Pharmacotherapy in the Patient with Dementia
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 $\rightarrow$ cholinesterase inhibitors to increase acetylcholine

Dying cells $\rightarrow$ 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

-2
-1
0
1
2
3
4
5

Mean Change in ADAS-Cog

Weeks

6–12 mg/d (n=231)
1–4 mg/d (n=233)
Placebo (n=235)

*P < .05 vs placebo
Effect of Donepezil on Cognition

Long-Term Follow-Up

Mean Change from Baseline in ADAS-COG Score

Weeks

0 6 12 14 26 38 50 62 74 86 98

-6

0

6

12

18

Improvement

Decline

Donepezil Therapy

Projected Decline

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
• Retains 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.

Howard R et al. NEJM 2012; 366:893-903.
Memantine and Donepezil combination

- Meta-analysis: N=13 studies; N=971 subjects with AD
- 3 randomized double-blind controlled trials
- Statistically significant effect sizes in favor of combination (cognition 0.45-0.52 p< 0.0001; functional outcomes 0.23-0.3 p<0.01) NPI (3.7-4.4; p<0.0001)
- Results are modest, not robust

Memantine and Donezepil combination

- FDA approval December 2014 based on bioequivalence study to confirm pharmacokinetics
- Clinical effects based on Memantine XR pivotal trial
- Pros: in the clinical world patients do not often get on full dosage of these agents let alone the combination
- Clinician, patient friendly: one pill contains both agents
- Capsules can be opened and sprinkled in applesauce

Cons:
- Fixed dose so change of individual agents not possible
- If side-effects occur both agents are to be stopped or it may be hard to ascertain which agent is the source
- Two drugs are started together and some may have tolerability issues

How Long Should You Treat?

- Optimal treatment duration is not established for ChEI or memantine
- Stop “once disease has won”
- 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
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

Paranoid Delusions
Hallucinations

Percent of patients experiencing hallucinations over different years of follow-up.
Agitation or Wandering

Percent

Years of Follow-up

0 0.5 1 1.5 2 2.5 3
Physical Aggression

Years of Follow-up

Percent
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 (most studied agent)

• 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.
- Gradual dose reduction (GDR) has been recommended
- Arai et al. Japanese prospective study (J-CATIA) duration 10 weeks; N=5148 completed (70.2%) mean age 81.8 years; N=2532 (49.2%) received antipsychotics. N=62 mortality 1.2%. No significant differences in mortality between those who did or did not receive antipsychotics (p=0.38)
- Common causes of death (pneumonia, CVD, cancer)
- When prescribing antipsychotics to patients with dementia, discuss the increased risk of mortality; document in a progress note or consent form
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>
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<tbody>
<tr>
<td>Olanzapine</td>
<td>8.1</td>
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<tr>
<td>Quetiapine</td>
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<tr>
<td>Risperidone</td>
<td>7.4</td>
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<tr>
<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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<td>Olanzapine</td>
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<td>Quetiapine</td>
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<tr>
<td>Risperidone</td>
<td>26.7†</td>
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<tr>
<td>Placebo</td>
<td>9.0</td>
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</table>

Overall \( P = .002 \)

*\( P < .001 \) vs Placebo

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

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

<table>
<thead>
<tr>
<th>Phase A</th>
<th>Phase B</th>
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<tr>
<td>Open Treatment</td>
<td>Randomized Trial</td>
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<tr>
<td>16 weeks</td>
<td>16 weeks</td>
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<tr>
<td>Responders</td>
<td>Arm 1</td>
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<tr>
<td>I----Risperidone------------I</td>
<td>I----Risperidone--------I</td>
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<tr>
<td>randomized</td>
<td>Arm 2</td>
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<tr>
<td>I----Risperidone------------I</td>
<td>I----Risperidone--------I</td>
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<td>Arm 3</td>
<td>I----Placebo------------I</td>
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<td>I----Placebo----------------I</td>
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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)

**Graph A**

- **Proportion Free of Relapse**
- **Weeks after randomization**
- **P = 0.02**

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Risperidone</th>
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<td>40 40 37 29 29 26 26 24 24 20 20 20 15 15 14 13</td>
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</table>
Antipsychotic Discontinuation in AD (ADAD Trial)

B

Proportion Free of Relapse

Weeks after randomization

No. at Risk

<table>
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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.

Citalopram for Agitation in AD

- Citalopram for agitation in AD study (CitAD)
- N=186; placebo N=92; citalopram N= 94; duration 9 weeks
- 40% of citalopram vs 26% placebo group had moderate/marked improvement as well as reduction in caregiver distress
- Prolonged QTc FDA warning for citalopram doses above 20 mg in patients above 60; most CitAD patients were on 30 mg and not enough on 20 mg to make assessment
- QTc interval was increased compared to placebo; increase in falls
- Prescription in elderly limited to 20 mg daily

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

Years of Follow-up

Percent

0 0.5 1 1.5 2 2.5 3

0 5 10 15 20 25 30
Depressed Mood With Sleep and Appetite Disturbance

Prevalence (%)

- Depressed Mood
- Depressed Mood Veg Signs

Intake 1 Year 2 Years 3 Years

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

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Odds Ratio</th>
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<td>1.4.1 Response Rates</td>
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<tr>
<td>- Petracca 1996a,c</td>
<td>9</td>
<td>11</td>
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<td>10.3%</td>
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<td>- Magai 2000b,d</td>
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<td>24</td>
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<td>Heterogeneity: Tau² = 0.52; Chi² = 11.26, df = 5 (P = 0.05); I² = 56%</td>
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<td>Test for overall effect: Z = 1.84 (P = 0.07)</td>
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<td>1.4.2 Remission Rates</td>
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<td>Test for overall effect: Z = 1.59 (P = 0.11)</td>
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Clinical Treatment Algorithm I

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). Exclude Pseudobulbar Affect (PBA)
• Depressed mood is the key symptom to identify and treat because of lack of specificity for other symptoms, e.g., apathy
Clinical Treatment Algorithm II

Neuropsychiatric symptoms of dementia

1. Realize this is a trial and error process and get the HCP / guardian as per your state of practice laws involved early in the care. Provide good references/websites

2. Must have a sound informed consent process as these patients are impaired regarding consent

3. Do an overall assessment based on exam, records, care staff and family and divide into one of three constructs (psychotic, depressive, aggressive /sexual). By the time a psychiatrist is called there is need for rapid action

4. Psychotic: use antipsychotics; depression: SSRIs/mirtazapine; aggression/ sexual: use antipsychotics/divalproex

5. Apathy: trial of stimulant e.g. methylphenidate if medically safe
Pseudobulbar Affect: PBA (emotional incontinence)

- Inability to control emotions; frequent episodes of crying and laughing
- Vascular and Alzheimer’s dementia, multiple sclerosis, Parkinson’s disease, ALS, TBI
- Disruption of pathways involving serotonin and glutamate
- Affects 2 million Americans with underlying neurological conditions
- Commonly mistaken for depression
- PBA episodes are short, uncontrollable, no link to negative thoughts or feelings
- Depression longer lasting, linked to thoughts of worthlessness and hopelessness

PBA Management

- FDA approved dextromethorphan/quinidine 20 mg/10 mg
- Dizziness (10.3%); falls (13.1%)
- Contraindications: long QT syndrome, Heart failure, AV block (unless pacemaker is in place), quinidine, mefloquine, quinidine, quinine and MAOIs in past 14 days
- 1 capsule daily for 7 days then 1 capsule every 12 hours
- Routine labs and EKG
Neuropsychiatric Complications of Dementia
Dextromethorphan/Quinidine

• Clinical experience: Non antipsychotic agent (off-label)
• Patients with uncontrolled persistent agitation nonspecific in nature
• “Super outspoken” marked personality change with dementia
• Persistent screaming “help me”
• Two to three month trial and stop if no effect
Prescription of Psychiatric Medications in Dementia Patients

• Remains a minefield as the entire field is off-label and no single agent works for all agitation all the time
• Through assessment, involvement of family and caregivers is key
• Informed consent preferably written is important
• Monitoring of efficacy and side-effects
• Slow titration
• Physician must know when to discontinue medication
• Using agents that have studies in the field to back their use is important e.g. risperidone and citalopram
10 Absolutes of Dementia Care

• Never *Argue* instead *Agree*

• Never *Reason* instead *Divert*

• Never *Shame* instead *Distract*

• Never *Lecture* instead *Reassure*

• Never say *Remember* instead *Reminisce*
10 Absolutes of Dementia Care

- Never say "I Told You" instead Repeat
- Never say "You Can’t" instead say "Do What You Can"
- Never Command or Demand instead Ask or Model
- Never Condescend instead Encourage and Praise
- Never Force instead Reinforce
Summary

• Early diagnosis is key with regard to dementia management followed by education
• By the time a patient begins to have problems they are often in the moderate stage
• Begin with ChEI, consider combination of memantine and ChEI
• Neuropsychiatric complications are the rule
• If mild symptoms try citalopram, though antipsychotics (risperidone) have better data but may be more toxic
• Screen the caregiver for depression (you may have N=2 patients)
• Periodic gradual dose reduction (GDR)