DEMENTIA UPDATE: How to Diagnose, Treat and Manage Cognitive Decline

Janice E. Knoefel, MD, MPH
University of New Mexico
New Mexico VA Healthcare System (retired)

DISCLOSURE

- I have no financial conflicts of interest
- However, I do hope for a long and healthy life

CONTACT INFORMATION

- Janice E. Knoefel, MD
- University of New Mexico
- Internal Medicine (Geriatrics) & Neurology
- Phone 505-272-2000 (UNM call line) to discuss cases
- Fax 505-272-9427 to refer cases for consultation

Overview

- Review of Aging & Dementia Demographics
- Screening
- Diagnosis
- Treatment Options
- Management issues
- Current Hot Topics

Demographics of Aging

- Persons over the age of 65 will increase up to 20% in the next 30 years
- At least 75 million by 2030
- Many of us routinely care for individuals in their 90s

Life Expectancy

- Average life expectancy is a function of current age.
- THE OLDER YOU GET, THE OLDER YOU GET
- Women at age 60 have a 50% chance of living to age 86, 65 years old to 87, 70 years old to 88.
- Men at age 60 have a 50% chance of living to 83, 65 year olds to 84 and 70 year olds to 86.

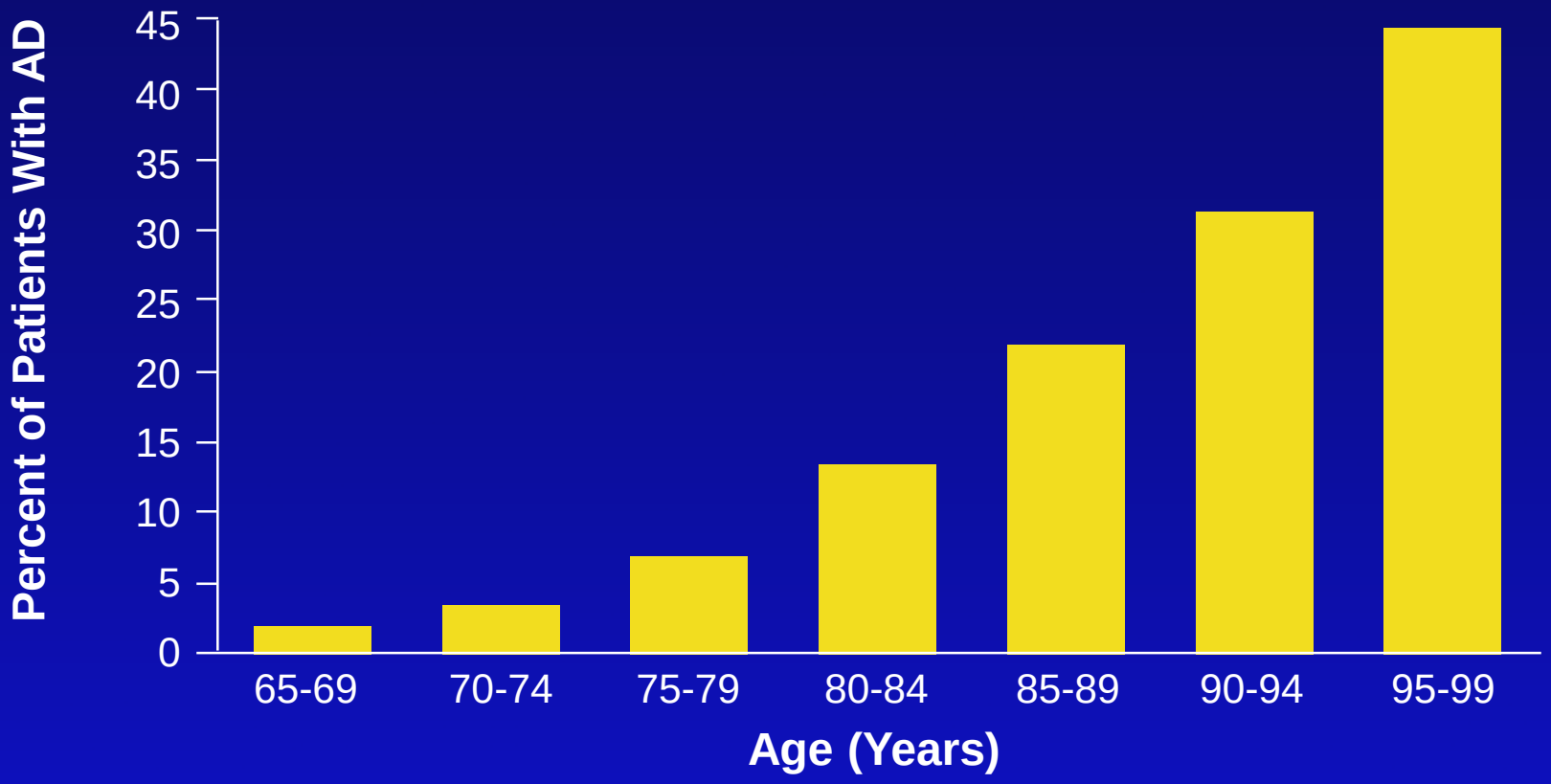
Life Expectancy

- Individuals of the baby boom generation are expected to enter their older years in better health, in better shape, with more preventative health care, financial resources and better nutrition than previous generations.
- THIS GENERATION WILL BE LIVING EVEN LONGER THAN PREVIOUS GENERATIONS

Demographics of Dementia

- Incidence increases with age
- Prevalence increases with age
- Incidence rates for men and women are roughly equal, for both AD and all dementia overall
- Current estimates are about 5 million AD, about 10 million for all dementias
- Increases are expected to parallel the increase in the general population

PREVALENCE OF ALZHEIMER'S DISEASE WITH INCREASING AGE



Adapted from Ritchie K, Kildea D. *Lancet*. 1995;346:931-934.

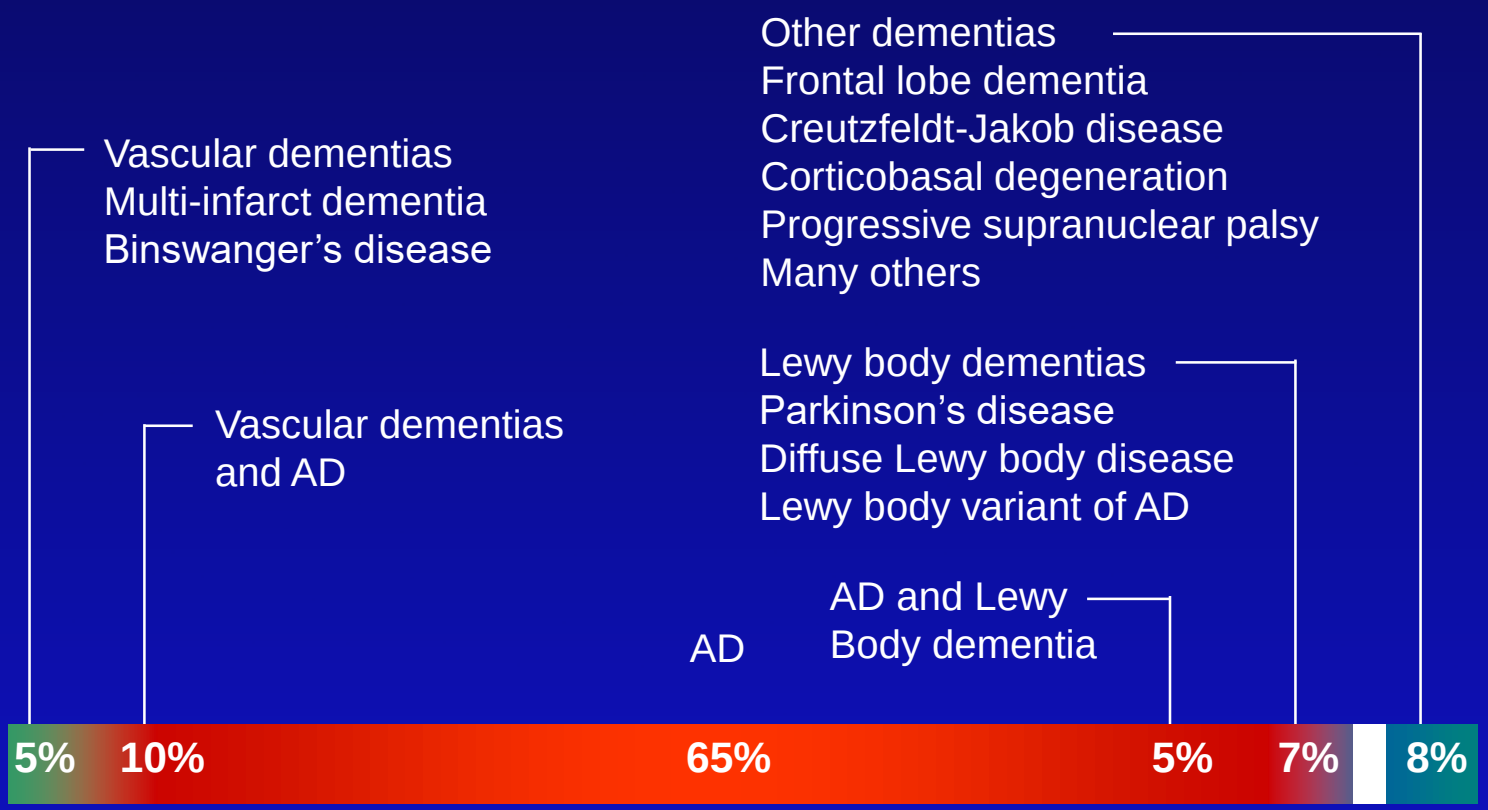
Disconnect between prevalence and incidence

- Incidence rates roughly equal between gender
- Prevalence rates favor women, due to longevity
- AD prevalence in women is roughly twice what it is in men
- For all dementias, prevalence in women is roughly triple the rate in men
- Above comparisons are based on the Framingham data

Alzheimer's and Other Dementias

- AD represents 45-65% of dementias in studies
- Most epidemiological studies performed prior to recognition of Lewy Body and frontal dementias
- Second most frequent dementia is vascular, representing from 10-20% of dementias
- Take home message: double the statistics for AD and that is impact for all dementias

DIFFERENTIAL DIAGNOSIS OF DEMENTIA



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IMPACT OF ALZHEIMER'S DISEASE ON SOCIETAL COSTS

- Alzheimer's disease costs $100 billion annually
- A cost of $35,000 per patient per year
- Alzheimer's patients/families spend >$200,000 over the life of the patient
- 10% to 30% of nursing home residents have Alzheimer's Disease
- Up to 70% have some form of dementia

Dementia Screening

- Widespread routine cognitive screening not recommended for general population
- Function in everyday life should be checked and related to cognition
- Clinical red flags of cognitive decline:
  - New medication non-compliance
  - Missed appointments
  - Complaints of memory impairment
  - Complaints of depression, no energy, etc
  - Family concerns for memory functioning

Dementia Screening

- MiniMental Status Exam(MMSE) widely used
- Montreal Cognitive Assessment(MoCA) is fine
- St Louis University Mental Status(SLUMS) is fine
- Shorter tests such as clock draw, 3-item recall OK
- These may be administered by support staff
- Dependent upon age and education specific norms, further testing may be pursued
- No magic cutoff score, needs to be adjusted for age and education
- Red flag is missing 2 or 3 of the 3 item recall
- Should be in annual Medicare Wellness Visit

Dementia Definition

- Impairment of at least 2 cognitive domains:
  - memory
  - language
  - visuo-spatial
  - executive/attention
  - affective/social behavior
- Represents decline from previous level of cognition
- Severe enough to interfere with daily function and independence.
- Occurs in the absence of other psychiatric, neurologic or systemic disease and delirium

Cognitive Domains

- Cognition grouped into domains determined by function:
  - Language
  - Memory
  - Frontal-executive / attention
  - Visuospatial
  - Emotional

Cognition: language

- Neuropsychological tests measure:
  - Fluency
  - Auditory / written comprehension
  - Repetition
  - Naming / vocabulary
  - Syntax
  - Writing
  - Narrative speaking
  - Speech production / articulation / rhythm
  - Social aspects: turn-taking, interruptions, non-verbal feedback, etc

Cognition: memory

- Memory is multifaceted
- Explicit memory = conscious level
  - Knowledge of facts
- Implicit memory = non-conscious level
  - Skills and habits, learned emotional responses, motor learning, reflex learning
- Processes of learning tested:
  - Encoding/acquisition -> getting it in
  - Consolidation of memories -> keeping it in
  - Retrieval of memories -> getting it out

Cognition: executive

- Simple / divided attention
- Mental tracking
- Switching / alternating between tasks
- Keeping on task / avoid distractions
- Higher order executive abilities:
  - planning ahead
  - problem-solving
  - initiation
  - execution
  - modification of goal-setting behavior

Cognition: visuospatial

- Drawing / recognition of figures
- Use of tools in 3-dimensional space
- Dressing
- Pathfinding in home and community
- Driving behaviors:
  - distance and speed judgments
  - scanning
  - right-of-way
  - merges
  - safe turns

Cognition: emotional

- In general, older adults regulate their emotions better than young, due to life experience and maturity
- However, older adults have higher incident of depressive / anxiety symptoms
- In assessing cognition, always address emotional state since cognitive functions are interdependent

Cognitive Domains

- Neuropsychological testing establishes what is expected for age & education
- Based upon pattern of cognitive deficits, clinical history and examination, a diagnosis of dementia is considered
- Dementia in general is under-recognized and under-diagnosed

Cognitive State

- Choices are :
  - Normal, as expected for age /education
  - Mild Cognitive Impairment: cognition not as expected but not severe impairment
  - Dementia: moderate to severe decline
  - Depressed / anxious

Dementia diagnosis

- However, a decline in cognitive status alone is not enough for diagnosis
- Decline in function is also required
- Types of function:
  - Self-care activities (activities of daily living - ADLs)
  - Community activities (instrumental activities of daily living - iADLs)

Dementia diagnosis

- Basic self-care activities (ADLs)
  - bathing
  - dressing
  - grooming
  - toileting
  - feeding
  - Ambulation
- Useful scale
  - Physical self-maintenance scale (PSMS)
  - giic.rgps.on.ca/sites/default/files/6%20The%20Lawton-Brody%20Modified%20Physical%20Self-Maintenance%20Scale.pdf

Dementia diagnosis

- Community activities (iADLs)
  - shopping / cooking
  - taxes and finances (affected early)
  - managing medication, family occasions
  - traveling out of neighborhood
    - driving may be affected early
  - understanding TV, books, newspaper
  - tracking events in community/country
- Useful scale
  - Functional Activities Questionnaire
  - healthcare.uiowa.edu/familymedicine/fpinfo/Docs/functional-activities-assessment-tool.pdf

Dementia diagnosis

- Once cognitive decline is severe (more than 2 standard deviations below expected) AND
- Decline from previous level of function is documented, THEN
- A diagnosis of dementia is proposed

Dementia diagnosis

- A specific type of dementia should be elaborated by testing, clinical interview and physical/neurological exams
- The proposed dementia type will guide treatment, help establish prognosis, may determine future care venue

Dementia Testing

- If positive screen, further testing by geriatrician, neurologist, psychiatrist, psychologist or experienced other clinicians
- Testing should include extensive history, both medical and neurological/psychiatric
- Medication review to eliminate CNS active meds as etiology such as anticholinergic, benzos, others
- Neurological exam to eliminate other neuro causes such as Parkinson's, CVA, vascular
- Labs include chemistries, B12, TSH, RPR, A1c

Dementia Testing

- Mental status exam tests various cognitive functions
  - Attention and orientation
  - Verbal memory and recall
  - Language such as spontaneous speech, fluency, naming to confrontation, word list generation, reading and writing
  - Executive function such as alternating motor and mental flexibility/switching set
  - Visuospatial function such as copy of drawings, clock draw

Dementia Testing

- Depression needs to be considered always
- Exam should include affective interview & depression screening
- The 15 item Geriatric Depression Scale(GDS) is in widespread use
- An quantitative index of functioning, such the Functional Activities Questionnaire (FAQ) for iADLs and the Physical Self Maintenance Scale (PSMS) for ADLs are useful

Dementia Testing

- Neuroimaging is somewhat controversial:
  - If history and testing typical for AD, likely not needed, BUT I prefer a one-time scan
  - If considering alternative dx such as vascular, mixed, frontotemporal, Lewy Body, I definitely recommend it
  - MRI preferable looking for vascular contribution to dementia as it shows white matter changes more effectively

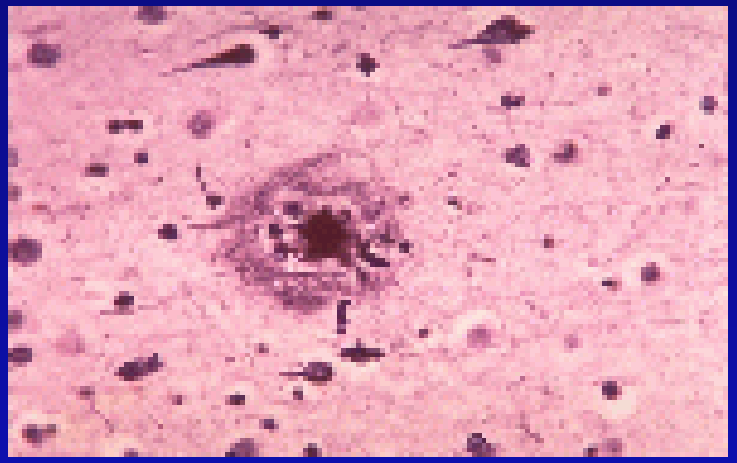
Subtypes of Dementia

- Alzheimer's disease 50-60%
- Vascular dementia 10%
- Mixed dementias (usually AD and vascular) 10-20%
- Dementia with Lewy bodies 10-20%
- Frontotemporal dementia 5%
- Parkinson's Disease Dementia 5%
- Alcohol-associated Dementia 1-2%
- Depression with dementia-like symptoms-unknown
- Normal Pressure Hydrocephalus (NPH) .1%
- Huntington's Disease with dementia .1%
- Creutzfeld-Jakob (mad cow) disease .001%

Dementia Types:
Alzheimer's Dementia

- Primary symptom of amnesia, gradual in onset and progressive
- Additional sx include anomia, agnosia, apraxia, visual spatial dysfunction
- Financial management and driving affected early
- Declining function in community may be covered/ compensated by family/coworkers
- Social behavior usually preserved
- Motor function usually normal

Dr. Alzheimer



Pathophysiology of AD

- Pathogenesis remains unknown, results from a complex interaction of multiple genetic factors, age, environment, education, occupation and current cognitive activities, physical exercise, nutrition, underlying medical co-morbidities and others
- Etiology remains under intense research scrutiny
- Is it amyloid?? Is it the phosphorylated tau??
- We don't know…Stay tuned!
- Until causative factors identified, therapeutic targets remain elusive
- Anti-amyloid strategies not successful to date

Pathophysiology of AD

- The cholinergic deficit hypothesis to explain the AD cognitive deficits is the most well known and is one strategy for current symptomatic therapy
- The cholinergic deficiency is felt to be the end result of the totality of pathology but, in and of itself, is not the cause of AD
- The cholinesterase inhibitors are the largest group of agents commonly in use:
  - Donepezil (Aricept)
  - Rivastigmine (Exelon)
  - Galantamine (Reminyl)

CHOLINERGIC CHANGES IN ALZHEIMER'S DISEASE

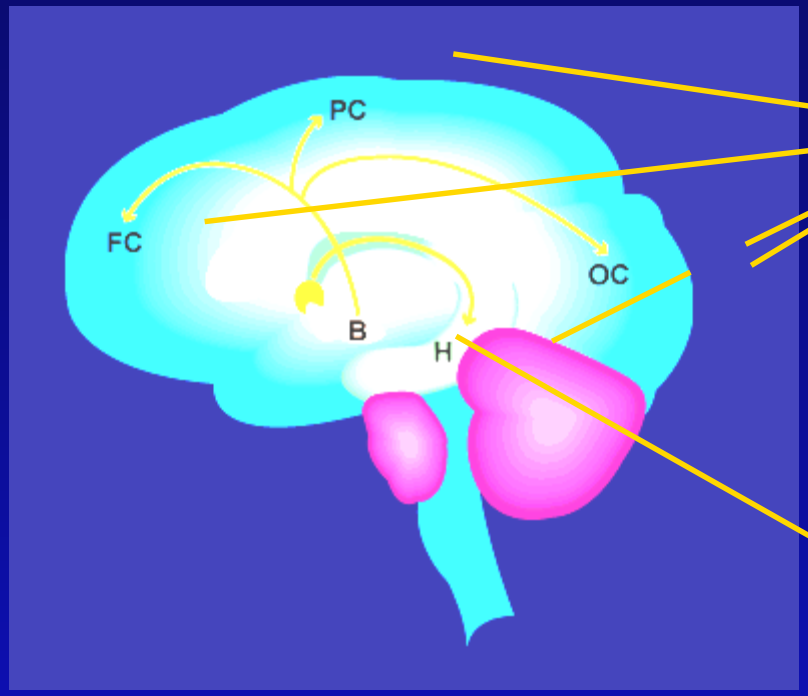
FC = Frontal cortex

PC = Parietal cortex

OC = Occipital cortex

H = Hippocampus

B = Nucleus basalis



↓ Activity of choline acetyltransferase

Loss of cholinergic neurons in nucleus basalis

Adapted from Coyle JT et al. *Science*. 1983;219:1184-1190.
McNeal. *Alzheimer's Disease: Unraveling the Mystery*. 1995:1-48.

Pathophysiology of AD

- Glutamate is the primary excitatory CNS amino acid
- Contributes to pathogenesis of AD by over-stimulating glutamate receptors leading to toxicity
- Pathologic receptor activation results in chronically open state, excess influx of calcium, and cell death
- N-methyl-D-aspartate (NMDA), a type of glutamate receptor, is located ubiquitously in the brain
- This is therapeutic target for NMDA antagonists
- Single FDA approved agent is memantine (Namenda)
- Useful in moderate to advanced stages of dementia

Dementia Types: Vascular Dementia

- Temporal association with stroke or TIAs
- Vascular risk factors present:
  - HTN
  - DM
  - smoking
  - cardiac dysfunction
  - carotid disease
  - hyperlipidemia
- Focal cognitive deficits due to CVA: aphasia, apraxia, agnosia, visuospatial dysfunction
- Executive dysfunction often predominant symptom
- Behavioral and personality preservation variable
- Focal and bilateral deficits in motor, sensory, cranial nerves, gait and reflexes

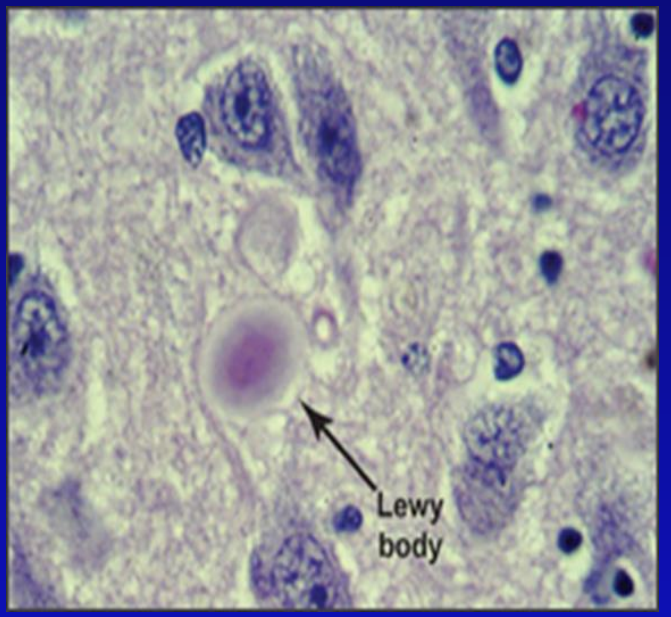
Dementia Types: Mixed Dementia

- Common, usually AD and vascular together
- Vascular risk factors present, may have remote CVA or TIA without associated cognitive decline at the time
- Presenting with gradual and progressive decline consistent with AD
- Cognitive picture variable, usually striking amnesia, executive dysfunction and variable other cortical deficits(anomia, agnosia, apraxia, visuospatial)

Dementia Types:
Lewy Body Dementia

- Cognitive deficits in a nonspecific profile
- Sx of Parkinsonism occur early but not severe
- Visual hallucinations are typical, usually of children, people or animals, often non-threatening
- Hallucinations actually sx of REM behavior disorder
- Sx of Parkinsonism worsen dramatically with rx with typical antipsychotics
- Sx of hallucinations and psychosis worsen dramatically with rx with Parkinson's meds
- Day to day fluctuations in function are dramatic

Dr. Lewy



Dementia Types: Frontotemporal Dementia

- Behavioral dysfunction out of proportion to other cognitive deficits on testing
- Diminished initiative, withdrawal from work/home, repetitive/compulsive and inappropriate behavior
- Language output sparse, evolving to mutism
- Tends to be in younger age groups 50s to 60s
- Often normal motor exam, may be mild PD sx in advanced stages

Dementia Types:
Parkinson's Disease Dementia

- Dementia very common in advanced Parkinson's of 10-20 years duration
- Slowed cognitive processing is the most common characteristic of decline
- Memory function better than seen in Alzheimer Disease
- BUT, some cases of PD with dementia look similar to AD and may represent a mixed dementia picture

Dementia Types: Alcohol-associated dementia

- Diagnosis in setting of alcohol overuse
- Patient and family need to be asked
- Alcohol causes cognitive decline in a number of ways:
  - Vitamin B1 (thiamine) deficiency in the brain
  - Direct toxic effect of alcohol on brain cell->death
  - The biological stress of repeated intoxication, withdrawal, perhaps seizures
  - Alcohol-related strokes and bleeding in the brain
  - Head injuries and concussions from falls while intoxicated

Dementia Types:
Depression with dementia symptoms

- Depression in elderly can present as memory loss and cognitive decline
- Cognition and function improve after effective anti-depressant Rx
- One of the few ‘reversible dementias’
- Do not miss depression presenting as memory loss since dementia medications will not help, but depression meds will

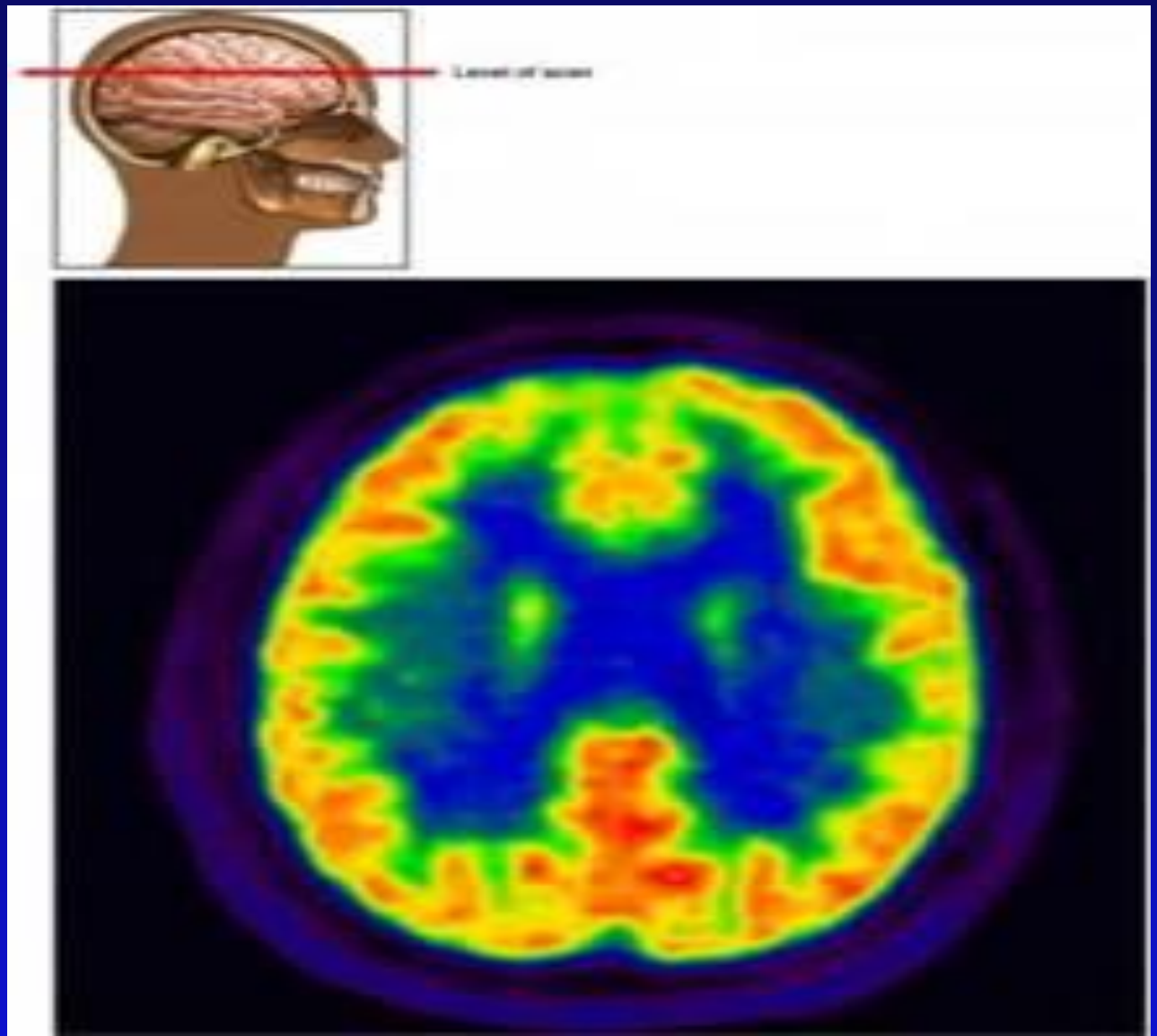
Dementia Types

- Other types of dementia are more rare:
  - Progressive Supranuclear Palsy
  - Corticobasilar degeneration
  - Binswanger's Disease
  - Hydrocephalus
  - Huntington's Disease

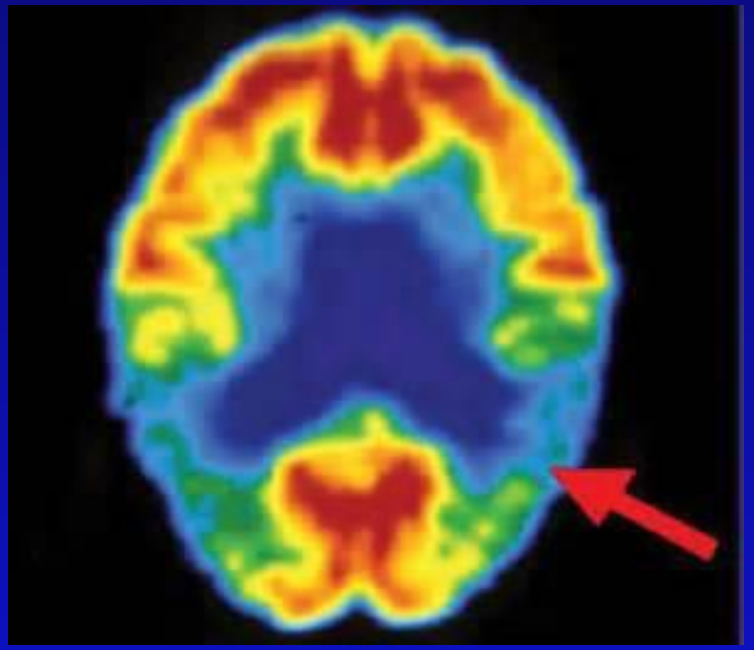
Dementia Testing

- Brain (structural scan) MRI is the gold standard
- Brain PET scan uses radioactive glucose tagged tracer FDG
- Demonstrates functional/metabolic brain activity
- Useful in distinguishing Frontotemporal Dementia (FTD) from AD
- Approved and funded by Medicare
- Therapy changes if FTD, hence the approved indication

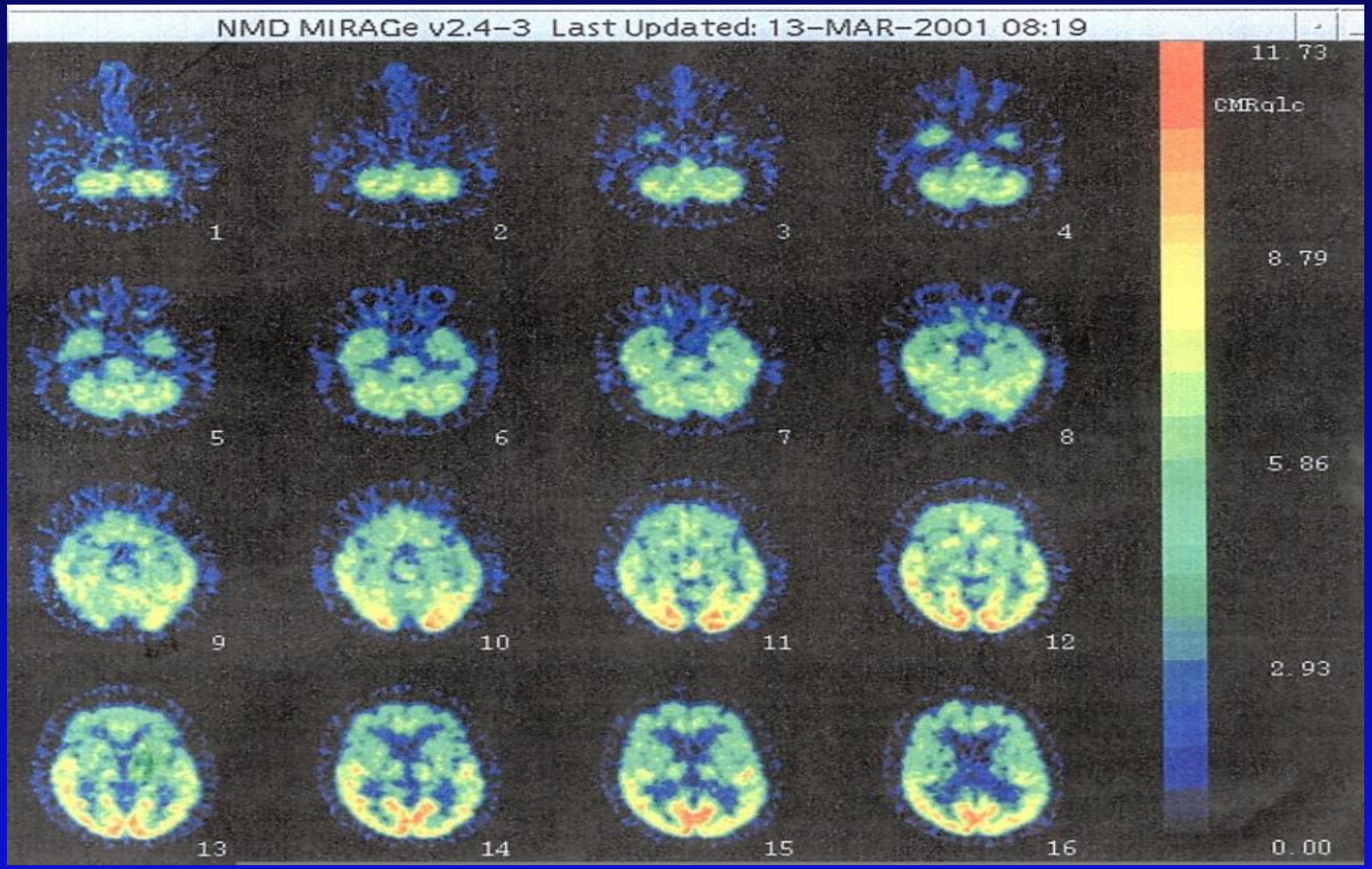
Dementia Testing: Normal FDG PET scan



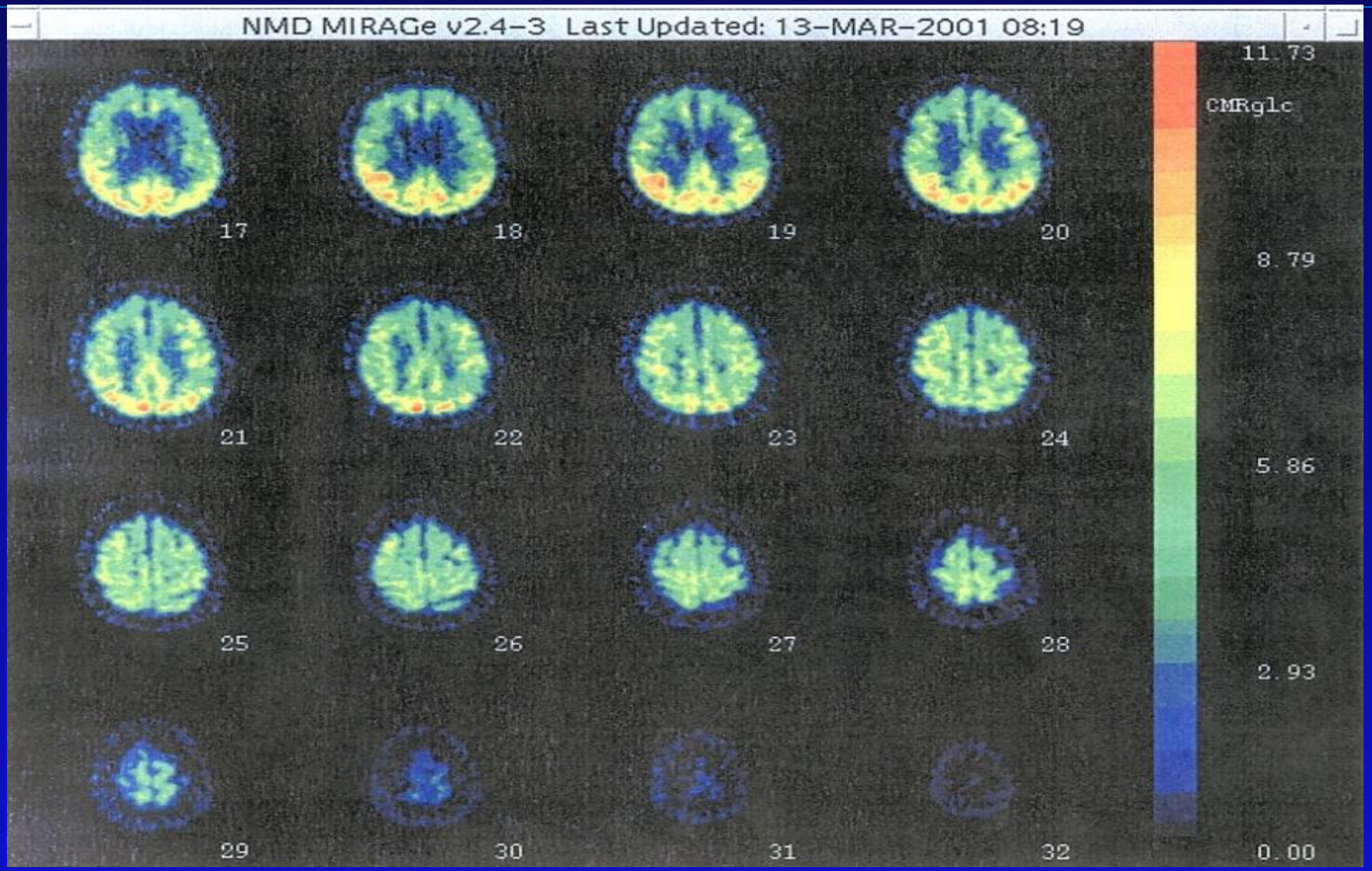
Dementia Testing:
Alzheimer FDG PET scan



Dementia Testing:
FTD FDG PET scan



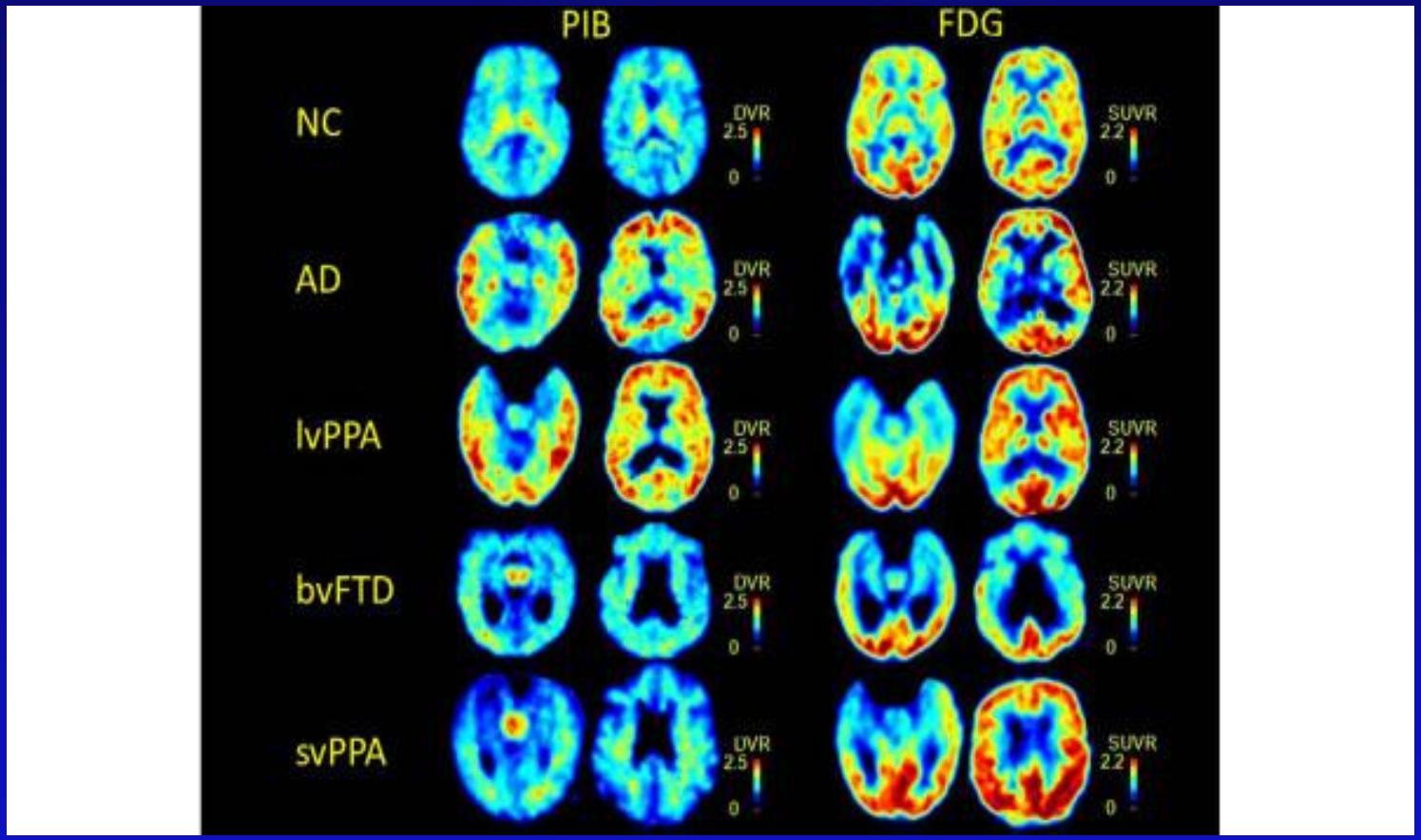
Dementia Testing:
FTD FDG PET scan



Amyloid Imaging

- Florbetapir, and other agents, are labeled tracers that bind to amyloid aggregates.
- Approved for use by FDA after Lilly developed a training program for physicians to accurately and consistently interpret the scans in a trial that the training works
- Medicare does not fund this imaging outside of approved and funded research studies

Amyloid Imaging



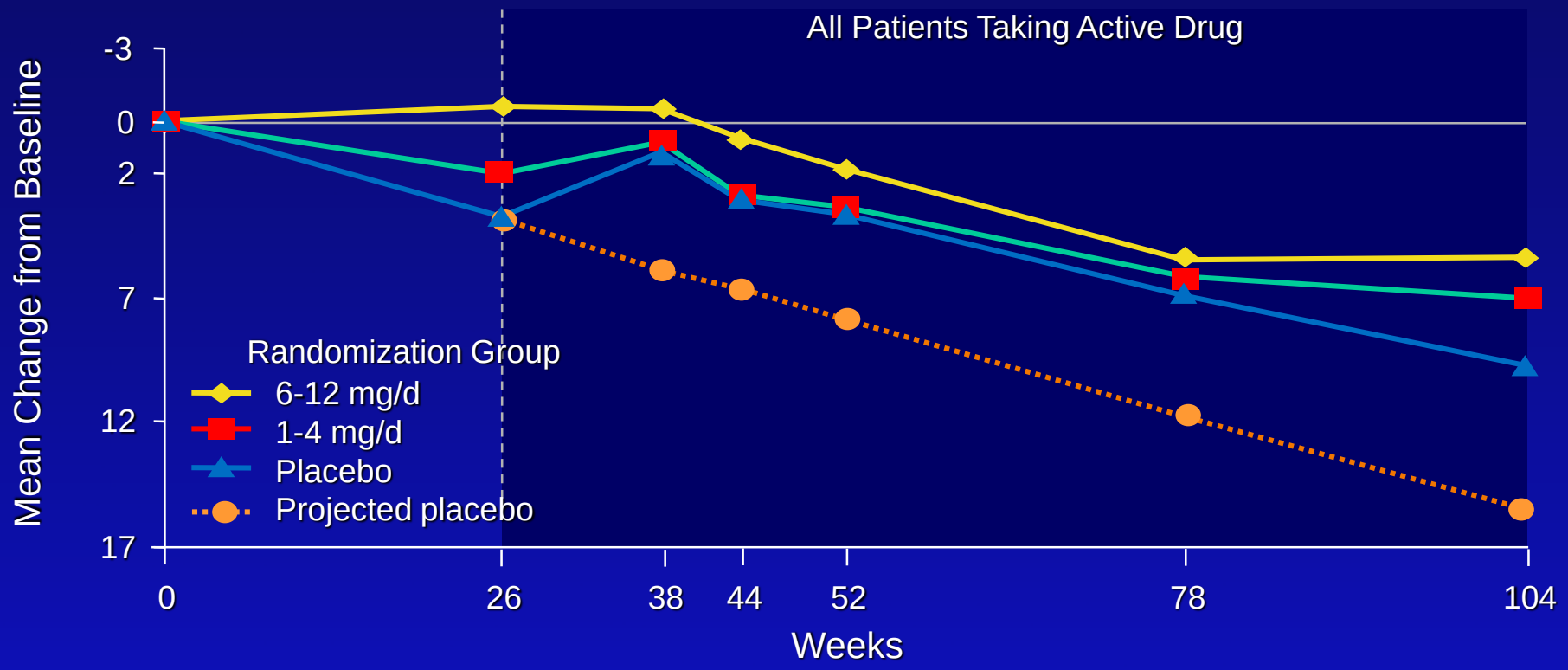
Treatment of Dementia

- Treatment of dementia depends on cause
- In progressive dementias, there is no cure / no treatment to stop progression
- Medications may temporarily improve dementia specific symptoms
- Antidepressant therapy may improve symptoms / function in any dementia type
- All other treatment is symptomatic

Current Therapeutic Options

- Review evaluation for reversible factors
- Treat depression if present
- Offer dementia-specific treatment
- Management of associated sx, sleep disorder, etc
- Discontinue offending CNS active medications

Therapeutic Strategies: symptomatic vs disease modulating



Current Therapeutic Options: Specific for individual dementia type

- Alzheimer's Disease:
  - Cholinesterase inhibitor as tolerated
  - NMDA antagonist memantine in advanced case, MMSE or MoCA <20

- Vascular dementia:
  - Prevention of recurrent CVA
  - Remediation of vascular risk factors
  - ASA or other platelet antiaggregant
  - Cholinesterase inhibitor as tolerated
  - Depression common, treat

Current Therapeutic Options: Specific for individual dementia type

- Mixed dementia:
  - Cholinesterase inhibitor as tolerated
  - NMDA antagonist as disease progresses
  - Prevention of recurrent CVA
  - Remediation of vascular risk factors
  - ASA or other platelet antiaggregant
  - Treat depression

Current Therapeutic Options: Specific for individual dementia type

- Lewy Body dementia:
  - Treat REM Behavioral Disorder with melatonin or clonazepam in increasing doses as needed
  - Hallucinations are RBD symptom
  - Avoid PD meds as they worsen the psychosis
  - Avoid all antipsychotics as they may worsen movement disorder and ineffective
  - Cholinesterase inhibitor as tolerated, some research trials support efficacy, FDA approved

Current Therapeutic Options: Specific for individual dementia type

- Frontotemporal dementia:
  - Cholinesterase inhibitors may worsen sx, so use cautiously and stop quickly as indicated
  - SSRIs may be best for behavioral control
  - NMDA antagonist as condition progresses
  - No studies looking at large scale cognitive treatment have been done
  - Structured and supervised environment is best
  - Safety, for patient and caregivers, is paramount

Current Therapeutic Options: Specific for individual dementia type

- Parkinson's Disease Dementia:
  - Usually need to adjust PD meds downwards
  - Tricky to balance motor vs cognitive symptoms
  - Cholinesterase inhibitors approved for this
  - SSRIs may be helpful
  - NMDA antagonist as condition progresses

Current Therapeutic Options: Specific for individual dementia type

- Alcohol associated dementia:
  - Urgent IM administration vitamin B1 (thiamine)
  - Use of oral B1 after intramuscular doses
  - Total cessation of alcohol use
  - Treatment available for symptoms of depression, agitation/anxiety, paranoia, insomnia, aggression and others
  - Alcohol use may exacerbate symptoms of any underlying, other dementia process
  - Cholinesterase inhibitor as tolerated

Current Therapeutic Options: Specific for individual dementia type

- Depression with dementia-like symptoms:
  - Recognition of the connection
  - Psychological counseling
  - Family support
  - Oral antidepressant treatment usually very effective
  - Socialization and constructive leisure activities
  - Review to rule out depression as a side effect of other medications

Management Issues: SLEEP

- Daytime agitation may be due to night time lack of sleep

- Ensure good night's sleep every night
  - increase day activities
  - physical exercise
  - limit daytime napping
  - eliminate caffeine from diet 100%
  - eliminate alcohol 100%

Management Issues: SLEEP

- If insomnia is due to psychosis, then first Rx choice would be low dose antipsychotic (more on this later)
- Melatonin is first choice due to little risk for s/e
- Trazadone 25-50mg hs and increase if needed
- Tylenol 500-1000mg hs for unreported pain
- Mirtazepine 7.5mg to start if concurrent depression

Management Issues: PSYCHOSIS

- Consider dx of psychosis only if delusions, paranoia present
  - Low dose antipsychotic may be effective
  - Recommend very low dose quetiapine 12.5mg HS; others are risperidone, olanzapine
  - Avoid haloperidol
  - Do not recommend antipsychotic rx for agitation
  - If sx is visual hallucination, the dx is Lewy Body Dementia, first line rx clonazepam or melatonin
  - Bottom line: I rarely use antipsychotics

Management Issues: DEPRESSION

- Consider depression if
  - Pt had prior history of depression
  - Pt not be able to clearly state feelings
  - Reduced participation in activities previously enjoyed per family report = “acting depressed”
  - Use AM dose SSRI, switch to HS if too sedating
  - Switch to mirtazepine if HS sedation needed
  - Other agents useful: buproprion, nefazadone, venlafaxine, mirtazapine,

Management Issues: AGITATION

- Certain events may increase agitation:
  - Visit from certain family members
  - Transfer to new living situation
  - Out of home or facility trips(social, medical)
  - May need to premedicate or cancel visits
- Hygiene may cause agitation
  - Certain caregivers?, need to change
  - Showering vs. bathing?
  - May premedicate prior to hygiene events

Management Issues: AGITATION

- Therapeutic deception is accepted management
- Attempts to regiment pt may escalate behavior, may need to let pt safely roam at will, do not insist pt sit for meals, orient to reality, maintain set meal or bedtimes, etc
- Family or friends may need to limit visits
- Other patients may be targeted or may target pt and need to physically separate permanently if occurs

Management Issues: AGITATION

- Only use meds if all behavioral approaches fail
- PRN use of benzodiazepines, recommend alprazolam, lorazepam, oxazepam
- If pt needing 2-3 prn doses routinely, need to switch to scheduled use of above agents
- Long/short term use of benzos worsen cognition
- Watch for s/e
- Avoid antipsychotics for agitation not associated with psychosis
- May consider dc of ChEIs

Management Issues: AGITATION

- Standard for use of antipsychotics for agitation is danger to self or others
- Consider addition of progesterone, especially in men
- Use of anticonvulsants as mood modulators, such as Valproate, have been reported as useful by others but watch for s/e
- Try the Merry Walker for unassisted ambulation and roaming

Management Issues: AGITATION

- May need to refer to inpatient psychiatry unit for uncontrolled and unsafe aggression
- Consider palliative approach with dc medications not directly contributing to pt's immediate comfort and calm: BP, cholesterol, cardiac, diabetes meds
- In general, AD pts eligible for hospice care when not eating, nonambulatory, nonverbal, incontinent
- Consider full use of hospice approach, clysis, etc to maintain calm in endstage

Additional Management Issues

- Family referral to Alzheimer Association
- Caregiver support, grief counseling
- Advance planning for medical decisions
- Designation of Durable Power of Atty
- Advance financial and legal planning

Case 1

- 49 year-old woman requests genetic testing for early onset AD
- She reports no cognitive complaints, has full time employment without difficulty
- Mother with AD symptoms at 52, diagnosis at 54, death at 63
- Scored average/above average on cognitive exam in all domains
- Depression scale is moderate for current symptoms
- Fully independent in all ADLs & iADLs

Genetics of AD

- Family members may wish testing
- However, the person with early onset AD should be tested first to establish the presence of the mutation
- If negative, the person has non-familial early onset AD
- If positive, the person has familial early onset AD
- In an asymptomatic family member, a positive test predicts future development of AD, but not when

Genetics of AD

- Use of genetic testing for deterministic mutations:
  - Used infrequently in clinical practice
  - Generally reserved for families with a known mutation
  - Essential to be performed with genetic counseling before and after testing
  - No effective prevention or treatment for AD is available = so is not recommended
  - Lack of genetic counselors for adult conditions (outside of cancer) is an obstacle

Genetics of AD

- Apolipoprotein E (apoE) gene is a blueprint for a protein that carries cholesterol in the blood.
- Types of apoE are E2, E3 and E4
- Each person has 2 genes for apoE, one from each parent
- E3 is the most common variant (60%), followed by E4 (30%) and E2 (20%)

Genetics of AD

- However, a copy of E4 does not guarantee development of AD
- A copy of E2 does not protect from AD
- AD occurrence in E4 carriers is estimated at 40-65% of the total cases
- However 1/2 of AD pts do not have any e4
- Hence APOE genes are risk genes, not deterministic genes like presenilin and APP mutations

Genetics of AD

- Combinations are common, example E2/E3, E2/E4, E3/E4.
- Risk of developing AD stratifies with APOE type:
  - E2 in any combination may decrease risk
  - E3 in any combination has no effect
  - E4 in any combination increases risk (3-30x)
  - 2 copies of E4 increases risk of AD more

Genetics of AD

- Use of genetic testing for risk genes:
  - Rarely used in clinical practice
  - Does not determine development of AD
  - False reassurance (apoE2) or false fears of developing AD (apoE4) possible
  - Testing not recommended
  - No disease modifying treatment available but this may change in the future
- The low positive predictive value 0.10 discourages use of apoE testing as a screen for AD

Conclusions

- AD and all forms of dementia are very prevalent, morbid conditions in the aging
- Research is making rapid and exciting advances into understanding the disease and risk factors
- Limited therapy is available but it has shown to be of benefit in treatment and management
- Symptomatic management throughout the illness and ultimately hospice approach needed