# Treatment of Dementia Patients

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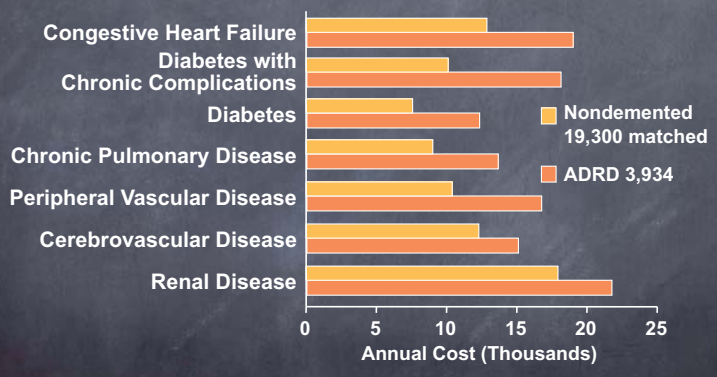
# Contents

- Recommended drugs for pharmacological treatment of AD patients
- Treatment for moderate to severe AD patiens
- Treatment of neuropsychiatric symptoms in AD patients

**Dementia Increases the Costs of Caring for Common Comorbidities in Managed Medicare Settings**




Hill JW, Futterman R, Duttagupta S, et al. Neurology. 2002(Jan 8);58(1):62-70.

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## Diagnosis of Dementia Increases Risk for Suicide

The majority of suicides (75%) occurred in those patients with a ne dementia diagnosis (ie, diagnosis during the study period)

- Potential predictors

| Independent Variable | Odds Ratio (95% CI) |
|---|---|
| Male sex | 2.49 (0.79 - 7.83) |
| White race | 1.49 (1.14 - 1.95) |
| Depression | 2.04 (1.45 - 2.85) |
| Inpatient psychiatric stay | 2.31 (1.54 - 3.46) |
| Antianxiety prescription | 1.98 (1.48 - 2.65) |
| Antidepressant prescription | 2.11 (1.57 - 2.84) |

- Age Effect

| Independent Variable | Odds Ratio (95% CI) |
|---|---|
| Age, 60 - 69 vs 90+ years | 2.23 (0.69 - 7.15) |
| Age, 70 - 79 vs 90+ years | 1.60 (0.51 - 5.06) |
| Age, 80 - 89 vs 90+ years | 1.21 (0.38 - 3.86) |

Alz Dementia. 2011;7:567-573.

## Alzheimer's disease

- Progressive, degenerative disorder
- Characterized by memory impairment plus one or more additional cognitive disturbances
- Gradual decline in three key symptom domains
  - Activities of daily living (ADL)
  - Behavior and personality
  - Cognition
- Most common cause of dementia in people aged 65 and over

## Proposed Risk and Protective Factors for LOAD

### Risk factors

- Age
- Genetic
  - Familial aggregation
  - APOE e4
  - Different genes (e.g. CR1, PICALM, CLU, TREM2, TOMM40) have been proposed (www.alzgene.org)
- Vascular and metabolic
  - Cerebrovascular lesions
  - Cardiovascular diseases
  - Diabetes mellitus and pre-diabetes
- Midlife positive association but late-life negative association
  - Hypertension
  - High BMI (overweight and obesity)
  - High serum cholesterol
- Lifestyle
  - Smoking
  - High alcohol intake
- Diet
  - Saturated fats
  - Low B vitamins/high homocysteine
  - Homocysteine
- Others
  - Depression
  - Traumatic brain injury
  - Occupational exposure (heavy metals, ELF-EMFs)
  - Infective agents (herpes simplex virus type I, Chlamydophila pneumoniae, spirochetes)

### Protective factors

- Genetic
  - Different genes (e.g. APP, APOE e2) have been proposed
- Psychosocial factors
  - High levels of education and SES
  - High level of complexity of work
  - Rich social network and social engagement
  - Mentally stimulating activity
- Lifestyle
  - Physical activity
  - Moderate alcohol intake
- Diet
  - Mediterranean diet
  - PUFAs and fish-related fats
  - Vitamins B6 and B12, folate
  - Antioxidant vitamins (A, C and E)
  - Vitamin D
- Drugs
  - Antihypertensive drugs
  - Statins
  - HRT
  - NSAIDs

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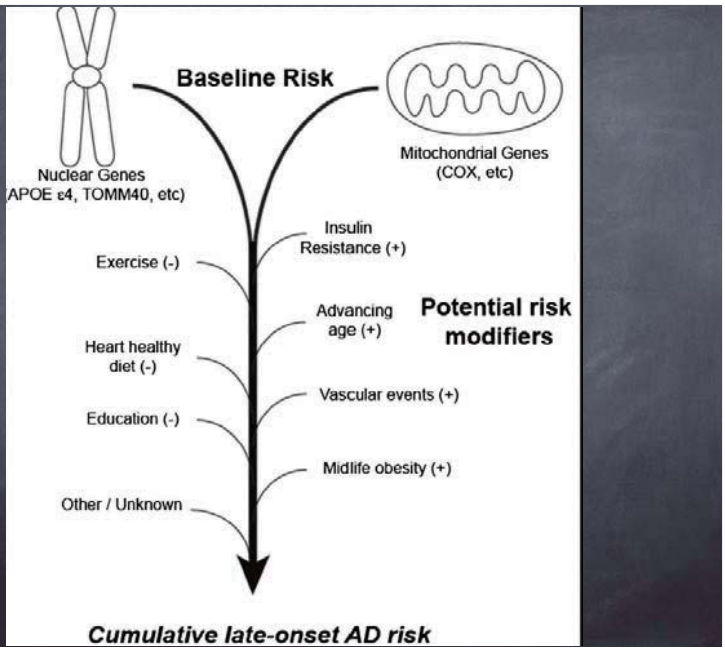
# Combined Effect

## Increased Risk

- Genetic and environmental factors in midlife
  - APOE e4 magnifies the effect of high alcohol intake, smoking, physical inactivity and high intake of saturate fat
- Vascular and metabolic factors in midlife
  - Co-occurrence of hypertension, obesity, hypercholesterolemia and/or physical inactivity has an additive effect
- Vascular and metabolic factors/diseases in late-life
  - Higher risk in individuals with brain hypoperfusion profile: chronic heart failure, low pulse pressure, low diastolic pressure
  - Higher risk in individuals with atherosclerosis profile: high systolic pressure, diabetes mellitus or prediabetes, stroke

## Decreased Risk

- Genetic and environmental factors in midlife
  - High education level reduces the negative effect of APOE e4
- Physical activity counteracts the risk due to APOE e4
  - Environmental factors in midlife
  - High level of complexity of work modulates the increased dementia risk due to low level of education
- Genetic and environmental factors in late-life
  - Active leisure activities or absence of vascular risk factors reduces the risk due to APOE e4




# Major cholinergic changes in AD

- Depletion of acetylcholine (ACh): especially in moderate to severe disease stages
- Decline in choline acetyltransferase (ChAT) activity
- Loss of cholinergic neurons
  - Loss of muscarinic (M2) receptors
  - Loss of nicotinic receptors (nAChR)
- AChE ↓
- Butylcholinesterase (BuChE) ↑

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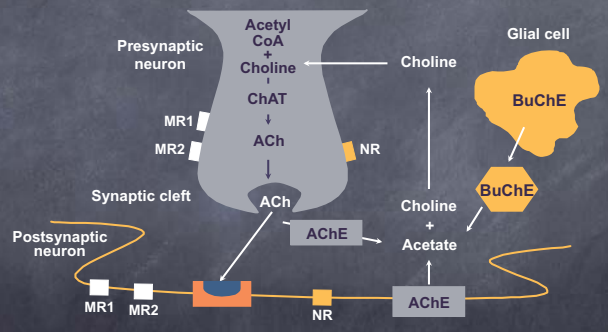
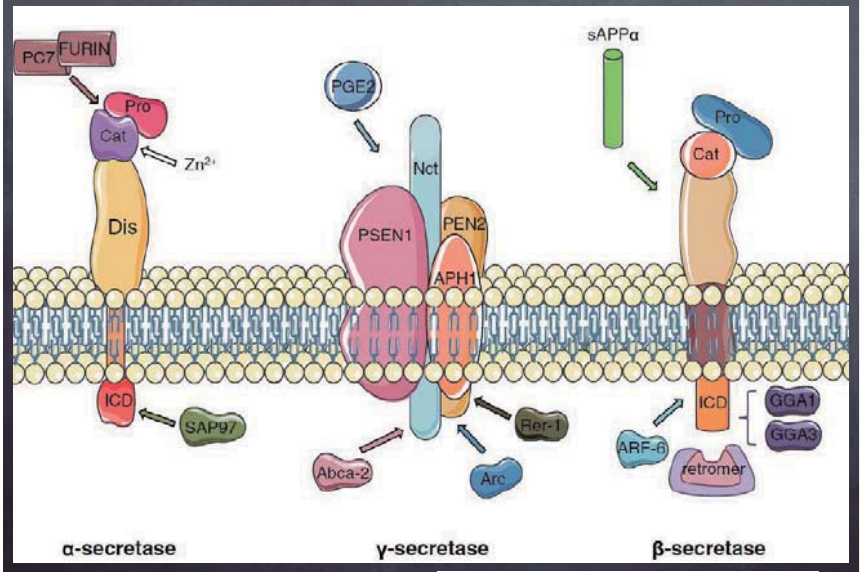
# Normal Cholinergic function

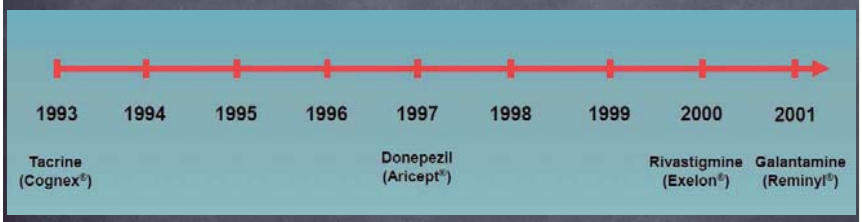



CoA=coenzyme A; MR=muscarinic receptor; NR=nicotinic receptor
Adapted from Adem, 1992.




Cellular Signalling 24 (2012) 1831–1840

# AChE inhibitors

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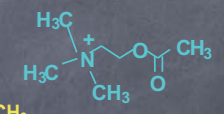
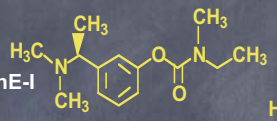
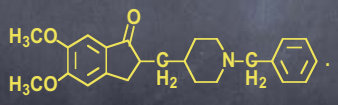
# Acetylcholine-esterase inhibitors

ACh

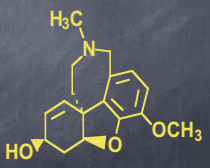


Rivastigmine
mechanism: AChE/BuChE-I





Donepezil
mechanism: AChE-I



Galantamine
mechanism: AChE-I

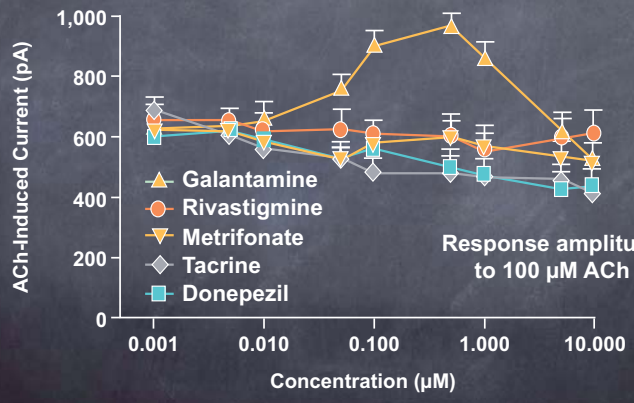
Physicians' Desk Reference, 2003.

# AchE inhibitor overview

| | AChE Inhibitors | | Dual AChE/ BuChE Inhibitor |
|---|---|---|---|
| Characteristic | Donepezil | Galantamine | Rivastigmine |
| Doses per day | 1 | 2 | 2 |
| Maximum dose (mg/d) | 10 | 24 | 12 |
| Brain region selectivity | No | No | Yes |
| Reversibility | Reversible | Reversible | Psuedo-reversible |
| Nicotinic allosteric modulation | No | Yes | No |
| Cytochrome P450 metabolism | Yes | Yes | No |

Enz et al, 1992, 1993; Samochocki et al, 2000; Svensson and Nordberg, 1997; Yamanishi et al, 1990; Cutler and Sramek, 1998; Inglis, 2002.

# Allosteric Nicotinic Receptor Modulation




Samochocki M, Zerlin M, Jostock R, et al. Acta Neurol Scand Suppl. 2000;176:68-73

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## Distribution of Cholinesterases in the Healthy Human Brain

Figure 1

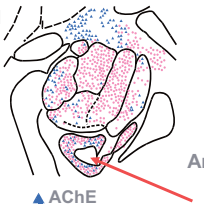
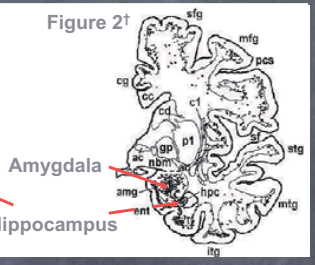



Figure 2†



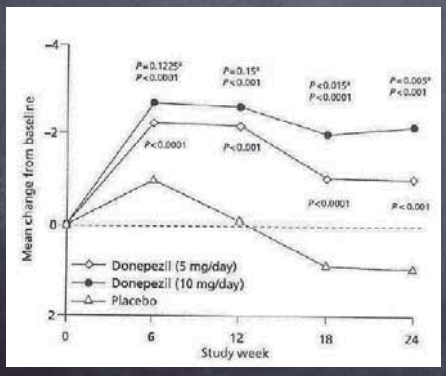

- **BuChE neurons are less abundant than AChE neurons**
- **BuChE is very rich in cortical and limbic areas (amygdala and hippocampus)**
- **BuChE accumulations in neuritic plaques**

*Darvesh S, Grantham DL, Hopkins DA. J Comp Neurol. 1998(April 13);393(3): 374-390. †Mesulam, 2000.

## Established Phrmacological Treatment for AD

| Pharmacological agent | Mechanism of action | Starting dose | Titration schedule | Maximum dose | Metabolism | Potential drug interactions |
|---|---|---|---|---|---|---|
| Donepezil | AChEI | 5 mg once daily | Increase by 5 mg every four weeks | 10 mg once daily | Hepatic – CYP2D6 and CYP3A4 | Ketoconazole and quinidine may increase donepezil level; donepezil may prolong effect of succinylcholine. |
| Galantamine | AChEI and nicotinic receptor modulator | 4 mg twice daily (or 8 mg extended release once a day) | Increase by 4 mg to 8 mg daily every four weeks | 12 mg twice daily (or 24 mg extended release once a day) | Hepatic – CYP2D6 and CYP3A4 | Ketoconazole and quinidine may increase galantamine level; amitriptyline, fluoxetine, and fluvoxamine may lower galantamine level. |
| Rivastigmine | AChEI and butyryl-cholinesterase inhibitor | 1.5 mg twice daily | Increase by 1.5 mg once to twice daily every four weeks | 6 mg twice daily | Nonhepatic, renal clearance | Rivastigmine may prolong the effect of succinylcholine. |
| Memantine | NMDA agonist-antagonist (partial agonist) | 5 mg once daily | Increase by 5 mg every week | 10 mg twice daily | Predominant renal clearance | Carbonic anhydrase (alkalinization of urine) may reduce the clearance of memantine and increase its toxicity. Avoid concurrent use of amantadine, dextromethophan, and ketamine. |

## Aricept (Donepezil)




Meta-analysis: 10 mg superior to 5 mg from week 18 onwards
*Int J Geratr Psychiatry* 2004;19:624-633

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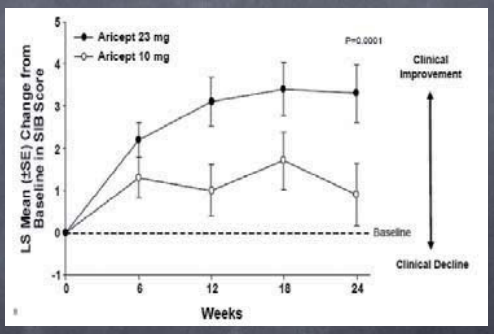
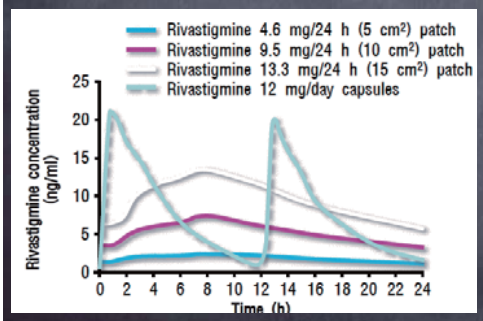
ARICEPT 23 mg as a treatment for moderate to severe Alzheimer's disease

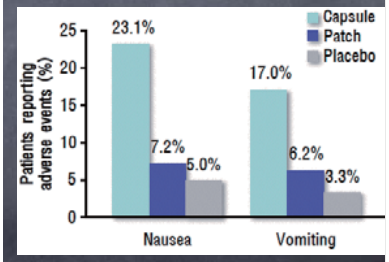
-The dose of 23 mg/day was statistically significantly superior to the dose of 10 mg/day.

Farlow MR, et al. Clin Ther. (2010)

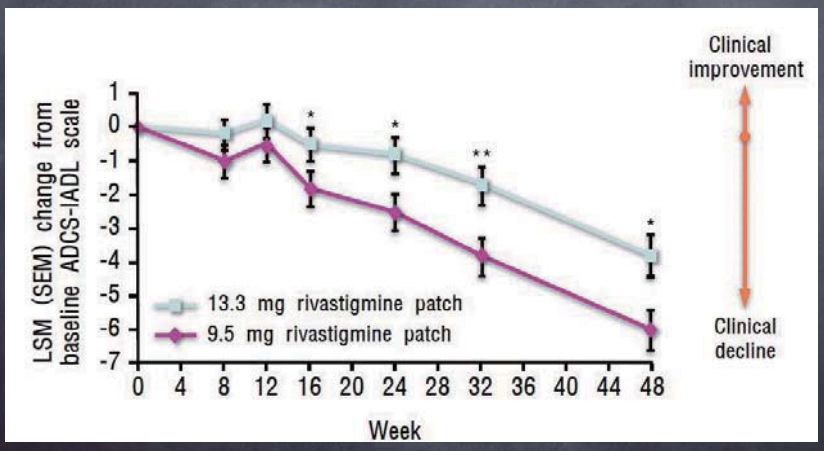



# Exelon (Rivastigmine)




Winblad B *et al. Int J Geriatr Psychiatry* 2007; 22: 456–67




LSM, least squares means; SEM, standard error of the mean
*p < 0.05; **p < 0.001 for 13.3 mg (15 cm²) *versus* 9.5 mg (10 cm²) rivastigmine patch
Cummings J *et al. Dement Geriatr Cogn Disord* 2012;33:341–53

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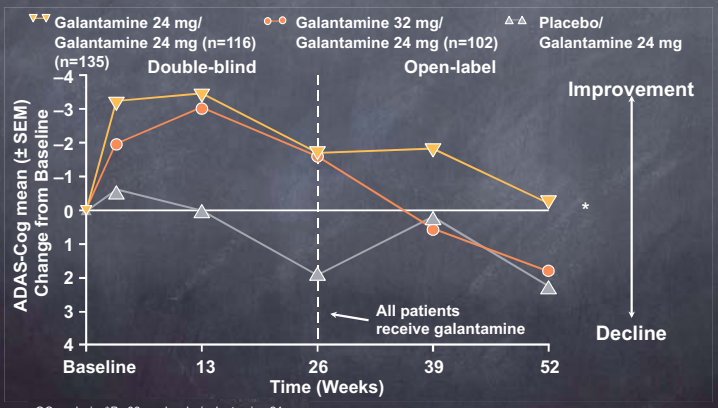
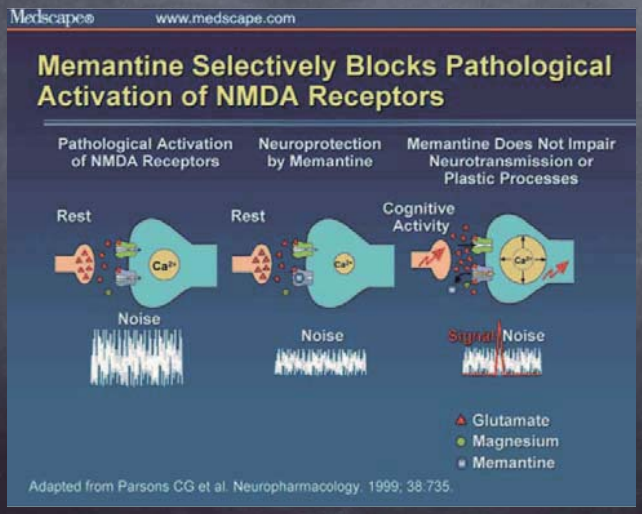
## Long-term Effects of Galantamine on Cognition: ADAS-Cog Change from Baseline

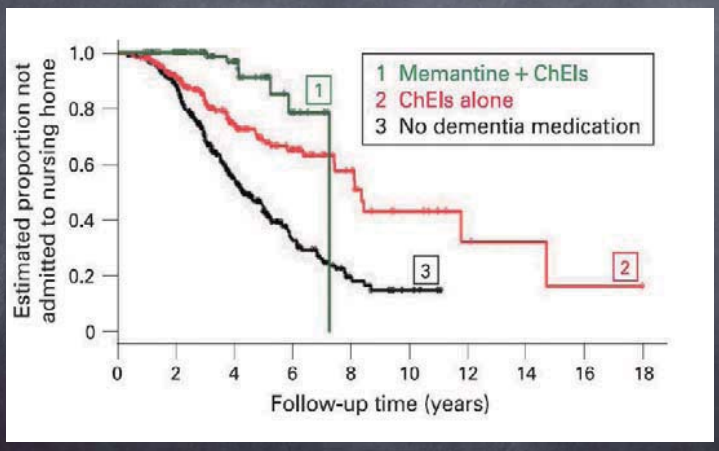



OC analysis; *$P$=.03 vs placebo/galantamine 24 mg
Raskind et al, 2000.

# Memantine




# Combination Therapy




J Neurol Neurosurg Psychiatry. (2009)

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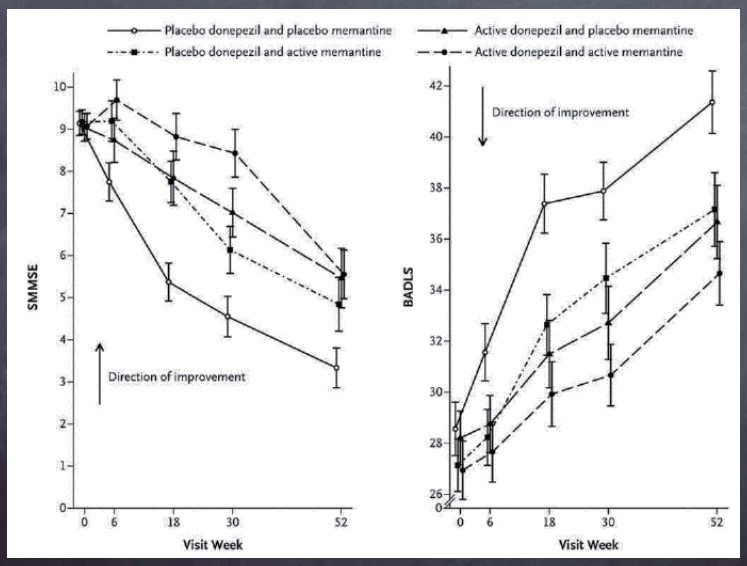


Howard R et al. N Engl J Med (2012)

# Adverse Effects

| Class | Adverse Effects |
|---|---|
| Cholinesterase inhibitors | Gastrointestinal effects, including nausea, vomiting, and diarrhea<br>Weight loss<br>Loss of appetite<br>Less common: syncope, leg cramps, dizziness, "ill-at-ease" feeling |
| NMDA receptor antagonists | Sedation<br>Dizziness<br>Constipation |

- Adverse effects are more frequent at treatment initiation
- Dosing can be increased as patients develop tolerance to adverse effects

Lanctôt KL, et al. *CMAJ*. 2003;169:557-564.[5]

## Stages of Alzheimer Disease

| Stage | Characteristics |
|---|---|
| Mild | • Impairment of memory and executive function<br>• Mild functional impairment such as difficultly making plans or managing the household |
| Moderate | • More severe cognitive deficits that have an impact on areas such as language and recognition<br>• Difficulty managing activities of daily living |
| Severe | • Requires almost complete care for daily existence |

Reisberg B, et al. *Am J Psychiatry*. 1982;139:1136-1139.[1]

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## Depression and Behavioral Disorders

**Depression and behavioral disorders are more prevalent as Alzheimer disease progresses**

- Early stages affect temporal lobes and the hippocampus
- Progressive involvement of the cortex as disease advances

**Common**

- Up to 80% of patients will have a behavioral disturbance
- Up to 50% will exhibit clinically significant depression

Cumbo E, et al. *J Alzheimers Dis*. 2014;39:477-485[2]; Mega MS, et al. *Neurology*.1996;46:130-135[3]; Desai AK, et al. *Prim Care Companion J Clin Psychiatry*. 2001;3:93-109.[4]

## Managing Expectations

**It is important to manage caregiver expectations about medication benefits**

- Cognitive enhancers do not treat underlying disease pathology
- Goal is to delay symptoms/prevent progression, which improves quality of life for both patients and caregivers
- Patients and caregivers should be informed of common side effects that can occur with medications and instructed to report unusual side effects to prescribing healthcare professional

## When do you stop medications?

- Each patient situation requires a cost-benefit assessment and should be decided on a case-by-case basis
- Medications indicated for severe stage Alzheimer disease may continue to be of benefit to patients
- Stopping medications may cause noticeable loss of benefit that cannot be regained

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# Multiple Drugs

- Multiple medications are common in elderly patients
  - Physiological changes that accompany aging increase the risk of drug-to-drug interactions
- Good records and communication are key
- Multidisciplinary approach is needed for the development of a comprehensive plan of care

# Behaiovral Symptoms Worsen as Cognition Declines


Dementia patients who display marked behavioral disturbances in a given time frame are more likely to display them again in the future.[1]

1. Rabins PV, et al. *Am J Psychiatry*. 2007;164(12 Suppl):5-56. 2. Holtzer R, et al. *J Am Geriatr Soc*. 2003;51(7):953-960. 3. Aarsland D, et al. *Int J Geriatr Psychiatry*. 2001;16(2):184-191. 4. Clarke DE, et al. *J Neuropsychiatry Clin Neurosci*. 2008;20(3):337-347. 5. Dujardin K, et al. *Mov Disord*. 2009;24(16):2391-2397. 6. Wilson RS, et al. *Am J Geriatr Psychiatry*. 2005;13(11):984-990. 7. Scarmeas N, et al. *Arch Neurol*. 2003;62(10):1601-1608.

# Behavioral Clusters


RBD=rapid eye movement (REM) sleep behavior disorder. PLMD=periodic limb movement disorder.
1. Lyketsos CG, et al. *Am J Psychiatry*. 2000;157(5):708-714. 2. Clarke DE, et al. *J Neuropsychiatry Clin Neurosci*. 2008;20(3):337-347. 3. Boyd M. *Psychiatric Nursing: Contemporary practice*; 2008.

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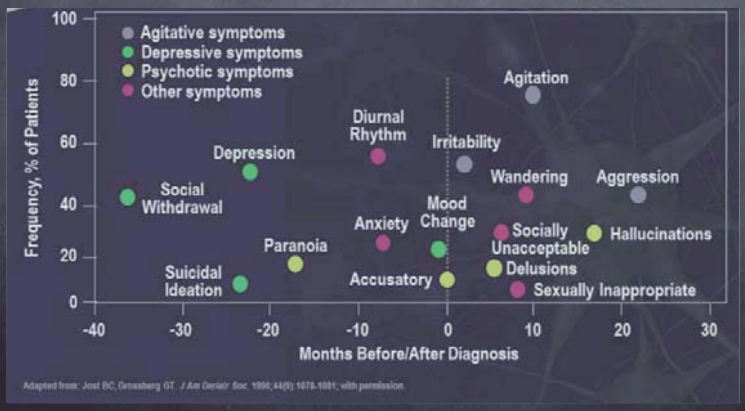
## Timeline and Epidemiology of Psychiatric Symptoms in AD




Adapted from: Jost BC, Grossberg GT. *J Am Geriatr Soc*. 1996;44(9):1078-1081; with permission.

## Neuropsychiatric symptoms in Dementias

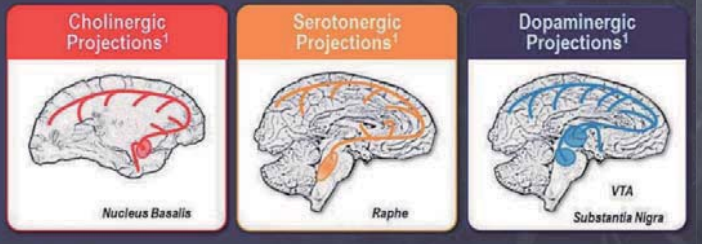
| NPI Item | AD | PDD | DLB | VaD | FTD |
|---|---|---|---|---|---|
| Delusions | ● | ● | ●● | ● | — |
| Hallucinations | — | ●●● | ●● | ● | — |
| Agitation | ●● | ●● | ●●● | ●●● | ●●● |
| Depression | ●● | ●●● | ●●● | ●● | ●●● |
| Anxiety | ●● | ●●● | ●●● | ●● | ● |
| Apathy | ●●● | ●●● | ●●●● | ●●● | ●●●● |
| Disinhibition | — | — | ● | ● | ●●●● |
| Irritability | ●● | ● | ●●● | ●● | ●●● |
| Sleep | ● | ● | ●●● | ●● | ●● |

— 0-14% ● 15-29% ●● 30-44% ●●● 45-59% ●●●● ≥60%

NPI=Neuropsychiatric Inventory. PDD=Parkinson's disease dementia. DLB=dementia with Lewy bodies. VaD=vascular dementia. FTD=frontotemporal dementia.
1. Benaiarcng V, et al. *Dement Geriatr Cogn Disord*. 2004;17(1-2):14-20. 2. Aarsland D, et al. *J Neurol Neurosurg Psychiatry*. 2007;78(1):36-42. 3. Tekin S, et al. *Ann Neurol*. 2001;49(3):355-361. 4. Aarsland D, et al. *Int J Geriatr Psychiatry*. 2001;16(2):184-191. 5. Kao AW, et al. *Alzheimer Dis Assoc Disord*. 2008;22(4):365-378. 6. Craig D, et al. *Am J Geriatr Psychiatry*. 2005;13(6):460-468. 7. Lyketsos CG, et al. *Am J Psychiatry*. 2000;157(5):708-714. 8. Banks SJ, Weintraub S. *J Geriatr Psychiatry Neurol*. 2008;21(2):133-141. 9. Caputo M, et al. *Acta Psychiatr Scand*. 2008;117(6):455-464. 10. Aalten P, et al. *Dement Geriatr Cogn Disord*. 2007;24(6):457-463. 11. Bonomi B, et al. *Arch Gerontol Geriatr*. 2008;46(1):101-109. 12. Fuh JL, et al. *J Neurol Neurosurg Psychiatry*. 2005;76(10):1337-1341. 13. Srikanth S, et al. *J Neurol Sci*. 2005;239(1-2):43-48. 14. Lyketsos CG, et al. *JAMA*. 2002;288(12):1475-1483. 15. Liu W, et al. *Neurology*. 2004;62(5):742-748.

## Neurotramsmitter systems related to Behavioral Symptoms of Dementia

- Dysfunction in multiple neurotransmitter pathways are implicated in neuropsychiatric symptoms




VTA=ventral tegmental area.
1. Tarazeneh R, Sahin JE. In: Weiner MF, et al., eds. *The American Psychiatric Publishing Textbook of Alzheimer Disease and Other Dementias*; 2009. 2. Goldsacher D. In: Weiner MF, et al., eds. *The American Psychiatric Publishing Textbook of Alzheimer Disease and Other Dementias*; 2009. 3. Tiraboschi P, et al. *Neurology*. 2000;54(2):407-411. 4. Bohnen NI, et al. *Arch Neurol*. 2003;60(12):1745-1748. 5. Kandel ER, et al. *Principles of Neural Science*; 2000

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# Managemnt of Dementia-Related Behavior

- Define Target symptoms and severity
- Environmental factors addressed
- Medical illness revisited
- Establish psychiatric diagnosis
- Nonpharmacological management
- Targeted pharmacotherapy (if needed)
- Initiate low and go slow
- Assess outcomes and re-evaluate

Adapted from: Gearhart M. *Clin Nurse Spec.* 2001;15:158-159.

# Non-pharmacological interventions

- Make a predictable routine
- Ensure familiarity (clothing, possessions)
- Simple language
- simplify tasks
- Distract and redirect
- Safe environment
- Orient (Clocks, calendarars, etc)
- Moderate lighting in day and night
- Reduce stimulation
- Consider Adult daycare

1. Cummings JL, et al. *Am Fam Physician.* 2002;65(12):2525-2534.

# Individualaized psychological intervention for agitation

| | |
|---|---|
| Physical pain or discomfort? | Medical treatment; nursing intervention; change environment |
| Looking for home? | Make place look/feel more like home |
| Need for social contact? Restless? | Social interaction (real or simulated); identify meaningful activities |
| Disturbing others? | Separate people who may trigger negative responses in each other |
| Hallucinations? | Check vision/hearing; try using familiar objects/people |
| Need more control? | Offer choices |
| Refusing help with ADL? | Perform ADL at a different time or by a different method |
| Need for stimulation/exercise? | Provide large enclosed environments; safety devices; change locks |

ADLsactivities of daily living.
1. Cohen-Mansfield J, et al. *J Gerontol A Biol Sci Med Sci.* 2007;62(8):906-916.

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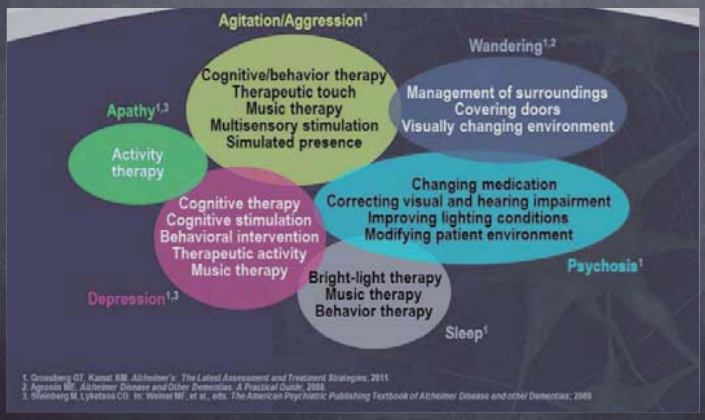
## Nonpharmacological therapy for Behavior Clusters




## Principles of Management of Behavioral Symptoms

- Anti-dementia drugs reduce BPSD
- Effective anti-dementia treatment seems to suppress the development of BPSD
- SSRIs and atypical antipsychotics play a role in treatment, bu the risks vs benefits are unclear

## Mortality Risks of Antipsychotics (Crude 6months mortality rates)

- 20% for haloperidol (adjusted relative risk [RR], 1.54; 95% confidence interval [CI], 1.38 - 1.73),
- 12.6% for olanzapine (RR, 0.99; 95% CI, 0.89 - 1.10),
- 12.5% for risperidone (reference drug),
- 9.8% for valproic acid and its derivatives (RR, 0.91; 95% CI, 0.78 - 1.06), and
- 8.8% for quetiapine (RR, 0.73; 95% CI, 0.67 - 0.80).

Am J Psychiatry. 2012;169:7-9, 71-79.

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