Management of behavioral and neuropsychiatric symptoms in dementia

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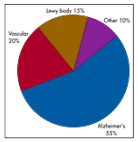
OBJECTIVES

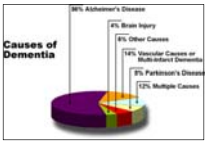
1) Define the diagnostic criteria for AD, FTD, & DLB
2) Describe the behavioral and neuropsychiatric manifestations seen in these disease states
3) Explain the potential uses of pharmacologic agents in developing a patient-centered treatment for the behavioral and neuropsychiatric manifestations of dementia
4) Apply these principles to a series of cases that will lead to accurate diagnosis, and the development of a symptom-targeted treatment strategy for each real-life case discussed

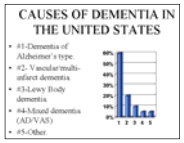
"Dementia

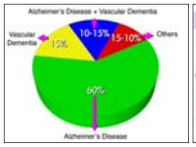
"~~Life~~ is a journey, not a destination"

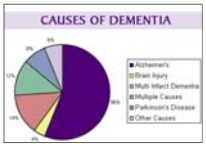
It's clear that dementia is a "mixed bag" of disorders

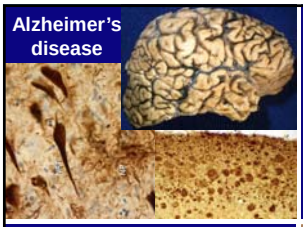






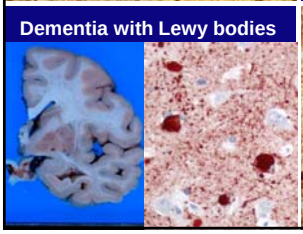


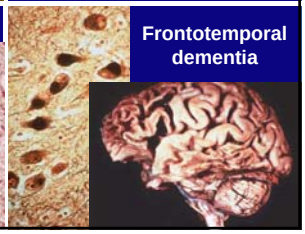




Behavioral and neuropsychiatric symptoms are seen in all dementias to varying degrees and at different time points in progression…

But the same features exist for all, and need to be treated symptomatically in the same way!





Current Diagnostic criteria for AD, DLB, & FTD

Alzheimer's disease (NINDS-ADRDA)

- Dementia by DSM-III-R/V criteria
- Deficits in two or more areas of cognition
- Progressive worsening of memory and cognitive dysfunction
- Onset age 40-90
- Absence of other systemic/brain disorders

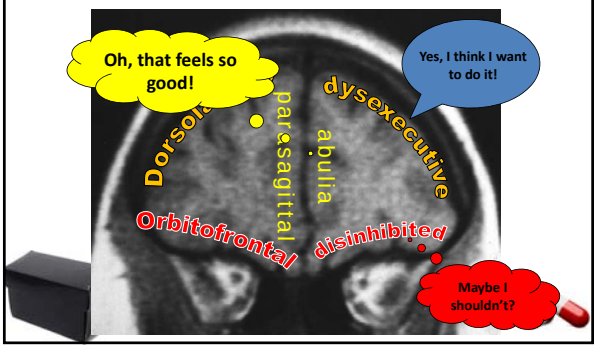
Dementia with Lewy bodies (3rd Int. Workshop on DLB)

- Dementia by DSM-III-R/V criteria
- Deficits in cognition may not be memory (usually attention/spatial)
- Parkinsonism
- Early hallucinations
- Fluctuations
- Supportive:
  - Depression
  - REM sleep behavior disorder

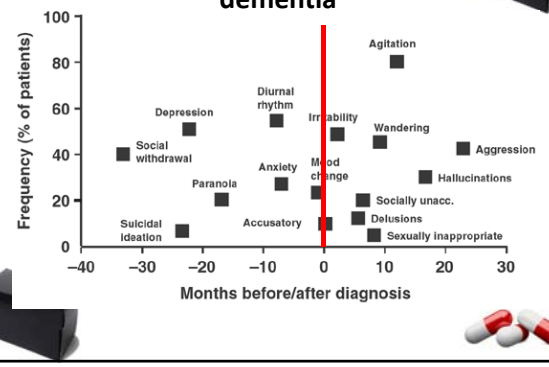
Frontotemporal dementia (NIH work group on FTD)

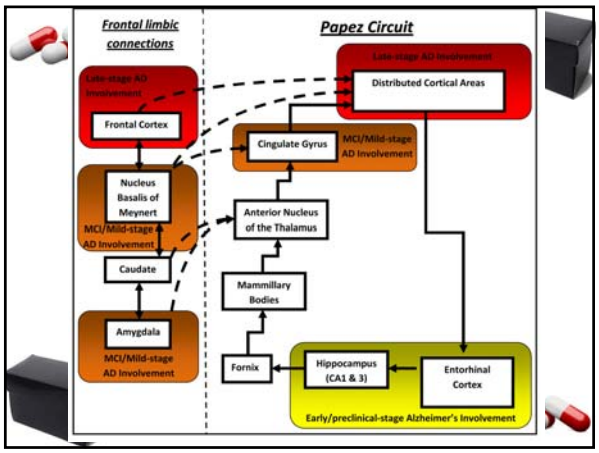
- Prominent behavioral disorder
  - Loss of interpersonal skills
  - Emotional blunting
  - Perseveration or impersistance or
- Language involvement
  - Comprehension or fluency
- Cognition typically preserved
- Can be assoc with MND/ALS

Brief note on "frontal symptoms"

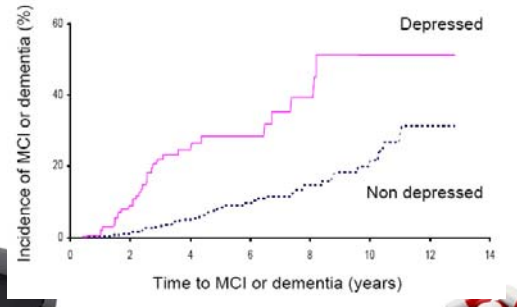


Psychiatric symptoms in dementia





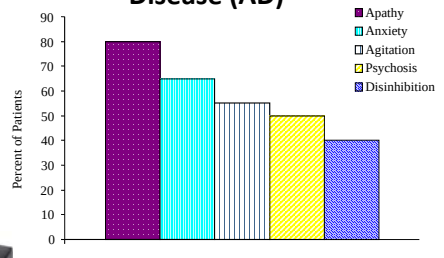
Depression can often precede dementia



Importance of Behavioral & Psychological Symptoms of Dementia (BPSD)

- BPSD account for 30% of cost associated with AD
- Strongly associated with caregiver depression
- Strongly associated with institutionalization
- Undermine caregivers ability to provide care

Behavioral Symptoms in Moderate Stage Alzheimer's Disease (AD)



Mega MS, Cummings JL, Fiorello T, et al. *Neurology.* 1996;46:130-135.

Causes of BPSD

- Psychosocial/psychological factors
  - Behaviors may be an expression of unmet psychological needs
    - Thirst
    - Hunger
    - Pain
    - Distress
    - Feelings of abandonment
    - Fear

Causes of BPSD

- Environmental factors
  - Excessive stimulation
  - Lack of daily structure/routine
  - Inadequate lighting
  - Confusing surroundings
  - Excessive demands
  - Distressing behavior of others
  - Loneliness/boredom

Assessment of BPSD

- History (current sx's, etiol. of dementia, PMH)
- R/O environmental disturbances (changes in home situation, over-stimulation, sensory deprivation, change in staff, death of family member)
- R/O contributing medical problem (infection, dehydration, pain, sleep disturbance, etc.)
- R/O drug effects (interactions, intoxication, withdrawal, poor compliance)
- Review prior psychiatric hx

K. Meador, 2006

Behavioral Interventions for BPSD

- Caregiver training significantly reduces both caregiver distress and problem behaviors
- Caregiver education and training can reduce depression in both patient and caregiver *(Teri et al, 1997)*
- Caregiver education and training reduced sx's of agitation comparably to haloperidol and trazodone with fewer AE's *(Teri et al, 2000)*

If we can't treat the disease yet, at least let us treat the symptoms!

- Can we do this?
  - Issues to consider:
    - Clinical heterogeneity
    - Pathological heterogeneity
- Of course we can!
  - The issues may appear in different order, may or may not come, but they can be categorized and there are treatments that can help!

Symptoms to treat…

- Cognitive impairment
- Behavioral symptoms
  - irritability, restlessness, agitation, or aggression
  - compulsions that dominate or significantly interfere with everyday life
  - hyposomnia, insomnia, night-time restlessness, or night-time roaming
  - euphoria, excitability, mania, impulsivity

Classes of medications to consider?

- Alzheimer's approved medications
  - Cholinesterase inhibitors and memantine
- Antidepressants
  - SSRIs, NERIs, DRIs, MAOIs
- Mood stabilizers
  - Antiepileptics and lithium
- Sedatives
  - Benzodiazepines and histaminergics
- Antipsychotics
  - Atypical and typical agents
- Stimulants
  - Ritalin, adderall, strattera, modafenil
- Antihypertensives
  - Clonidine and b-blockers

For the caregiver…

- Keep a diary of symptoms
  - Helps with medical and behavioral/environmental management
    - What are the symptoms?
    - When do they occur?
    - How bothersome (so we can target treatments one at a time)?
    - What triggers them?
    - What seems to help?
    - What makes things worse?

Dementia Symptom Diary

DATE: _____

Name: _____

DOB: _____

Symptom	Time started	Time ended	Triggers (what were they doing when symptom started?)	How bothersome is symptom to patient (rate on scale of 1 to 10)	How bothersome is symptom to caregiver (rate on scale of 1 to 10)	What makes symptom better?	What makes symptom worse?	Medication effects?

RATING SCALE: 1 to 10 for symptom severity with 1 being the least severe, and 10 being the most severe

*Use additional sheets as necessary to record all events of concern

One step at a time…

- Remember we can only adjust one medicine at a time
- This allows us to understand how that one change influenced symptoms and possible adverse events
- PATIENCE is KEY!

Give each medication a "good college try"

- Up's and down's in daily function are common and may not reflect medication effects
- Make sure you reach an effective dose before discounting a medication benefit
- Stay on the medication for 4-6 weeks to truly know if it is helping or not
- Don't ever jump from medicine to medicine, or you will never know what might help
- It's OK to start and stop medicines to test the effect in a metered fashion

Empiric Approach to Treatment

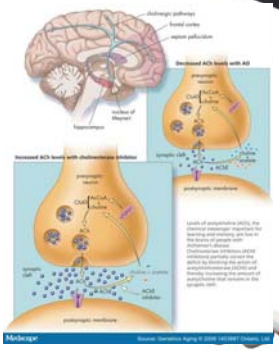
Assess symptoms in hierarchical fashion and target main symptom

Cognitive issues identified as major problem	Behavioral issues identified as major problem	Psychiatric issues identified as major problem	Motor issues identified as major problem
Attempt cholinesterase inhibitor or memantine	Attempt SSRI, antipsychotic, or mood stabilizing anti-epileptic	Attempt SSRI, antipsychotic, benzodiazepine or other agent	Attempt carbidopa-levodopa, dopamine agonist, or riluzole

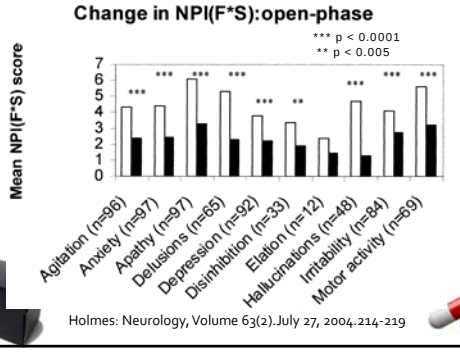
Evaluate effectiveness and re-prioritize symptom hierarchy every 3 mos

Enhancing cognition…

- Cholinesterase Inhibitors
  - May hyperactivate leading to more behavioral problems
  - May improve cognition
  - Decreases behavioral problems!

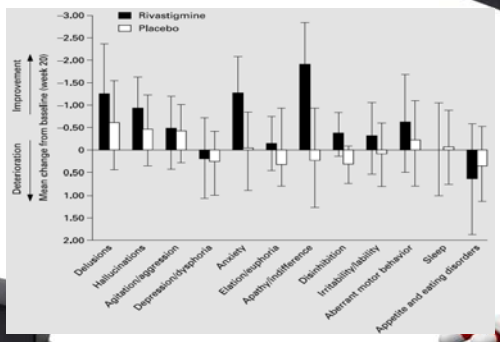


Change in NPI over 12 weeks treatment with donepezil in AD



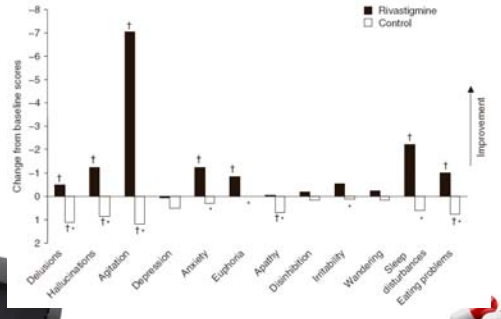
Holmes: Neurology, Volume 63(2).July 27, 2004.214-219

Psychiatric symptoms improve with AChEI in DLB



McKeith et al, Lancet 2000;356-2031-2036

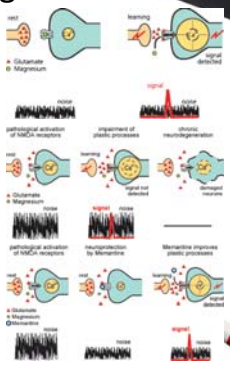
AChEI treat behavioral and psychiatric Sx in FTD



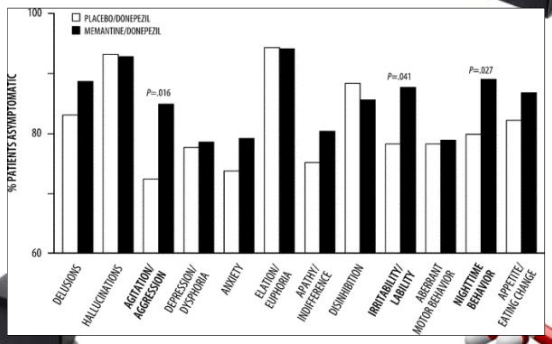
Moretti et al, Drugs Aging 2004;21:931-937

Enhancing cognition…

- Memantine
  - Acts via glutamate receptors found widespread through the cortex



Memantine?

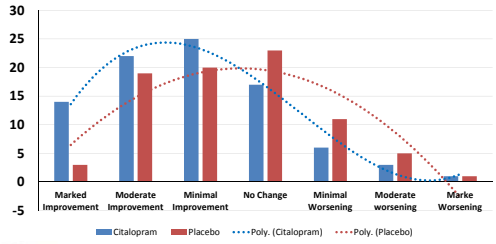


Antidepressants

- SSRIs- selective for serotonin, low in side effects
- NERIs- activating, most have SSRI qualities as well
- DARIs- activating, most have NERI qualities as well

CITAD Trial

% subjects with Change in CIBIC+



Citalopram 20 mg (n=94) vs. placebo (n=92)
Estimated treatment effect, OR 2.13 (1.23, 3.69), p= 0.007

Porsteinsson et al., JAMA. 2014 Feb 19;311(7):682-91

Mood Stabilizers

- Most are antiepileptics
- Valproic acid/Depakote- can cause weight gain (sometimes beneficial) and tremor, thought to inhibit GSK-3β
- Lamotrigine/Lamictal- activating, can cause fatal drug rash (Stevens-Johnson syndrome
- Carbamazepine/Tegretol- cheap (only mood stabilizer on the Walmart plan), can cause hyponatremia, interferes with OCPs
- Lithium- narrow therapeutic window, thought to inhibit GSK-3β

Sedatives

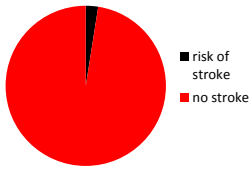
- Benzodiazepines
  - Works like alcohol
  - Would you give you patient a bottle of bourbon?
- Antihistamines
  - Benedryl
  - Vistaril

Antipsychotics

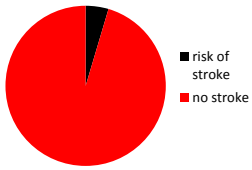
- FDA Black box warning
  - Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.
  - Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients.
  - Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.
  - Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.
  - Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality.
  - The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

Antipsychotics

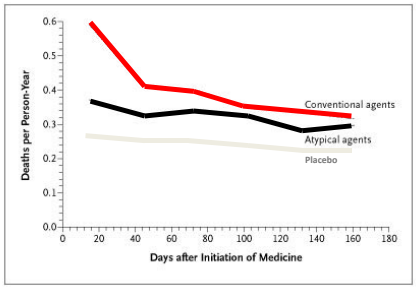
no meds



Antipsychotic

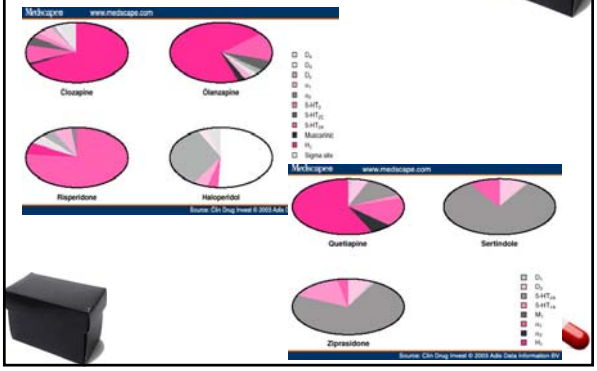


Atypicals are really not that bad



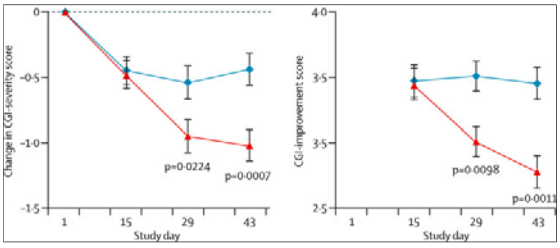
Wang et al. NEJM 2005;353:2335-2341

Antipsychotics



Pimavanserin:

a selective inverse agonist of the serotonin 5-HT2A receptor



Pimavanserin 40mg (n=95) vs. Placebo (n=90) with Parkinson's psychosis

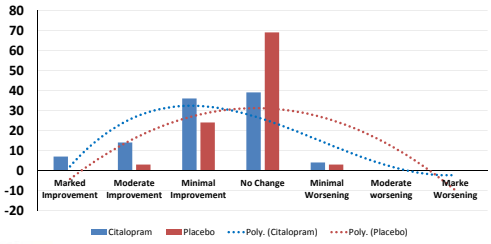
Cummings et al., Lancet. 2014 Feb 8;383(9916):533-40

Stimulants

- Apathy is a major problem!
- Motivation doesn't come in a pill
- Stimulants can increase anxiety, irritability, agitation, and psychotic features

ADMET Trial

% subjects with Change in CIBIC+



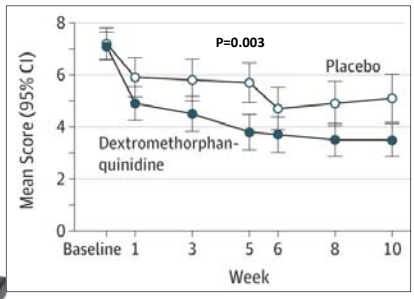
Methylphenidate (n=29) vs. placebo (n=31)
Estimated treatment effect, OR 3.7 (1.3 to 10.8), p= 0.02

Rosenberg et al., J Clin Psychiatry. 2013 Aug;74(8):810-61

Antihypertensives

- Alpha blockers (clonidine)
  - Can reduce agitation
  - Safe if BP can handle
  - Rebound HTN
- Beta-Blockers
  - Effective for anxiety
  - Safe if BP can handle
  - Non-specific, propranolol may work best (avalable on Walmart plan)

Dextromethorphan/Quinidine (Neudexta)



Neudexta (n=93) vs. Placebo (n=127)

Cummings et al., JAMA. 2015 Sep 22-29;314(12):1242-54

Case #1

- 75 yo M with new onset delusions of wife having an affair with his best friend and their Pastor at church
- MMSE 29 (world), 27 (serial 7s), missed pentagons only
- Neuro exam is completely normal
- DX?
- TX?

Case #2

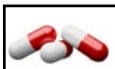
- 84 yo F with 6 years progressive memory loss
- Dependent for IADLs but still dresses, grooms, and feeds self
- Severe apathy with mild intermittent crying spells
- 1-2 x/week she gets extremely agitated and "wants to go home"
- DX? TX?

Case #3

- 56 yo F with 2 years of behavioral disturbance characterized by SIB, OCD, motor restlessness
- Insists on picking up trash
  - Wanders even into streets to get trash she sees
  - Has gotten lost several times, typically found miles from home picking up trash
  - Family cannot keep her safe or get her to sit still
  - DX? TX?

Case #4

- 81 yo M with new onset depression
- MMSE 30
- Neuro exam normal
- No PHx depression or other psych sx
- No environmental explanation for depression onset
- DX? TX?



The Future…

- Disease modifying therapies on their way!
- We will cure this disease!
- For the time being, let's focus on QOL for the person with dementia and minimize their behavioral and neuropsychiatric symptoms!
- It can make a world of difference!