Pharmacotherapy in the Patient with Dementia

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Disclosure Statement

• Consultant
  – AbbVie
  – Lundbeck
Neuropathology of Alzheimer’s disease

Beta Amyloid Deposits (Neuritic Plaques)

Abnormally Phosphorylated Tau Proteins (Neurofibrillary Tangles)

Number of amyloid plaques shows little correlation and number of tangles shows moderate correlation with cognitive status prior to death.
Treatments for Alzheimer’s Disease

Degeneration of cholinergic neurons → cholinesterase inhibitors to increase acetylcholine

Dying cells → memantine to decrease glutamine excitation (NMDA receptor) implicated in cell death

Investigational treatments:

Upstream interventions to prevent amyloid deposits

Beta and Gamma secretase inhibitors   Anti-amyloid vaccines

Other drugs that have largely failed in clinical trials

Estrogens      Ginkgo Biloba      Anti-inflammatory drugs   Omega-3
Statins       Vitamin E           Nutraceuticals

Lifestyle changes have a very small but measurable positive impact

Mediterranean diet      Exercise

Insulin nasal spray is currently under investigation in a multicenter trial
Effect of Rivastigmine on Cognition: ADAS-Cog Mean Change From Baseline

- Mean Change in ADAS-Cog
- *P < .05 vs placebo
Effect of Donepezil on Cognition

Long-Term Follow-Up

Mean Change from Baseline in ADAS-COG Score

Weeks
**Chel Effect Size and Long-term Effects**

- Advantage over placebo in a large number of studies: 1-4 points on the ADAS-cog which is a 70-point scale
- Retain a very small cognitive advantage over the trajectory for placebo during several years of treatment
- When the Chel is stopped, cognitive ability declines to the expected trajectory line of deterioration
- Chel do not consistently show delayed time to nursing home placement or decreased progression of disability
- “Symptomatic” rather than “disease-modifying” therapy
Use of Chel in the clinic

- **Donepezil**
  - Marginally greater efficacy for 10 mg compared to 5 mg daily dose
  - 23 mg dose: approved for moderate to severe AD
  - Main side effects: diarrhea, nausea and vomiting.
  - Side effects increase with dose

- **Galantamine**
  - Profile similar to donepezil; recommended b.i.d. dosing
  - Daily doses 8 to 32 mg; 16-32 mg shown to be superior to placebo
  - Rivastigmine
  - Similar efficacy (oral 6-12 mg daily) with possibly more GI side effects
  - Transdermal patch: 4.6 mg for 4 weeks, then 9.5 mg and 13.3 mg daily
Memantine

- Uncompetitive NMDA receptor antagonist
- May inhibit calcium influx thereby modulating excitotoxicity
- Approved for the treatment of moderate to severe AD
- Initial dose 5 mg daily with weekly increases up to 10 mg twice daily
- Extended release: 7, 14, 21, 28 mg daily using similar titration schedule
- Side effects uncommon:
  - dizziness, constipation, headache, confusion, ? agitation.
- Combining donepezil with memantine was initially shown to be better than donepezil alone but a recent study did not find this effect
How Long Should You Treat?

- Optimal treatment duration is not established for ChE1 or memantine.
- Studies indicate advantage over placebo for 9-12 months, and likely up to 18 months based on open-label extension phase studies.
- Maintenance treatment can be continued as long as a therapeutic benefit is apparent.
- Difficulty in making this assessment because the deteriorating course of AD is highly variable between patients and because the medication effect is stabilization or slower worsening which is difficult to assess.
- Clinical observation of minimal or no clinical worsening may be sufficient reasons to continue medication treatment if patients are tolerating therapy.
- Discontinuation of donepezil is known to be associated with cognitive decline to the estimated trajectory line of deterioration.

Caregivers and Institutionalization

Family members provide 80% of community care for patients with AD

Common Antecedents to Institutionalization

- Agitation
- Wandering
- Incontinence
- Psychosis
Psychopathology in AD

SYMPTOMS

• Agitation
• Aggression
• Delusions
• Hallucinations
• Depression
• Insomnia
• Anxiety
Multicenter Study

“n”

Columbia University  
Johns Hopkins University  
Massachusetts Gen. Hosp.  

CU        JHU        MGH
94        80        61

236 patients with mild to moderate AD followed at 6-month intervals to map the natural course of illness
Prevalence of Symptoms

Baseline
CUSPAD: 64.3% had one or more symptoms

Follow-up
Only 8.5% remained free of all symptoms of psychopathology during the first 3 years of follow-up

Devanand DP et al. *Arch Gen Psychiatry* 1997; 54:257-263.
Paranoid Delusions

Years of Follow-up

Percent
Agitation or Wandering

![Bar chart showing the percentage of agitation or wandering over years of follow-up.](chart.png)
Physical Aggression

Percent

Years of Follow-up

0 0.5 1 1.5 2 2.5 3

0 5 10 15 20 25 30 35 40 45 50
Summary: Psychosis/Agitation in AD

• Most patients with AD develop psychiatric symptoms
• Psychosis and agitation in AD often lead to institutionalization
• Agitation is common, persistent, and increases with disease severity
• Aggression is uncommon in mild stages but increases with disease severity
• Proportions with paranoid delusions and hallucinations do not change appreciably during mild to moderate stages of the disease
• Findings have been replicated in clinical and community samples

Behavioral Interventions for Agitation in AD

- Person-centered problem solving approach with patients and caregivers (British NHS guidelines support this)
- Meta-analysis of 23 studies: small but overall significant advantage for caregivers trained with behavioral strategies to employ with patients compared to caregiver controls
- Limitations: no double-blind study, therapy exposure in intervention group vastly greater than comparison groups in all studies (usual care with no intervention, waitlist)
- Contrast with equal time and effort for drug and placebo groups in double-blind clinical trials
- Cost-effectiveness of person-centered behavioral strategy?
- No systematic randomized controlled trial comparing behavioral and medication treatment strategies

Antipsychotic Treatment of Psychosis/Agitation

• Most AD patients with psychosis also have agitation or aggression
• Antipsychotics are not FDA-approved (risperidone is approved in Germany) to treat psychosis or agitation in dementia
• Antipsychotics remain the mainstay in clinical practice with response rates of 60-85% in open treatment studies
• Both psychosis and agitation/aggression show comparable improvement with antipsychotics across studies
• Second generation antipsychotics: less neurological side effects, possibly less mortality risk in dementia compared to typical antipsychotics

Risperidone for Psychosis/Agitation in AD

- 625 patients with AD or mixed dementia
  Response: 50% reduction in BEHAVE-AD scores
  Placebo 33%, 1 mg 45%, 2 mg 50%
  Dose for optimal benefit/risk ratio: 1 mg/day

- 3 of 4 studies in nursing home patients (total n=941) with AD or mixed dementia (AD + vascular dementia) showed an advantage for risperidone over placebo in efficacy outcomes of psychosis and/or agitation

Olanzapine for Psychosis/Agitation in AD

206 nursing home patients

- Randomly assigned:
- Placebo, 5, 10, or 15 mg daily for 6 weeks
- All three doses were significantly superior to placebo
- 5 mg was as effective as higher doses with less side effects
- EPS did not differ among groups
- Sedation and weight gain were not prominent (short-term trial)

Street J et al. Arch Gen Psychiatry 2000; 57: 968-967.
Quetiapine for Psychosis/Agitation in AD

- EPS is minimal to absent
- No dose-comparison study in dementia
- Dosage 25 to 400 mg tolerated by elderly AD patients
- Low doses often used for sedation

- Limited equivocal information for aripiprazole, none published for ziprasidone and newer antipsychotics in the treatment of psychosis/agitation in dementia

Toxicity of Antipsychotics in Dementia

- Increased risk of EPS, TD in elderly patients with dementia
- Risk varies based on which antipsychotic is prescribed
- Orthostatic hypotension, autonomic effects are rare with low doses

FDA black box warning: increased risk of mortality in dementia

- Relative risk of 1.5-1.7 based on a pooled analysis of 16 placebo-controlled trials. No significant increase in mortality risk over placebo was seen in any single trial
- In an Australian study, stroke was associated with increased mortality
- Not replicated in other studies; most deaths attributed to cardiopulmonary causes
- When prescribing antipsychotics to patients with dementia, discuss the increased risk of mortality. Transmission of this information to the patient/family, and their willingness to receive antipsychotics, should be documented in a progress note

Other Antipsychotic Side Effects

- Ontario, Canada medical records study of 97,777 patients
- Acute kidney injury defined by diagnosis code and creatinine levels
- Acute kidney injury: relative risk of 1.5 to 2 compared to patients who did not receive antipsychotics
- Attributed to complications, e.g., orthostatic hypotension, that secondarily lead to renal complications

CMS Nursing Home Data

- 75,445 patients in Medicare/Medicaid database
- Mortality risk greatest for haloperidol compared to risperidone; quetiapine slightly lower risk
- High dose haloperidol associated with double the mortality risk of low dose haloperidol
- High dose risperidone associated with 35% greater mortality risk compared to low dose risperidone
- High doses used were above the therapeutic window identified in dose comparison studies
- Start low and go slow: important dosing principle

CATIE-AD Study Design

- 45 sites in the US (26 university, 7 VA centers, 12 private)
- Phase 1: random, double-blind assignment to flexible dose olanzapine, quetiapine, risperidone, or placebo (2:2:2:3 ratio)
- If the physician judged response as inadequate, treatment could be switched to the next phase at any time after 2 weeks’ treatment
- Phase 2: random, double-blind assignment to one of the drugs to which they were not initially assigned or to citalopram
- Responding patients continued treatment up to 36 weeks

Phase 1: Time to All-Cause Discontinuation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Med Time Discont (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>8.1</td>
</tr>
<tr>
<td>Quetiapine</td>
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<td>Risperidone</td>
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<td>Placebo</td>
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</table>

Overall $P=\text{NS}$
Phase 1: Time to Discontinuation Due to Lack of Efficacy


<table>
<thead>
<tr>
<th>Drug</th>
<th>Med Time Discont (weeks)</th>
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<tbody>
<tr>
<td>Olanzapine</td>
<td>22.1*</td>
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<tr>
<td>Quetiapine</td>
<td>9.1</td>
</tr>
<tr>
<td>Risperidone</td>
<td>26.7†</td>
</tr>
<tr>
<td>Placebo</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Overall $P = .002$

* $P < .001$ vs Placebo

† $P < .01$ vs Placebo
Phase 1: Time to Discontinuation for Intolerability, Adverse Effects, or Death

![Graph showing treatment discontinuation rates](image)

**Table: Drug Discontinuation Rate (%)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Discont Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>24*</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>16†</td>
</tr>
<tr>
<td>Risperidone</td>
<td>18†</td>
</tr>
<tr>
<td>Placebo</td>
<td>5</td>
</tr>
</tbody>
</table>

Overall $P = .0001$

* $P < .001$ vs Placebo
† $P = .006$ vs Placebo

Effect of Antipsychotics on Caregiver Burden in the CATIE-AD Study

• Caregivers of patients treated with second-generation antipsychotics scored significantly lower than caregivers of patients receiving placebo on both the Burden Interview (P = .009) and the NPI Caregiver Distress Scale (P = .021)

• These differences appeared to have been mediated by lower levels of agitation, hostility, and psychotic distortions in patients on antipsychotics
Discontinuation of Antipsychotics in AD

• Federal regulations require discontinuation of antipsychotics in nursing homes 4 months after initiating treatment unless the physician provides a written rationale to continue treatment.

• Requirement is based on concerns about side effects.

• A few placebo-controlled studies of antipsychotic discontinuation showed mixed results and some recent studies showed little difference on drug versus placebo.

• The largest study (n=100) that discontinued AD patients from different antipsychotics showed greater worsening on placebo by 12 months in patients with greater baseline psychopathology.

Antipsychotic Discontinuation in AD (ADAD Trial)

8-site multicenter study funded by the National Institute of Aging

**Phase A**
Open Treatment

| 16 weeks | Responder
|---------|-
| I-------Risperidone------I------Risperidone------I

**Phase B**
Randomized Trial

| 16 weeks | 16 weeks | Randomizer
|---------|---------|-
| Arm 1   | I-------Risperidone------I------Risperidone------I
| Arm 2   | I-------Risperidone------I------Placebo------I
| Arm 3   | I------Placebo------I------Placebo------I

Main Hypothesis. In the first 16 weeks of Phase B, relapse risk will be lower with continuation risperidone (Arms 1 and 2) compared to placebo (Arm 3).

Secondary Hypothesis. In the second 16 weeks of Phase B, relapse risk will be lower with continuation risperidone (Arm 1) compared to discontinuation to placebo (Arm 2).

Antipsychotic Discontinuation in AD (ADAD Trial)

A

Proportion Free of Relapse

P = 0.02

No. at Risk

Risperidone: 70 68 63 55 54 47 47 46 46 45 44 44 43 42 41 41
Placebo: 40 40 37 29 29 26 26 24 24 20 20 20 15 15 14 13

Weeks after randomization
Antipsychotic Discontinuation in AD (ADAD Trial)

B

Proportion Free of Relapse

Weeks after randomization

No. at Risk

Placebo    | 27 | 27 | 26 | 22 | 22 | 21 | 20 | 20 | 17 | 16 | 16 | 16 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15

P = 0.02
ADAD Trial: Implications

• In AD patients with psychosis/agitation who maintained response to the antipsychotic medication risperidone for 4 to 8 months, antipsychotic discontinuation was associated with greater relapse risk for at least another 4 months.

• In clinical practice, the increased risk of relapse after discontinuation needs to be weighed against the risk of side effects if the antipsychotic is continued.

• Federal regulations urging early antipsychotic discontinuation, e.g., OBRA 1987, may need reconsideration.

• Nonetheless, CMS recently added a stipulation requiring 15% reduction of antipsychotic use in all nursing homes.

Other Medications to Treat Agitation in Dementia

- **Anticonvulsants**
  Carbamazepine was shown to be efficacious in a small sample
  Largest valproate study (Abbott Labs) was negative
  Other anticonvulsants have not been systematically studied
  Since efficacy is not established, consider discontinuation of anticonvulsants if there has been no improvement in target symptoms

- **Benzodiazepines**
  Earlier studies suggested efficacy
  Side effects: addiction with tolerance, withdrawal
  Can worsen cognition, even in normal elderly
  Used for short-term crisis management; can long-term use lead to AD?
  Lorazepam 0.25 to 1 mg daily or equivalent

- **Citalopram (CATIE-AD, CitAD), other SSRIs**

- **Stimulants, bromocriptine, amantadine: anecdotal reports**

- **Trazodone, mirtazapine mainly for sedation**

- **Cholinesterase inhibitors**
Depression in Patients with AD

- Prevalence of major depression in AD: 10%-40%
- Patients can complain of depression
- Caregiver’s report of depression in the patient with AD often indicates depression in the caregiver
- Problems in assessment and differential diagnosis: several symptoms are common to depression and dementia
  - apathy
  - anhedonia
  - insomnia
  - agitation
  - memory loss
  - difficulty concentrating
- Difficulty in assessment of depression in severe dementia

Depressed Mood in AD

![Bar chart showing the percentage of depressed mood over years of follow-up. The x-axis represents years of follow-up (0, 0.5, 1, 1.5, 2, 2.5, 3), and the y-axis represents percent. The chart shows a peak in the percentage of depressed mood at 1 year of follow-up.](image-url)
Depressed Mood With Sleep and Appetite Disturbance

Prevalence (%)

- Depressed Mood
- Depressed Mood Veg Signs

Devanand DP et al. Arch Gen Psychiatry 1997; 54:257-263.
Behavior Therapy for Depression in Dementia

- One randomized controlled trial using behavioral treatment
- Caregivers
  - Education, coping skills, reducing burden
  - Modest benefits did not persist beyond duration of treatment
- Systematic studies have not been done with other types of psychotherapy in patients with AD

Effect of Bright Light and Melatonin

- Whole day bright light, dim light, and melatonin versus placebo in 189 patients in Dutch nursing homes
- 2 X 2 factorial design
- Bright light slightly improved both cognition and depressive symptoms
- Melatonin improved sleep but worsened mood, and the authors recommended it only in combination with light treatment

Riemersma van der Lek RF et al. JAMA 2008; 299: 2642-2655.
### Antidepressant Trials in Depressed Patients with Dementia

#### Study or Subgroup

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Odds Ratio</th>
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<tbody>
<tr>
<td><em>1.4.1 Response Rates</em></td>
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</tr>
<tr>
<td>Petracca 1996&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>9</td>
<td>11</td>
<td>10.3%</td>
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<td>Magai 2000&lt;sup&gt;b,d&lt;/sup&gt;</td>
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<tr>
<td>Lyketsos 2003&lt;sup&gt;b,d&lt;/sup&gt;</td>
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<td>24</td>
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<tr>
<td>de Vasconcelos Cunha 2007&lt;sup&gt;b,d&lt;/sup&gt;</td>
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<td>14</td>
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<tr>
<td>Rosenberg 2010&lt;sup&gt;b,d&lt;/sup&gt;</td>
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<td>67</td>
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<td><em>Heterogeneity: Tau&lt;sup&gt;2&lt;/sup&gt; = 0.52; Chi&lt;sup&gt;2&lt;/sup&gt; = 11.26, df = 5 (P = 0.05); I&lt;sup&gt;2&lt;/sup&gt; = 56%</em></td>
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<td>Test for overall effect: Z = 1.84 (P = 0.07)</td>
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<tr>
<td><em>1.4.2 Remission Rates</em></td>
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<td>Test for overall effect: Z = 1.59 (P = 0.11)</td>
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Clinical Treatment Algorithm

Agitation with or without psychosis

1. Behavioral strategies with caregivers for specific problem behaviors
2. Mild agitation: consider citalopram up to 20 mg/day or trazodone 50-200 mg/day if insomnia is present
3. If above fail or agitation is severe or psychosis is present, second generation antipsychotic: risperidone 0.5-2 mg/day, olanzapine 2.5-5 mg/day, quetiapine 25-100 mg/day, aripiprazole 2-10 mg/day
4. Discontinuation of antipsychotic: weigh higher risk of relapse against side effects; resume antipsychotic if relapse occurs

Major depression

• Prescribe SSRIs at the same doses used in middle-aged adults
• If the SSRI does not work, SNRI or other antidepressant (bupropion, mirtazapine, or SSRI augmentation with low-dose antipsychotic)
• Depressed mood is the key symptom to identify and treat because of lack of specificity for other symptoms, e.g., apathy