Management of Alzheimer’s Disease
Partner’s Pharmacy
Education National Series
Patient & Caregiver: Take a Look at Mental Health

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Thank you.
Disclaimer

• Speakers Bureau and Advisor to Avanir
  • Nuedexta for PBA (Pseudobulbar Affect)
• Speakers Bureau for Forest (Namenda XR)
• Dementia Connection markets Antipsychotic Reduction Boot Camp Seminars/Webinars to facilities

Off-label use

• Will discuss research: off-label uses of cholinesterase inhibitors and Memantine for non-Alzheimer’s dementia
• Will mention research on risks of using antipsychotics off-label for dementia

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Objectives

• The LTC nurse will appraise FDA-approved uses of cholinesterase inhibitors and memantine in Alzheimer’s disease (AD)
• The attendees will analyze efficacy and safety in optimal Alzheimer’s pharmacology.
• The nurse will classify meds that increase confusion/decrease function in underlying Alzheimer’s disease.
3 Cholinesterase Inhibitors (ChI):
All affect acetylcholine and all are approved for mild to moderate Alzheimer’s disease by FDA

**Donepezil** (Aricept): Additionally is the only ChI approved for late stages of Alzheimer’s

**Rivastigmine** (Exelon): only ChI approved for a non-Alzheimer’s dementia (Parkinson’s) in addition to mild to moderate AD

**Galantamine** (Razadyne): only approved for mild to moderate Alzheimer’s disease
Who should not take Cholinesterase Inhibitors? (Aricept/Exelon/Razadyne)

- Bundle Branch Block
- Acute GI bleed or a significant past GI bleed
- COPD
- Seizure disorder
- Temporarily held during surgery due to anesthesia interaction
How to use Cholinesterase Inhibitors

Start at the lowest dose: wait 4-6 weeks; then increase to next dose
Always titrate at 4-6 week intervals
Go to highest dose resident can tolerate!
If side effects (not allergies of course) emerge when the dose is increased; then back down to the previous dosage

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Is our cholinesterase inhibitor Rx consistent?

- **Continue** same agent if resident doing well
- **Switch**: if decline occurs or side effects remain
- **Warn families and staff**: Are they aware that discontinuing the cholinesterase inhibitor may cause loss of functional, cognitive and communication gains made on therapy?
- **Use good communication/documentation** for hospital transfers and discharges!!

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How to use Cholinesterase Inhibitors

• Residents, staff and families need to know that *no change is actually a gain* in treatment of AD

• Should not stop for more than a week (i.e. if surgery)

• Urinary incontinence meds like Tolterodine (Detrol) and Ditropan (Oxybutynin) are pharmacologically opposite of Donepezil, Rivastigmine, and Razadyne and may cause them not to work.
How to use Cholinesterase Inhibitors

• Drug interactions

• Use with caution with NSAIDS (may increase cholinergic activity with increased gastric acid secretion)

• Gingko can inactivate Cholinesterase Inhibitors
Donepezil (Aricept)
Donepezil (Aricept)
Prescribing Information

Mild to Moderate Alzheimer’s Disease
5 mg or 10 mg once daily

Moderate to Severe Alzheimer’s Disease
10 mg or 23 mg once daily

Starting dose:
5 mg daily for 4 to 6 weeks, then titrate upward:
Increase dose: to 10 mg once daily for 3 months; then continue 10 mg as maintenance dose OR

If moderate to severe AD:
Dose of 23 mg daily may be attempted after being on 10 mg once daily for at least 3 months
Donepezil (Aricept)

Available in:

**Tablets**: 5 mg, 10 mg and 23 mg

**Orally Disintegrating Tablets (ODT)**:

5 mg and 10 mg
Effect of donepezil on cognition in severe Alzheimer's disease: a pooled data analysis

- Severe Impairment Battery (SIB) data were pooled from four donepezil clinical trials (N=904).
- Changes from baseline to week 24 were compared between placebo and donepezil groups, who were separated by dementia severity (Mini-Mental State Examination [MMSE] scores 1-5, 6-9, 10-12 and 13-17)
- Difference between donepezil- and placebo-treated patients mean change in SIB total scores from baseline to week 24 was 6.22 (p < 0.0001)
Effect of donepezil on cognition in severe Alzheimer's disease: a pooled data analysis


• Treatment-placebo differences were statistically significant for each baseline severity stratum, being greatest for the MMSE 6-9 stratum.

• “Change in total SIB score correlated significantly with change in measures of activities of daily living and global status. These results indicate that donepezil provides cognitive benefits in patients with severe AD, including those most markedly impaired….differences are clinically meaningful.”
Effects of donepezil on activities of daily living: integrated analysis of patient data from studies in mild, moderate and severe Alzheimer's disease


• Evaluated **effect of donepezil on function in AD pts** in outpatient, assisted living, and skilled nursing facilities.
  • 6 studies of donepezil AD trials selected.
  • For each domain of ADL/IADL, mean change from baseline to 24 weeks in placebo and donepezil groups compared.

• Study settings included 2183 patients (donepezil-1261; placebo-922) with baseline (MMSE) scores 5-26.

• Significant treatment differences favoring donepezil were observed.

• **Patients with moderate AD at baseline (MMSE 10-17) demonstrated the greatest treatment effect.**
Can Donepezil/Aricept Help Behaviors?
Rosenblatt et.al. American Journal of Alz. & Other Dementias 6/17/10

76 participants completed this ALF study
• 5 mg Donepezil (Aricept) daily for 6 wks
• Followed by 10 mg daily for 6 weeks
• Changes from baseline:
  Cognition: Mini-Mental State Examination (MMSE)
  Behaviors: Neuropsychiatric Inventory: NPI: looks at numerous BPSD
Donepezil (Aricept) ALF Study: Behaviors + Cognition
Rosenblatt et al. American Journal of Alz. & Other Dementias 6/17/10

• Mean MMSE score (18.7 at baseline) statistically significant improvement of 1.8 points in only 3 months = 5.4 pts/year (Average MMSE decline is 2-4 points/year in AD):

• Behavioral improvement in total score of: hallucinations, delusions, aggression, agitation, anxiety, disinhibition, irritability, night behaviors, appetite.
Acetylcholinesterase inhibitors in assisted living: patterns of use and association with retention

Rosenblatt A, Samus QM et al. Johns Hopkins School of Medicine, Baltimore, MD

- Maryland Assisted Living Study (MD-AL)
- 198 residents of 22 ALFs
- Dementia was diagnosed in 134: specific to Alzheimer's disease in 79
- Only CHI use was significantly associated with retention of persons w AD in AL at 6 months
- CHI use was associated with 228.75 days longer ALF retention in participants with AD!
Rivastigmine
(Exelon)
Rivastigmine (Exelon) Patch
Exelon prescribing information

• Initiate treatment: **4.6 mg/24 hours**
Rivastigmine (Exelon) patch

• After a minimum of 4 weeks, if tolerated, increase dose to **9.5 mg/24 hours** *(minimum effective dose)*

• Following a minimum additional 4 weeks, patch be increased to a maximum dosage of **13.3 mg/24 hours**
Switching from Capsules or Oral Solution: Rivastigmine www.exelon.com

• “A patient who is on a total daily dose of <6 mg of oral (capsules or solution) rivastigmine can be switched to rivastigmine (Exelon Patch) 4.6 mg/24 hours.

• A patient who is on a total daily dose of 6-12 mg of oral rivastigmine may be directly switched to rivastigmine (Exelon Patch) 9.5 mg/24 hours.

• It is recommended to apply the first patch on the day following the last oral dose.”
Rivastigmine (Exelon) Patch
Exelon prescribing information

For treatment interruption longer than three days, re-titratate dosage starting at 4.6 mg/24 hours

Consider dose adjustments in patients with:
• Moderate to severe renal impairment
• Mild to moderate hepatic impairment
• Low (<50 kg) body weight

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Effects of Rivastigmine in Alzheimer's Disease Patients with and Without Hallucinations


• Researched whether hallucinations in AD were associated with greater treatment benefits with rivastigmine.
• Data pooled from two randomized, double-blind, 6-month, mild-to-moderate AD trials comparing rivastigmine with placebo.
• Alzheimer Disease Assessment Scale-cognitive subscale (ADAS-cog) and Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus).
• Efficacy data analyzed for two groups: those with and those without hallucinations at baseline.
Effects of Rivastigmine in Alzheimer's Disease Patients with and Without Hallucinations


• 927 patients, 194 (21%) reported hallucinations at baseline.

• On the ADAS-cog, mean rivastigmine-placebo differences of 3.7 points in hallucinators and 2.2 points in non-hallucinators were reported at 6 months (both p < 0.001).

• In hallucinators, a significant rivastigmine-placebo difference of -1.0 CIBIC –plus points (beneficial)

• Hallucinations predicted greater treatment responses to oral rivastigmine.
Galantamine (Razadyne)
Galantamine treatment in Alzheimer’s disease: response and long-term outcome
Neuropsychiatr Dis Treat. 2011; 7: 565–576
AK Wallin, C Wattmo, L Minthon

• 280 w diagnosis of AD, open-label, multicenter Swedish Alzheimer Treatment Study, and received galantamine treatment.

• Mini-Mental State Examination (MMSE) and Alzheimer’s Disease Assessment Scale Cognitive Subscale (ADAS-cog), functional rating (Instrumental Activities of Daily Living Scale [IADL]), and global rating.

• Assessments before treatment and every 6 months for 3 years
Galantamine treatment in Alzheimer’s disease: response and long-term outcome
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• After three years of treatment,
• change from baseline was 2.6 points in MMSE
• 5.6 points in ADAS-cog scores.
• Globally, half of the patients improved or remained unchanged for two years.
How long are cholinesterase inhibitors effective in Alzheimer’s?


Open-label follow-up studies of RCTs of various durations: how long is benefit??

- **Donepezil:** 2.8 years to 4.9 years
- **Rivastigmine:** 2 years to 5 years
- **Galantamine:** 1.5 years to 3 years.
Memantine (Namenda)
Memantine (Namenda)
FDA approved for Moderate to Severe Alzheimer’s
Start at Moderate Stage: Continue through Severe Stage

• Memantine (Namenda) is not FDA approved for early Alzheimer’s
• Start to use it in moderate stage of Alzheimer’s
  • Score of 19 on MMSE starts moderate stage
  • Stage 5 on FAST begins moderate stage
• Memantine (Namenda) does not affect Acetylcholine: works on Glutamate
• Glutamate: main excitatory NT in CNS
• Blocks overactive glutamate transmission (neurotoxicity)
• Goal: normalize transmission to maintain/improve cognition and possibly prevent neurotoxicity

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Alzheimer’s Disease (not other dementias)

Are residents on Combination Treatment?

Moderate Stage Rx: Use CHI + Memantine (Namenda) together

- **Dose Titration:**
  - 5 mg daily for week 1
  - 5 mg twice daily for week 2
  - 10 mg in AM and 5 mg in PM for week 3; then
  - 10 mg twice daily from then on till end of illness

  - If prescribers don’t increase dose to 10 mg twice daily…..your resident will get less efficacious results.

  - 5 mg twice day is highest dose for renal impairment

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Memantine (Namenda XR)

- Memantine (Namenda XR) is available as an extended-release capsule: 7 mg, 14 mg, 21 mg, 28 mg
- Initial Dose Memantine (Namenda XR) 7 mg daily
- Maintenance Dose Memantine (Namenda XR) 28 mg daily
- Minimum of 1 week of treatment with the previous dose prior to increasing the dose.
- Target dose of 14 mg once daily is recommended in patients with severe renal impairment.

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Switching from Memantine bid to XR
namendaxr.com prescribing info

Switching from Memantine (Namenda) Tablets to Memantine (Namenda XR) Capsules:
Recommended that pt on \textbf{10 mg bid} of Memantine (Namenda) Tablets be switched to Memantine (Namenda XR) \textbf{28 mg capsules once daily} the day following the last dose of a 10 mg tablet.

If severe renal impairment, it is recommended that a patient who is on a regimen of \textbf{5 mg twice daily of tablets} be switched to Memantine (Namenda XR) Capsules \textbf{14 mg once daily capsules} the day following the last dose of a 5 mg tablet.

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Renal Impairment and Memantine (Namenda)

• No dosage adjustment is recommended in patients with mild or moderate renal impairment.

• A target dose of 14 mg/day is recommended in patients with severe renal impairment (creatinine clearance of 5 – 29 ml/min)
Combination Treatment: CHI + Memantine (Namenda) together

- **Middle Stage AD**: Memantine (Namenda) should be used WITH Donepezil (Aricept) or Rivastigmine (Exelon) or Galantamine (Razadyne)

- **Late Stage AD**: Memantine (Namenda) can be used alone or with Donepezil (Aricept): the only ChI with late-stage FDA approval

- Treat at full dose Memantine (Namenda) until person reaches the very late stages of Alzheimer’s (hospice stage)
Retrospective Study on Benefits of Combined Memantine and ChI rx in Aged pts w AD: MEMAGE Study
Gareri P, Putignano D, Castagna A et al.

- 240 pts (mean age 77.9) assessed MMSE, ADL, IADL, behaviors with NPI (Neuropsych inventory) and comorbidities.
- MMSE increased at 6th month
- Improvements in NPI total score
- MMSE increased with Donepezil and Memantine compared with Rivastigmine + Memantine
Efficacy and safety of memantine in patients with moderate-to-severe Alzheimer’s disease

- Outpts meeting AD DSM/NINCDS
- MMSE of 5-14
- Moderate to severe AD on FAST (functional assessment staging test)
- 315 placebo and 318 on Memantine 20 mg/d
Efficacy and safety of memantine in patients with moderate-to-severe Alzheimer’s disease

• Memantine statistically significantly superior to placebo on CIBIC Plus (global assessment) and subscale BEHAVE-AD (behavioral and psychological symptoms) showed less worsening of behavioral symptoms

• Less worsening of language ability, visuospatial cognition, attention compared with placebo
Memantine in patients with Alzheimer's disease receiving donepezil: new analyses of efficacy and safety for combination therapy

*Atri A, Molinuevo JL et al.*


- Meta-analyses from two 24-week, randomized, DB, PC trials of Memantine 20 mg/day versus placebo: added to a stable cholinesterase inhibitor.
- 2 sub-groups:
  - Pts w moderate to severe AD (MMSE 5-19)
  - Pts w moderate AD (MMSE 10-19)
- Measured efficacy of Rx on: cognition, function, and global status.
- Also assessed clinical worsening, defined as concurrent deterioration from baseline
Memantine in patients with Alzheimer's disease receiving donepezil: new analyses of efficacy and safety for combination therapy


• Week 24: Both the moderate AND the moderate to severe subgroup, pts receiving memantine added to donepezil significantly outperformed those receiving placebo added to donepezil in measures of cognition, function and global status

• Significantly fewer patients receiving memantine added to donepezil showed marked clinical worsening than those receiving placebo added to donepezil, in both subgroups
Long-term Course and Effectiveness of Combination Therapy in Alzheimer’s Disease: 3-year Harvard/Mass General/NIA sponsored study

- Compared AD pts treated with combination therapy consisting of cholinesterase-inhibitor (ChI) plus memantine versus ChI alone versus no treatment.

- 382 pts with probable AD: serial clinical evals at a memory disorders unit over a period of several years. Detailed cognition and functional assessment done each visit.
3 groups in study: 0, 1 or 2 meds

- 144: no antidementia medications
- 122: received cholinesterase inhibitor (CI) monotherapy
- 116: received combination Rx with a cholinesterase inhibitor plus memantine.

Combination group on both memantine and ChI Rx: significantly lower annual rates of deterioration in both cognition and ADL scores compared with the cholinesterase therapy group alone and the subjects without antidementia medications.
• The impact on cognition and ADL in the combination group increased with the duration of treatment.

• Results for cognition significantly favored the cholinesterase inhibitor group alone versus no medication treatment group.
Persistent treatment with cholinesterase inhibitors and/or memantine slows clinical progression of Alzheimer disease
Susan D Rountree¹*, Wenyaw Chan², Valory N Pavlik³ et al.
Alzheimer's Research & Therapy 2009, 1:7

• 641 probable AD pts followed over 20 years. Cumulative drug exposure was expressed as a persistency index (PI) reflecting total years of drug use divided by total years of disease symptoms.

• Baseline and annual testing consisted of Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), Baylor Profound Mental Status Examination (BPMSE), Clinical Dementia Rating-Sum of Boxes (CDR-SB), Physical Self-Maintenance Scale (PSMS), and Instrumental Activities of Daily Living (IADL).
Persistent treatment with cholinesterase inhibitors and/or memantine slows clinical progression of Alzheimer disease
Rountree SD, Chan W, Pavlik VN et al.
Alzheimer’s Research & Therapy 2009, 1:7

Results
Persistency of medication use (PI) was associated with significantly slower rates of decline on MMSE, PSMS, IADL, and CDR-SB.
Persistency of medication use (PI) slowed ADAS-Cog decline temporarily. The magnitude of the favorable effect of a rate change in PI was: MMSE 1 point per year, PSMS (ADL) 0.4 points per year, IADL 1.4 points per year, and CDR-SB (global scale) 0.6 points per year.
Persistent treatment with cholinesterase inhibitors and/or memantine slows clinical progression of Alzheimer disease
Rountree SD, Chan W, Pavlik VN et al. 
Alzheimer’s Research & Therapy 2009, 1:7

Conclusions
“Persistent drug treatment had a positive impact on AD progression assessed by multiple cognitive, functional, and global outcome measures. The magnitude of the treatment effect was clinically significant. Positive treatment effects were even found in those with advanced disease.”
Stopping Memantine (Namenda) in LTC Residents & Utilization of Psychotropic Medications

Howard Fillit et al.

Researchers reviewed charts of LTC residents in 13 US nursing home sites.

2 groups:

• 248 residents who discontinued Memantine (Namenda)
• 273 residents who took Memantine (Namenda) ongoing
Stopping Namenda in Nursing Home Residents with AD is Associated with Increased Utilization of Psychotropic Medications

• Persons who discontinued memantine therapy had a significantly higher rate of psychotropic use (32.3% vs 16.5%).
  – antipsychotics
  – anxiolytics
  – antidepressants
  – anticonvulsants

• Findings: stopping Memantine (Namenda) was associated higher odds of increased psychotropic use
Meds to Avoid in Alzheimer’s and other Dementias
2012: New, Updated Beers List
Journal of American Geriatrics Society

• Based on review over 2000 research articles
  “All benzodiazepines increase risk of cognitive impairment, delirium, falls fractures.”

• For anxiety:
  • Alprazolam (Xanax)
  • Lorazepam (Ativan)
  • Clonazepam (Klonopin)
• “Avoid benzodiazepines (any type) for Rx of insomnia, agitation or delirium!!

• STRONG strength of recommendation
• HIGH quality of evidence
Benzos for sleep in elders

• “Avoid benzodiazepines (any type) for treatment of insomnia, agitation or delirium

• Examples:
  • Temazepam (Restoril)
  • Triazolam (Halcion)
  • Estazolam (ProSom)
2012: New, Updated Beers List
Journal of American Geriatrics Society

- Avoid even the non-benzodiazepine hypnotics
- Eszopiclone (Lunesta)
- Zolpidem (Ambien)
- Zaleplon (Sonata)
- “Adverse events similar to those of benzodiazepines in older adults (delirium, falls, fractures)"
- Strong recommendations not to use!
Choice of observational study design impacts on measurement of antipsychotic risks in the elderly: a systematic review

- This evidence-based review included:

44 studies associated with antipsychotic prescribing in elders:
  - 16 evaluated the risk of death
  - 18 evaluated cerebrovascular events
  - 8 evaluated the risk of hip fracture
  - 6 evaluated the risk of pneumonia

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Choice of observational study design impacts on measurement of antipsychotic risks in the elderly: a systematic review


RISK-BENEFIT RATIO IN THIS REVIEW OF 44 STUDIES

• 20% to 30% increased risk of death
• One excess death for every 11 to 33 person helped with these medicines
• One excess hospitalization for hip fracture for every 4 to 12 patients helped
• One excess hospitalization for pneumonia for every 2 to 5 patients helped
Choice of observational study design impacts on measurement of antipsychotic risks in the elderly: a systematic review
RISK-BENEFIT RATIO IN THIS REVIEW OF 44 STUDIES

5. Increase of one extra death per 100 patients with atypical antipsychotics compared to non-use

6. 2 to 3 times increased risk of all cerebrovascular events (strokes)

7. 2 to 3 times greater risk of pneumonia

8. 20% to 40% increased risk of hip fracture

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Antipsychotics and oropharyngeal dysphagia in hospitalized older patients.

• Persons on antipsychotic meds: significantly worse on the Dysphagia Severity Rating Scale

• Higher doses of antipsychotic medication: associated with worse swallowing function
Atypical antipsychotic use in patients with dementia: managing safety concerns

“Adverse effects in patients with dementia include an increased risk of mortality and cerebrovascular events, as well as metabolic effects, extrapyramidal symptoms, falls, cognitive worsening, cardiac arrhythmia, and pneumonia.”
Goals of Optimal Prescribing

• Outpatient Prescribers:
  • Can slow down cognitive, functional decline in Alzheimer’s and possibly other dementias
  • Greater impact in middle stages

• LTC Prescribers:
  • ALF/Nursing home: LTC staff spend on average 79 hours per week battling behaviors of dementia.