / Management Options
• Summary

Types of Dementia

• Alzheimer’s Disease
• Vascular Dementia
• Wernicke-Korsakoff
• Multiple Sclerosis
  • Frontotemporal Dementia (FTD)
    • Pick’s Disease
  • HIV-Related Dementia
• Parkinson’s Disease
• Huntington’s Disease
• Dementia with Lewy Bodies
• Creutzfeldt-Jakob Disease
“A Peculiar Disease of the Cerebral Cortex”

Alzheimer’s Original Case Report (1907)
The first case report of Alzheimer’s disease highlighted the presence of psychosis and agitation in these patients

- “The first noticeable symptom of illness was suspiciousness of her husband.... and believing that people were out to murder her”
- “She screams that her doctor wants to cut her open; at times, she seems to have auditory hallucinations”

Source: Alzheimer’s, Allegmeine Zeitschrift für Psychiatrie, 1907;64:146-148.

Alzheimer’s Disease (AD): More Than Just Memory Loss

- Loss of memory and other cognitive functions
- Decline in ability to perform activities of daily living (ADLs)
- Changes in personality and behavior
- Increases in resource utilization
- Eventual nursing home placement

Caregivers

- 73% of AD patients need help
  - Day to day activities
  - Medication
- More than 70% of people with AD are living at home
- Spouse/friend/family member
- Workload increase
- Physical / emotional stress
- Increased Depression & Pain
DSM-IV Criteria for AD Dementia

- Memory Impairment AND
- One or more of the following:
  - Aphasia (inability to communicate)
  - Apraxia (inability to carry out motor activities)
  - Agnosia (failure to recognize objects)
  - Executive Function Disturbance (organize, planning, etc.)
- Must affect their occupational and social function and are at a significant decline from previous state
- Other disease states and causes have been ruled out

Name Change.....

- The word “dementia” is related to a Latin word for "mad," or "insane."
  Because of this, the introduction of the term "neurocognitive disorder" attempts to help reduce the stigma associated with both the word dementia and the conditions that it refers to.
  - The APA acknowledges that because the word dementia is in common use and easily understood by everyone, it will remain in use. The terms major neurocognitive disorder and minor neurocognitive disorder are likely to be used only by healthcare professionals and organizations. However, not all care professionals and organizations are likely to use the new term.
  - The Alzheimer's Association still uses the word dementia, not neurocognitive disorder.

DSM-5 Criteria for
Major Neurocognitive Disorder (NCD)
vs Mild Neurocognitive Disorder

- Still Memory Impairment
- Neurocognitive dysfunction
- Must affect their ‘independence’ vs occupational and social function
- Other disease states and causes have been ruled out
6 domains

MMSE: Mini-Mental State Exam

- Assess mental status
- 11 questions
  - Tests cognitive function:
    - Orientation
    - Registration
    - Attention
    - Calculation
    - Recall
    - Language
  - Maximum score is 30
  - 24 or lower is indicative of cognitive impairment
**Projected Prevalence of AD**

![Projected Prevalence of AD graph](image)


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**Natural Course of Illness**

![Natural Course of Illness diagram](image)

Reproduced with permission from Feldman and Gracon, 1996.

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**Pathophysiology of Alzheimer's Disease**

*As determined by levels of choline acetyltransferase.*


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Pathophysiology of Alzheimer’s Disease (cont)

• Formation of amyloid plaques

• Formation of neurofibrillary tangles

• Early degeneration of cholinergic neurons

• Widespread degeneration of cortical neurons with atrophy as the disease progresses
Risk Factors

- Age
- Family History
- Familial Forms
  - (Chromosomes 1, 5, 14, 19, 21)
- APO-E-4 on Chromosome 19
- Head injury
- Lower educational level

Differential Diagnosis

- Dementing disorders
- Delirium
  - Medical illness
  - Iatrogenesis
- Psychosocial triggers*
- Physical discomfort
- Primary psychiatry illness
Mnemonic for the Differential Diagnoses of Cognitive Impairment

- **D** = drugs !!!
- **E** = eyes and ears
- **M** = metabolic (endocrine, electrolytes, vitamin def.)
- **E** = emotional (depression)
- **N** = neurological (Parkinson’s, Alzheimer’s)
- **T** = trauma / tumor
- **I** = infections
- **A** = arteriosclerosis

Prescriptions for Persons with Dementia

- 41% antihypertensives
- 38% acetylcholinesterase inhibitors
- 21% SSRIs
- 15% antipsychotics
  - 12% atypical
  - 3% typical
- 13% Benzodiazepines

Over 50% of prescriptions for Dementia patients affect cognition


Iatrogenesis: Focus on Medications

Inappropriate use of medications with anticholinergic effects may lead to:

- Confusion and Memory Loss
- Delirium
- Delusions, hallucinations
- Agitation

Source: Schneider LS. J Clin Psychiatry. 1999;60(suppl 8):54-60.
Medications With Anticholinergic Properties (cont)

Commonly prescribed in the elderly:
- Cimetidine
- Prednisolone
- Theophylline
- Digoxin
- Furosemide
- Ranitidine
- Nifedipine
- Isosorbide
- Warfarin
- Dipyridamole
- Codeine
- Triamterene and hydrochlorothiazide
- Captopril


Target Symptoms for Treatment
- Cognitive decline
- Physical aggression
- Agitation
- Delusions / paranoia
- Hallucinations
- Sleep / wake cycle changes
- Depression, withdrawal
- Eating problems
- Verbal outbursts

Pharmacotherapy of Alzheimer’s Disease

Medications for treating target symptoms
- Acetylcholinesterase Inhibitors*
- NMDA-Receptor Antagonist
- Antidepressants
- Anticonvulsants (for aggression / mood lability)
- Benzodiazepines
- Antipsychotics
Early diagnosis

Best Responders

Treatment with cholinesterase inhibitor

Average Responders

Minimal Responders

Cholinesterase Inhibitors: Proposed Pharmacology

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Mechanism of Action</th>
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<tbody>
<tr>
<td>Tacrine</td>
<td>Cognex™</td>
<td>acetyl- &amp; butaryl-</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Aricept™</td>
<td>acetyl-</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Exelon™</td>
<td>acetyl- &amp; butaryl-</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Razadyne ER™</td>
<td>acetyl- &amp; nicotinic-receptor modulator</td>
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</table>

Cholinesterase Inhibitors: Recommended Dosing

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand Daily Tx. Dose &amp; Regimen</th>
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<tbody>
<tr>
<td>Tacrine</td>
<td>Cognex™ 40-160 mg QID</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Aricept™ 5-10 mg QD</td>
</tr>
<tr>
<td></td>
<td>23 mg QD</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Exelon™ 6-12 mg BID</td>
</tr>
<tr>
<td></td>
<td>RTS 4.6-9.5 mg QD</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Razadyne ER™ 16-24 mg QD</td>
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</table>
Cholinesterase Inhibitors: Pharmacokinetics

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<thead>
<tr>
<th></th>
<th>Tacrine</th>
<th>Donepezil</th>
<th>Galantamine</th>
<th>Rivastigmine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>10-30%</td>
<td>100%</td>
<td>90%</td>
<td>36-40%</td>
</tr>
<tr>
<td>T1/2</td>
<td>3.5H</td>
<td>7H</td>
<td>7H</td>
<td>Cap: 1.5H Patch: 3H</td>
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<tr>
<td>Protein Binding</td>
<td>55%</td>
<td>96%</td>
<td>18%</td>
<td>40%</td>
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<tr>
<td>Metabolism</td>
<td>CYP1A2</td>
<td>CYP2D6 &amp; 3A4</td>
<td>CYP2D6 &amp; 3A4</td>
<td>Minimal hepatic involvement</td>
</tr>
<tr>
<td>Vd</td>
<td>349L</td>
<td>12L/kg</td>
<td>1.75L</td>
<td>1.8-2.7L/kg</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal</td>
<td>Renal/Fecal</td>
<td>Renal</td>
<td>Renal/Fecal</td>
</tr>
</tbody>
</table>

Cholinesterase Inhibitors: Safety & Tolerability

- Gastrointestinal Side Effects: (class effect)
  Rivastigmine oral > Donepezil = Galantamine

- Sleep Disturbances:
  Donepezil > Rivastigmine > Galantamine

Clinical Pearl:
What is another common class of medications prescribed to the elderly with GI & Sleep adverse effects?

Cholinesterase Inhibitors: Precautions

- Bradycardia
- Heart block
- History of asthma/COPD
- Low weight
- Active PUD
Galantamine IR at 16 & 24 mg/day:
Mean (± SE) Change From Baseline in ADAS-cog

Donepezil at 5 & 10 mg/day

Rivastigmine 26-Week
ADAS-Cog
Memantine

- **Brand:** NAMENDA™
  - NMDA-receptor antagonist
- **Pharmacokinetics:**
  - $t_{1/2} = \sim 60-80 \text{ hrs.}$
- **Dosing:**
  - Titration phase:
    - 5mg qHS x 5 days
    - 5mg qAM + 5mg qHS x 5 days
    - 5mg qAM + 10mg qHS x 5 days
  - Treatment dose:
    - 10mg qAM + 10mg qHS

**Adverse effects:**
- Low incidence of ADRs (<10% incidence)
- GI Disturbances (constipation / vomiting)
- Fatigue, Dizziness, HA
- Confusion, Somnolence, Hallucination

**Drug Interactions:**
- Not significant

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**Memantine 28-Week (SIB)**

![Graph showing the comparison between Memantine and Placebo over 28 weeks.](image-url)
Memantine + Donepezil

- **MoA:**

- **Dosing:** 10mg+7mg or 10mg+14mg/day
  - **Tx:** 28/10 mg per day

- **ADRs:** HA, GI/diarrhea, dizziness, somnolence, confusion
A problem with many studies is that.....

*Individuals have Alzheimer’s Disease for longer than six months.*

So..........

*What about long-term treatment outcomes?*

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**Long-term Efficacy of Donepezil**

![Graph showing long-term efficacy of Donepezil](Reprinted with permission from Rogers SL et al. Eur Neuropsychopharmacol. 2003;13:105-126.)
Donepezil 3-Year Study
Long-term donepezil treatment in 565 pts. with AD (AD2000): randomized double-blind trial

AD2000:

• **Study Conclusions:**
  • No significant difference seen with donepezil compared to placebo in institutionalization or progression of disability.
  • No significant differences were seen between donepezil and placebo in behavioral and psychological symptoms, caregiver psychopathology, formal costs of care, ADRs or death, or between 5mg and 10mg donepezil.

  • ”Donepezil is not cost effective, with benefits below minimally relevant thresholds”

A 52-week study of the efficacy of rivastigmine in patients with mild to moderately severe AD
**Long-term Cognitive Benefits of Galantamine Treatment**

- **Double-blind**
- **Open-extension**

![Graph showing long-term cognitive benefits of galantamine treatment.](image)

* p < 0.05 vs placebo/galantamine (not statistically different from baseline).

**Galantamine: Long-term change from baseline in ADAS-cog/11 Scores**

![Graph showing long-term change in ADAS-cog/11 scores.](image)

**Galantamine vs Donepezil: Responders**

- (improvement / no decline for 52 weeks)

![Bar chart comparing responders (improvement/no decline for 52 weeks) between donepezil and galantamine.](image)

Data on file
**Target Symptoms for Treatment**

- Cognitive decline
- Physical aggression
- Agitation
- Delusions / paranoia
- Hallucinations
- Sleep / wake cycle changes
- Depression, withdrawal
- Eating problems
- Verbal outbursts

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**Behavioral & Psychological Symptoms of Dementia**

- Also referred to as BPSD or the neuropsychiatric symptoms associated with dementia
- Includes a myriad of symptoms
  - Psychosis
  - Delusions
  - Hallucinations
  - Agitation
  - Aggression

<table>
<thead>
<tr>
<th>BPSD Symptom</th>
<th>Mean (%)</th>
<th>Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosis</td>
<td>41.1</td>
<td>12.2-74.1</td>
</tr>
<tr>
<td>Delusions</td>
<td>37.1</td>
<td>9.3-61.0</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>19.9</td>
<td>3.8-41.0</td>
</tr>
<tr>
<td>Other</td>
<td>22.2</td>
<td>3.6-38.9</td>
</tr>
</tbody>
</table>


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**Psychosis and Agitation**

- Psychosis and agitation often coexist
- Treatment plan should provide for safety of the patient and the caregiver
- Psychotic symptoms can occur at any point during the disease
- Disordered behavior is a common cause of institutionalization
- Appropriate interventions may prevent or delay institutionalization
Other Triggers of Agitation

- Psychosocial
  - “A demented patient’s behavior disturbance may have more to do with the nursing home roommate than with dopamine or other receptors in the brain”

- Physical discomfort
  - Pain or constipation


Issues to Remember in Medication Selection

*Unconsciousness / Sleep DOES NOT EQUAL Tranquilization (antipsychotic effect)
Drug Risks for Falls

- Drowsiness / Sedation
- Orthostatic Hypotension
- Dizziness
- Reversible Movement Disorders

- Feb. 2017: All Antipsychotics have ‘Falls’ as a general warning

Typical Vs. Atypical APs

- Overall similar efficacy
- Anticholinergic effects
- Metabolic effects
- Hypotension
- Short term basis at the lowest effective dose

- All are on Updated Beer’s List for Potentially Inappropriate Medication Use in Older Adults

Conventional Antipsychotics

- Extensive clinical experience
- Modest efficacy
- Side effects can hinder treatment
- High risk of tardive dyskinesia
- Commonly used in geriatrics
  - Haloperidol

Conventional Antipsychotics: Side Effects Are Predictable

- Extrapyramidal symptoms
- Anticholinergic effects
- Cognitive toxicity
- Sedation
- Orthostatic hypotension
- Tardive dyskinesia


Conventional Antipsychotics: Meta-Analysis of Controlled Trials

- 33 studies: comparison of conventional antipsychotics to placebo or to each other in elderly patients with dementia
- Combined analysis showed modest efficacy; conventional antipsychotics produced an 18% improvement vs placebo
- Considerable toxicity was reported in elderly patients treated with conventional antipsychotics

Conventional Antipsychotics: High Risk of TD in Elderly Patients

Duration of Therapy (y)  TD Prevalence (%)
1  26%
2  52%
3  60%


Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name</th>
<th>Company</th>
<th>Year</th>
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<tbody>
<tr>
<td>Clozapine</td>
<td>Clozaril</td>
<td>Novartis</td>
<td>1990</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal</td>
<td>Janssen</td>
<td>1994</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Zyprexa</td>
<td>Lilly</td>
<td>1995</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Seroquel</td>
<td>Zeneca</td>
<td>1997</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Geodon</td>
<td>Pfizer</td>
<td>2001</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Abilify</td>
<td>BMS/Otsuka</td>
<td>2002</td>
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<tr>
<td>Paliperidone</td>
<td>Invega</td>
<td>Janssen</td>
<td>2007</td>
</tr>
<tr>
<td>Illoperidone</td>
<td>Fanapt</td>
<td>Novartis</td>
<td>2009</td>
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<tr>
<td>Asenapine</td>
<td>Saphris</td>
<td>Merck</td>
<td>2009</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Latuda</td>
<td>Sunovion</td>
<td>2010</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>Rexulti</td>
<td>Otsuka</td>
<td>2015</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>Vraylar</td>
<td>Allergan</td>
<td>2015</td>
</tr>
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</table>

Risperidone in Dementia (cont)

Total BEHAVE-AD

Mean Improvement from Baseline

<table>
<thead>
<tr>
<th>Dose of Risperidone</th>
<th>0.5 mg n = 146</th>
<th>1.0 mg n = 148</th>
<th>2.0 mg n = 162</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Improvement</td>
<td>4.2</td>
<td>4.5</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Mean shift at endpoint

* P < .002 vs placebo
† P < .001 vs placebo.

Risperidone in Dementia (cont)
Physical Aggression Subscale—CMAI

Mean Improvement

<table>
<thead>
<tr>
<th>Dose of risperidone</th>
<th>Placebo</th>
<th>0.5 mg</th>
<th>1.0 mg</th>
<th>2.0 mg</th>
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<tbody>
<tr>
<td>n = 162</td>
<td>n = 164</td>
<td>n = 167</td>
<td>n = 165</td>
<td></td>
</tr>
<tr>
<td>Mean shift at endpoint</td>
<td>1.1</td>
<td>1.8</td>
<td>3.8</td>
<td>4.2</td>
</tr>
</tbody>
</table>

*P ≤ .05 vs placebo.


Risperidone in Dementia (cont)
Incidence of EPS

Incidence (%)

<table>
<thead>
<tr>
<th>Dose of risperidone</th>
<th>Placebo</th>
<th>0.5 mg</th>
<th>1.0 mg</th>
<th>2.0 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 163</td>
<td>n = 149</td>
<td>n = 147</td>
<td>n = 165</td>
<td></td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>7.4</td>
<td>6.7</td>
<td>12.8</td>
<td>21.2</td>
</tr>
</tbody>
</table>

*P ≤ .05 vs placebo.


Risperidone in Dementia (cont)
Incidence of Falls

Incidence (%)

<table>
<thead>
<tr>
<th>Dose of risperidone</th>
<th>Placebo</th>
<th>0.5 mg</th>
<th>1.0 mg</th>
<th>2.0 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 163</td>
<td>n = 149</td>
<td>n = 147</td>
<td>n = 165</td>
<td></td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>20</td>
<td>16</td>
<td>12</td>
<td>22</td>
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</tbody>
</table>

Clinical Trials of Atypical Antipsychotics in Patients With Alzheimer’s Dementia

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Trial</th>
<th>N</th>
<th>Mean Age</th>
<th>Duration</th>
<th>Efficacy vs Placebo</th>
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</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>Katz et al</td>
<td>625</td>
<td>83 y</td>
<td>12 wk</td>
<td>Superior</td>
</tr>
<tr>
<td></td>
<td>De Deyn et al</td>
<td>344</td>
<td>81 y</td>
<td>12 wk</td>
<td>Superior</td>
</tr>
<tr>
<td></td>
<td>Brodaty et al</td>
<td>337</td>
<td>83 y</td>
<td>12 wk</td>
<td>Superior</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Satterlee et al</td>
<td>238</td>
<td>Not available from abstract (≥65 y)</td>
<td>8 wk</td>
<td>No Difference</td>
</tr>
<tr>
<td></td>
<td>Street et al</td>
<td>206</td>
<td>83 y</td>
<td>6 wk</td>
<td>Superior (5mg &amp; 10mg)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Tariot et al</td>
<td>284</td>
<td>84 y</td>
<td>10 wk</td>
<td>Agitation only</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>De Deyn et al</td>
<td>208</td>
<td>82 y</td>
<td>10 wk</td>
<td>Inconsistent</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>None</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

These are not head-to-head trials, therefore, no comparison can be made between products. Median age.


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<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

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Expert Consensus Panel for Using Antipsychotics in Older Patients


- Agitated dementia +/- delusions: AP (risp 1st)
- Late-life schizophrenia: AP (risp 1st)
- Psychotic major depression: AP + AD
- Severe non-psychotic mania: AP + MS
- Psychotic mania: AP + MS
- Parkinson's disease w/psychosis: AP (quet 1st)
Black Box Warnings

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

“.....Pick your Antipsychotic.....” is not approved for the treatment of patients with dementia-related psychosis

BBW on Antipsychotics

- April 2005:
  - Increased mortality in elderly patients (4.5% vs 2.6% with overall RR = 1.54) with dementia related psychosis
  - Risk vs. Benefit
    - Increased risk of stroke or death
    - Anticholinergic properties: confusion
    - Past CV events
- May 2016 APA Guidelines:
  - Risperidone for ‘Psychosis’
  - Risperidone, Olanzapine, Aripiprazole for ‘Agitation’

Risk of Death
(all cause mortality)

- Aripiprazole 1.73
- Olanzapine 1.91
- Quetiapine 1.67
- Risperidone 1.30
- Overall 1.54

Schneider L. NIMH-NCDEU Meeting. Boca Raton, FL June 6, 2005
Alternatives for Dementia-Related Agitation / Behavioral Disturbances

- **SSRI’s** (best evidence*)
  - related to central serotonin deficits
  - *Citalopram*
    - equal to risperidone, decreased side effects
  - *Sertraline*
    - (proven efficacy)
  - *Antiepileptic:*
    - (fair evidence)
    - Valproic Acid
    - Carbamazepine

- **Anxiolytics** (poor evidence)
  - Benzodiazepines
  - Buspirone

- **Beta Blockers** (poor evidence)
  - Propranolol
  - Pindolol

- **Behavioral***

Citalopram vs. Perphenazine vs. Placebo

- **a.** Significant difference within group between baseline and termination scores (Wilcoxon signed-rank test, p<0.05).
- **b.** Significant difference between the citalopram and placebo groups (Kruskal-Wallis test, p<0.05).
Citalopram vs Risperidone for Psychosis associated with Dementia

- Dementia patients hospitalized for psychosis or agitation had similar efficacy in reducing psychosis
- Citalopram group experienced less side effects


Sertraline vs. Placebo in AD Patients

- Donepezil (Aricept®) augmented with up to 200 mg/day of Sertraline (Zoloft®) or Placebo for 12 weeks
- Post hoc analyses: Sertraline significantly decreased CGI-I scale; other parameters were not significant between group


Benzodiazepines

- Minimal efficacy data
- Sedating
- Cause falls
- Further inhibit learning and memory
- Paradoxical disinhibition
- Commonly used
  - lorazepam
  - oxazepam

AD Pharmacotherapy of the Future?

• More Cholinesterase Inhibitors?
  – Huperzine (Herbal)

• Anti-Oxidant Therapy (e.g. Vitamin E?)

• Other Glutamatergic agents
  – NMDA antagonists?

• Vaccines (e.g. amyloid-beta peptide)
  – Positive responses in animal studies
  – Early human studies were suspended due to ADRs
    • showed some pathological response
    • may provoke the removal of plaques
    • May need a concomitant anti-inflammatory to prevent ADR

AD Pharmacotherapy of the Future?

• Anti-inflammatory Therapy
  – Older NSAIDs: indomethacin, ibuprofen
    • Weak data, mostly retrospective / epidemiological
  – COX-2 inhibitors: celecoxib?

• Gamma, Beta-Secretase Inhibitors
  – High expectations due to in-vitro / animal studies
  – Human trials ongoing
  – Results have been disappointing
    • Some even showed worsening compared to PLB
Pharmacotherapy of the Future?

- HMG-CoA Reductase Inhibitors “Statins”?

- Estrogen Therapy?
  - Develop non-feminizing estrogen-like compounds
  - Selective estrogen receptor modulators (SERMs)
  - Phytoestrogens – bioflavinoids – negative data

- Apo-E Modulation / Inhibitors of aggregation?

- Gingko Biloba?
  - vascular vs anti-oxidant vs anticoagulant properties
  - negative PLB-controlled data

Pharmacotherapy of the Future?

- Muscarinic / Nicotinic Receptor Agonists?
- Multi-neurotransmitter compounds?
  - Reuptake inhibitors or transmission enhancers for….
  - 5-HT, NE, DA, ACh
- Nerve Growth Factors / Neurotrophins?
- Gene Therapy?
- Others……?
Types of Dementia

- Alzheimer’s Disease
- Vascular Dementia
- Wernicke-Korsakoff
- Multiple Sclerosis
  - Frontotemporal Dementia (FTD)
  - Pick’s Disease
- HIV-Related Dementia
- Parkinson’s Disease
- Huntington’s Disease
- Dementia with Lewy Bodies
- Creutzfeldt-Jakob Disease

Nuedexta

A new treatment to connect with.

Nuedexta

• FDA approved for the acute treatment of Pseudobulbar Affect (PBA)
  - Approved 2010
  - Studies in Amyotrophic Lateral Sclerosis (ALS) & Multiple Sclerosis (MS)
  - ?? Dementia / TBI / Stroke ??

• Pharmacology
  - Exerts actions via sigma-1 receptor agonist and NMDA-receptor antagonism (dextromethorphan)
Nuedexta

- **Pharmacokinetics**
  - Extensively absorbed
  - $T_{max}$: 3-4 hrs, $t_{1/2}$: 13 hrs
  - PB: 60-70% for Dex., 80-90% for Quin.
    - Bioavailability: 96%
  - Metabolism
    - Hepatic via CYP 2D6* (inhibited by Quinidine)
    - 3A4

- **Dosage**
  - 20/10 mg/day QD x 7 days, then BID thereafter
Nuedexta efficacy in ALS (n=197) & MS (n=129)

Pimavanserin
- NUPLAZID® is indicated for the treatment of hallucinations and delusions associated with Parkinson’s disease psychosis
- Dose: 34 mg, taken orally as two 17 mg strength tablets once daily, without titration.
- BW (Mortality: same as all antipsychotics)
- QT Interval Prolongation

https://www.nuplazidhcp.com/
Pimavanserin

• The effect of pimavanserin could be mediated through a combination of... 
  
  **inverse agonist** and antagonist activity at serotonin 5-HT2A receptors and to a lesser extent at serotonin 5-HT2C receptors. *in vitro*, pimavanserin acts as an inverse agonist and antagonist at serotonin 5-HT2A receptors with high binding affinity (Ki value 0.087 nM) and at serotonin 5-HT2C receptors with lower binding affinity (Ki value 0.44 nM).

Pimavanserin

• **Common Adverse Reactions:** 
  - peripheral edema (7% NUPLAZID 34 mg vs. 2% placebo) and confusional state (6% NUPLAZID 34 mg vs. 3% placebo).
  - GI: Nausea/Constipation
  - ~$2300.00/month
Primary Efficacy Analysis Result Based on SAPS-PD (N=185)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment Group</th>
<th>Mean Baseline Score (SD)</th>
<th>LS Mean Change from Baseline (SE)</th>
<th>Placebo-subtracted Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPS-PD</td>
<td>NUPLAZID</td>
<td>15.9 (6.12)</td>
<td>-5.79 (0.66)</td>
<td><strong>-3.06</strong> (-4.91, -1.20)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>14.7 (5.55)</td>
<td>-2.73 (0.57)</td>
<td>--</td>
</tr>
<tr>
<td>Hallucinations‡</td>
<td>NUPLAZID</td>
<td>11.1 (4.58)</td>
<td>-3.81 (0.46)</td>
<td><strong>-2.01</strong> (-3.29, -0.72)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>10.0 (3.80)</td>
<td>-1.80 (0.46)</td>
<td>--</td>
</tr>
<tr>
<td>Delusions‡</td>
<td>NUPLAZID</td>
<td>4.8 (3.59)</td>
<td>-1.95 (0.32)</td>
<td><strong>-0.94</strong> (-1.83, -0.04)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>4.8 (3.83)</td>
<td>-1.61 (0.32)</td>
<td>--</td>
</tr>
</tbody>
</table>

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
Difference (drug minus placebo) in least-squares mean change from baseline. Statistical significantly superior to placebo. Supportive analysis.

SAPS-PD Change From Baseline Through 6 Weeks

NUPLAZID 34 mg showed a 37% improvement in SAPS-PD from baseline at Week 6 versus 14% for placebo.
Management of Alzheimer's Disease: Cognition & Disturbed Behaviors

• The cholinesterase inhibitors & memantine may benefit the Alzheimer’s patient by delaying or slowing the course and rate of cognitive impairment.

• Patients with AD may benefit through decreased or delayed presentation of behavioral disturbances from cholinesterase inhibitors & memantine.

• Consider setting a new expectation of 12 months for keeping patients “at-or-above baseline” with select agents.

Management of Alzheimer’s Disease: Cognition & Disturbed Behaviors

• Some antipsychotics have demonstrated efficacy and safety in the AD patient with psychosis & agitation, but all atypical AP agents have warnings for increased morbidity & mortality.

• Other Secondary Pharmacotherapy may include Antidepressants (SSRIs) and Mood Stabilizers to address the behavioral disturbances associated with AD.

• Certain sedatives (BZDs) should be avoided.

Conclusion & Discussion