Prazosin Reduces Disruptive Agitation in Dementia

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Disruptive Agitation: What is it?

- Distressing behaviors that often cluster together:
  - irritability
  - uncooperativeness with necessary care
  - anger outbursts, aggression
  - sleep disruption
  - pressured pacing and restlessness

Why is it Important to Treat Disruptive Agitation in AD

- Patient is distressed.
- Caregivers are distressed.
- Ability to provide care is compromised.
- Behavior can pose a threat of harm to self and others.
- Behavior contributes to functional disability.
- Increases rate of decline.

Psychosis in AD Differs Phenomenologically from Psychosis in Schizophrenia

- Hallucinations
  - visual
  - simple
  - memory loss-related
- Delusions
  - auditory
  - complex
  - bizarre

Atypical Antipsychotic Drugs in AD: Pros

- Antipsychotics are the only drug class demonstrated effective.
  - largest data base for risperidone and olanzapine
- Better tolerated than typicals re: reduced parkinsonism; as effective; more costly.
- Atypicals’ “metabolic problems” less concern in very elderly.

Atypical Antipsychotic Drugs in AD: Cons

- Antipsychotic drug studies in AD with psychosis and “aggression” modestly positive for agitation/aggression, but not “psychosis”.
- Effect sizes are small to moderate and nonresponder rate is substantial.
- Antipsychotics not effective for visual hallucinations and simple delusions of theft.
- Small increased risk of stroke and mortality likely secondary to excessive sedation.\(^1,2\)

Placebo-Controlled Trials of Antipsychotics for Psychosis and Agitation in AD

- **Risperidone**
  - 1-2 mg/day more effective than 0.5 mg/day or placebo in 625 patients with AD in the nursing home setting
  - dose-related increases in somnolence, EPS, and peripheral edema
  - no significant decrements in cognition or self-care

Risperidone Effects on Clinical Global Impression of Change (CGIC) in Nursing Home Residents with AD

<table>
<thead>
<tr>
<th>Risperidone 1 mg/day</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2 (minimally improved to unchanged)</td>
<td>4.2 (unchanged to minimally worse)</td>
</tr>
</tbody>
</table>

Placebo-Controlled Trials of Antipsychotics for Psychosis and Agitation in AD (cont.)

- **Olanzapine**
  - mean dose of 2.4 mg/day not more effective than placebo in 238 outpatients with AD
  - 5-10 mg/day more effective than 15 mg/day or placebo in 206 nursing home patients with AD
  - Increased death in olanzapine subjects associated with sedation

Olanzapine Effects on Neuropsychiatric Inventory (NPI) in Nursing Home Residents with AD

<table>
<thead>
<tr>
<th>Change in NPI Score from baseline to study end</th>
</tr>
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<tbody>
<tr>
<td>Olanzapine</td>
</tr>
<tr>
<td>-18.7</td>
</tr>
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</table>

Dementia with Lewy bodies

- Second or third most common type of dementia after AD.
- Parkinsonian signs and symptoms
- Early psychotic symptoms (especially visual hallucinations).
- Fluctuating cognition.
- Neuroleptic sensitivity - even some atypicals.
- Rivastigmine FDA approved for DLB.

The Brain Noradrenergic System

- The noradrenergic system is the brain “adrenaline” system for attention and arousal.
- Excessive noradrenergic outflow and/or responsiveness produces anxiety and agitation.
- Does excessive noradrenergic activity contribute to agitation in AD?
Noradrenergic System Pathology in Alzheimer’s Disease

• Despite loss of noradrenergic locus coeruleus neurons there is:
  » increased cerebrospinal fluid (CSF) norepinephrine (NE) in AD\(^1\)
  » increased agitation response to NE in AD\(^2\)

\(^2\)Peskind, et al., Arch Gen Psychiatry, 1995

CSF Norepinephrine: Effects of Aging and AD

• In animal studies, partial denervation of the locus ceruleus causes compensatory upregulation of norepinephrine (NE) biosynthetic capacity in surviving locus ceruleus neurons.

• Does this phenomenon occur in AD and DLB?

• Locus ceruleus NE biosynthetic capacity antemortem can be estimated by measuring tyrosine hydroxylase mRNA in postmortem brain tissue.

• We found increased TH mRNA/LC neuron at all levels of LC in AD (\(n = 15\)) and DLB (\(n = 15\)) compared to nondemented older controls (\(n = 17\)).

\(^\ast\)significantly higher than young subjects
\(^\ast\ast\)significantly higher than all other subject groups

In AD and DLB, surviving noradrenergic neurons are compensating by increasing the mRNA expression of the rate-limiting enzyme in the synthesis of NE at multiple levels of the LC.


**We Stimulated Brain Noradrenergic Systems With the Drug Yohimbine**

- We measured CSF NE responses to placebo or yohimbine in 9 AD (MMSE = 14 ± 2), 10 normal older, and 17 normal young subjects.
- We measured behavioral responses using Brief Psychiatric Rating Scale (BPRS) items “tension”, “excitement”, “anxiety”.


**Change in CSF NE Concentrations Between Placebo and Yohimbine Conditions**

* significantly higher than young subjects

Effects of Yohimbine Administration on Tension, Excitement, and Anxiety Ratings

Postsynaptic Adrenergic Receptor Antagonists for Agitation in AD

- Enhanced agitation response to adrenergic stimulation in AD.
- Would reducing brain responsiveness to NE by adrenergic receptor blockade reduce agitation in AD?
- Only one antagonist for each receptor crosses the blood-brain barrier:
  - beta receptor antagonist: propranolol.
  - alpha, receptor antagonist: prazosin.

Peskind, et al., Arch Gen Psychiatry 1995.

Beta receptor antagonists in AD

- Would reducing brain responsiveness to NE by CNS active adrenergic receptor antagonist reduce agitation in AD?
- Beta receptor antagonist: propranolol.
  - Two open-label studies suggest propranolol reduces disruptive agitation in dementia.
  - Increased density of postsynaptic beta-adrenergic receptors in cerebellum in AD patients with antemortem aggression.

Propranolol for Agitation in Nursing Home Residents with AD

- Thirty-one AD nursing home patients
- Treatment resistant disruptive agitation, severe to very severe
- Age 85 ± 8 years
- Propranolol X 6 weeks, 10-40 mg tid (30-120 mg/day)
- Well-tolerated

Propranolol for Agitation in Dementia

- Effective and well tolerated “adjunct” in antipsychotic nonresponders.
- Unfortunately, improvement not sustained at 6-month follow-up.
- High rate of medical exclusions.

**3H Prazosin Binding - Hippocampus**

- control (n = 17)
- AD (n = 15)
- AD/PD (n = 22)


**3H Prazosin Binding - Prefrontal Cortex**

- control (n = 17)
- AD (n = 15)
- AD/PD (n = 22)


**3H Prazosin Binding - Temporal Cortex**

- control (n = 17)
- AD (n = 15)
- AD/PD (n = 22)


**Open-Label Trial of Prazosin for Agitation in AD Nursing Home Residents**

- Eleven AD nursing home residents.
- Treatment resistant disruptive agitation, severe to very severe.
- Age = 84 ± 5 years.
- Prazosin for 8 weeks, 1-5 mg/day.
- Well-tolerated.

**Prazosin for Disruptive Agitation in Dementia: Rationale**

- Increased expression of postsynaptic alpha-1 adrenergic receptor in prefrontal cortex in AD.
- alpha-1 receptor antagonist: prazosin.
  - long lasting benefits in posttraumatic stress disorder³
  - would prazosin be helpful in AD?


**Prazosin Side Effect Profile**

- Non-sedating.
- Does not cause pseudoparkinsonism.
- Blood pressure reduction possible.
Open-Label Trial of Prazosin for Agitation in AD Nursing Home Residents

CGIC (8 weeks)

- markedly improved: 1
- moderately improved: 2
- minimally improved: 3
- no change: 4
- minimally worse: 5
- moderately worse: 6
- markedly worse: 7

Placebo-Controlled Trial of Prazosin for Disruptive Agitation in Dementia

- Twenty-two persons (mean age 81 ± 11 years) with DSM-IV dementia (possible or probable AD) and frequent disruptive agitation.
- Randomized to prazosin (n=11) or placebo (n=11) for 8 weeks.
- Prazosin dose range 2-6 mg/day (mean dose 5.7 ± 0.9 mg/day).
- Primary outcome measures: NPI, BPRS CGIC.

Placebo-Controlled Trial of Prazosin for Disruptive Agitation in Dementia: NPI

Placebo-Controlled Trial of Prazosin for Disruptive Agitation in Dementia: BPRS

Adverse Events Were Similar for Prazosin and Placebo Groups

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Prazosin group</th>
<th>Placebo group</th>
<th>Both groups combined</th>
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</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Confusion</td>
<td>2</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness on Standing</td>
<td>1</td>
<td>0</td>
<td>1</td>
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Conclusions

• Prazosin may be effective for the treatment of disruptive agitation in AD.
• Prazosin is generally well-tolerated.
• Larger placebo-controlled efficacy trials of prazosin for disruptive agitation are needed.