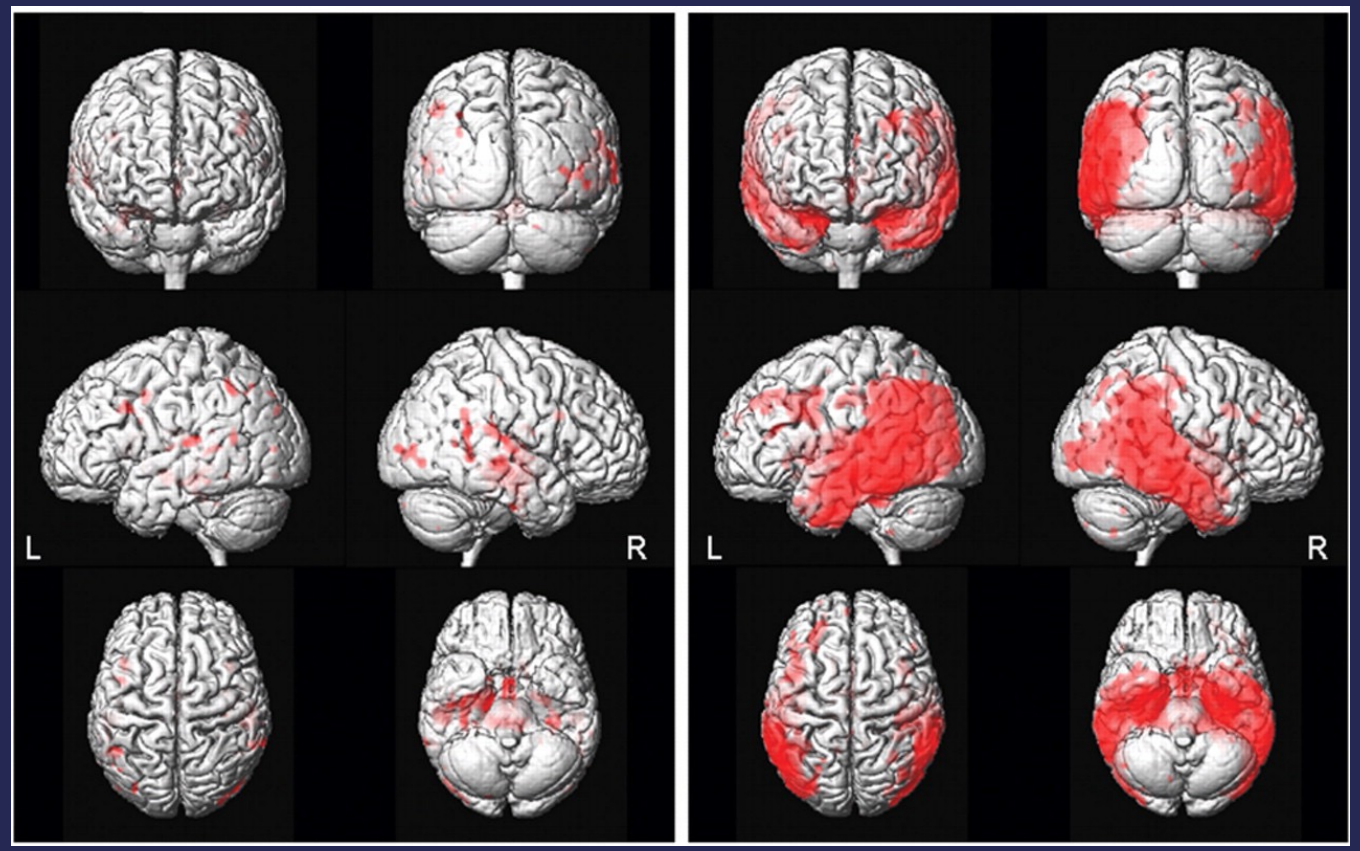
PARKINSON'S DEMENTIA AND RELATED CONDITIONS



Diagnosis and Therapy

Sean Rogers, MD, PhD

INOVA®
Parkinson's and Movement Disorders Center
Memory Disorders Program

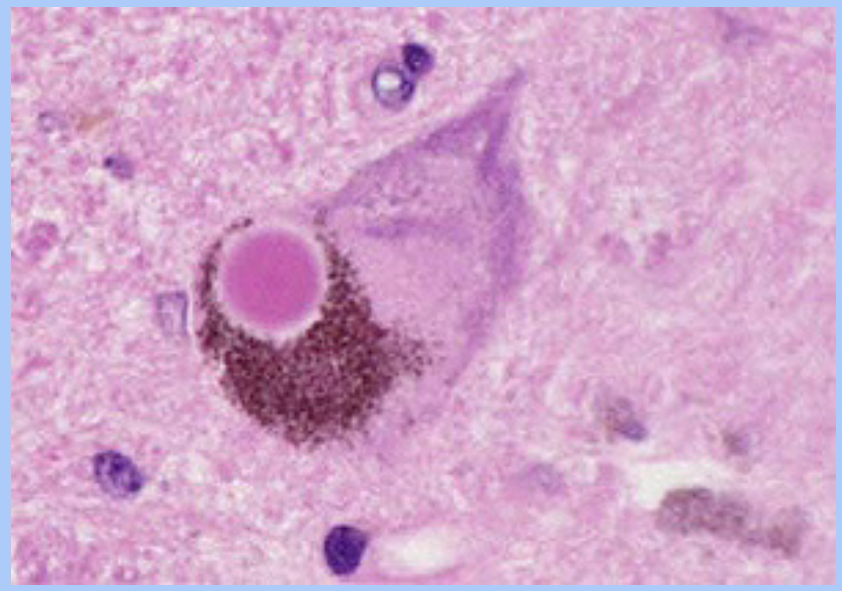
Inova.org/move

DISCLOSURES

- Nothing to disclose

LEWY BODIES AND THEIR LOCATIONS

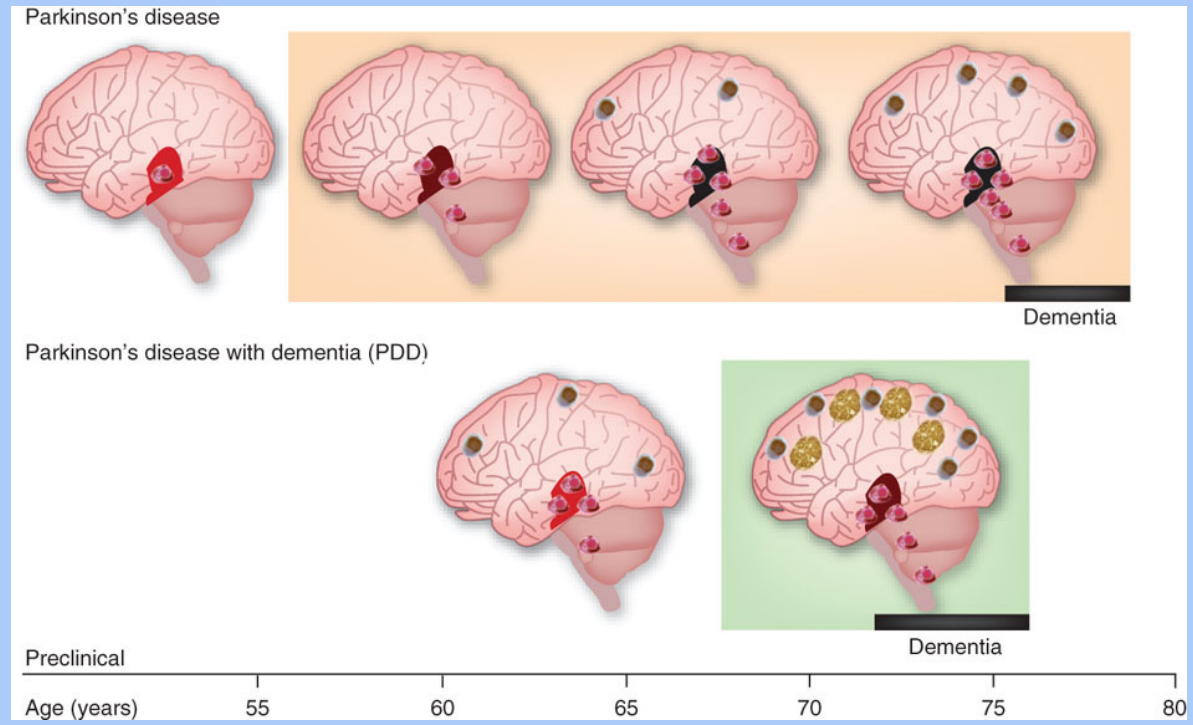
- Abnormal Build-up of Protein in Cells:
  - Alpha-synuclein – Abnormally Folded Protein
  - Garbage Disposal is overwhelmed
- Classically found in “Synucleinopathies”
  - Parkinson’s Disease
  - Lewy Body Dementia
  - Multisystem Atrophy



Ref 12 – Lewy body in the Substantia Nigra.

LEWY BODIES AND THEIR LOCATIONS

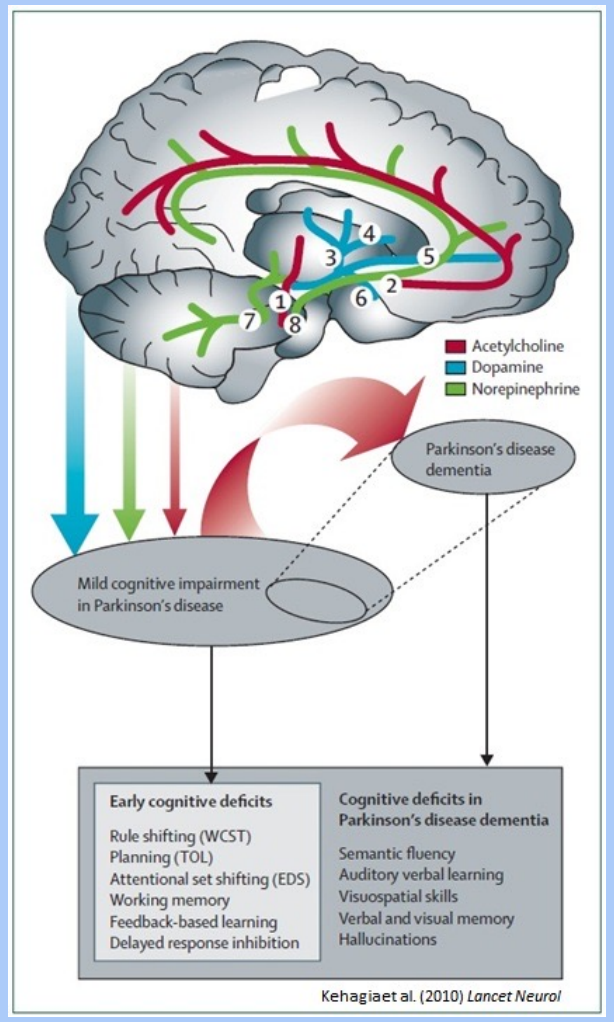
- Location, location, location
- Begins peripherally
  - GI
  - Skin
- Travels up the Vagus Nerve[3]
  - Transported by axons
- Dementia - expansion to bilateral fronto/parietal lobe projections and hippocampal circuit
  - Rapid vs slow
  - Timing can often determine Diagnosis and Prognosis



Ref 14 – Lewy body locations, and amyloid plaque/neurofibrillary tangle development

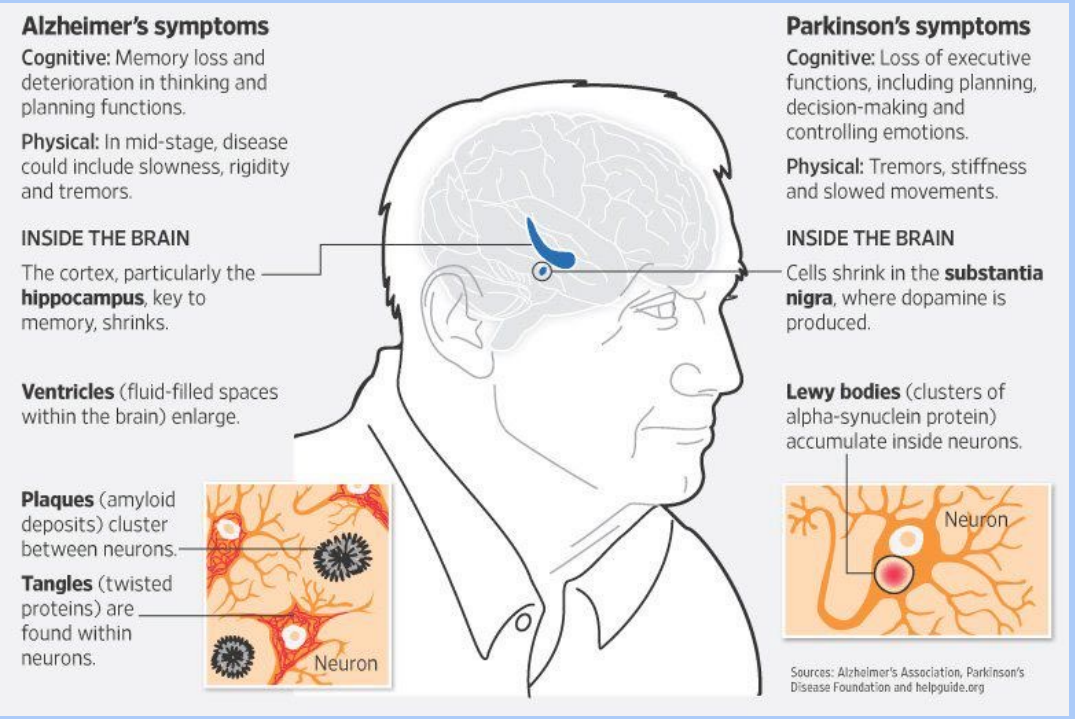
DEMENTIA IN PARKINSON'S DISEASE

- Motor Symptoms:
  - Basal ganglia – inputs of Dopamine, Acetylcholine, Norepinephrine
  - Substantia Nigra pars compacta - ~400,000 dopamine neurons
  - 70% loss with initial symptoms
- Memory/Cognitive Symptoms
  - Eventual extension of pathology to hippocampal circuit and bi-frontal/parietal areas
  - Early Mild Cognitive Impairment
  - Later can have similarities with Alzheimer's
  - Tau = neurofibrillary tangles in AD



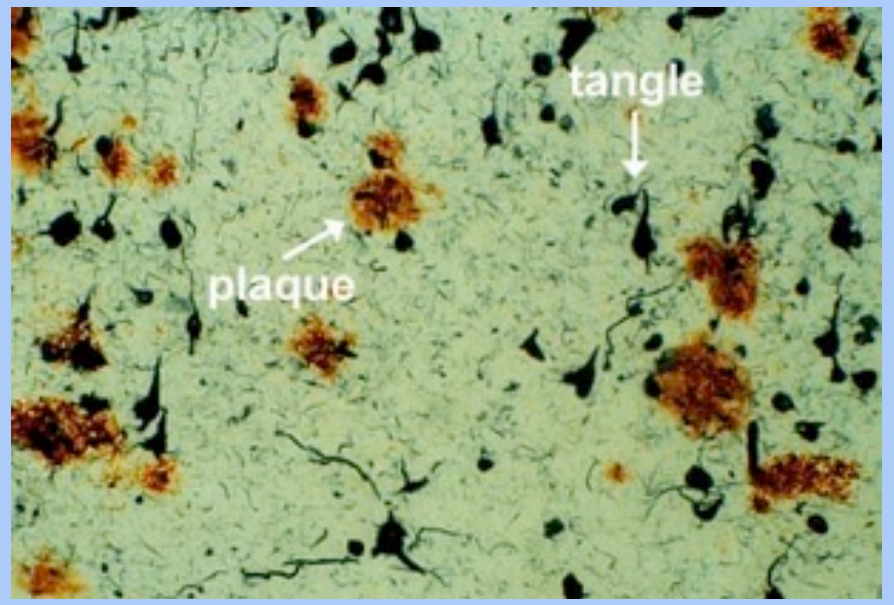
LEWY BODY DEMENTIA

- Dementia with Lewy Bodies, Diffuse Lewy Body Disease
- 30% of all dementias[4], second to Alzheimer's.
  - 1.4 million people[6]
- Classically associated with:
  - EARLY cognitive change (within 1 yr of PD symptoms)
  - Relatively rapid onset
  - Fluctuating cognitive impairment
  - Visual hallucinations
  - Parkinsonism
  - Sensitivity to
    - Dopamine replacement – hallucinations, side-effects
    - Neuroleptics – catatonia, rigidity
- REM Behavioral Sleep Disorder now part of diagnostic criteria[5]



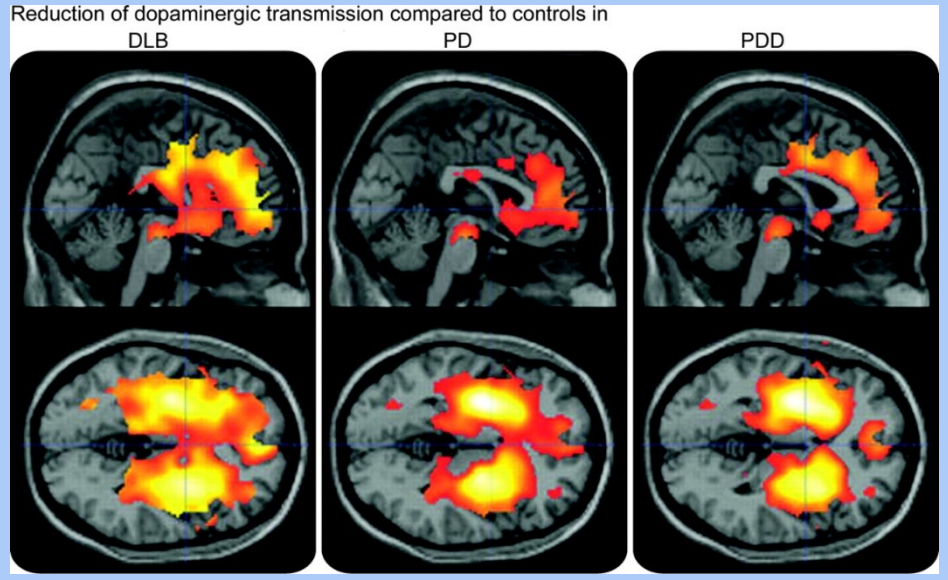
LEWY BODY DEMENTIA

- Pathology:
  - Alzheimer's pathology usually present on autopsy (neurofibrillary tangles/tau)
  - Significant loss of:
    - Cholinergic neurons – cognitive change similar to AD
    - Dopaminergic neurons – Parkinsonian symptoms
- Eventually, Parkinson's Disease Dementia and Lewy Body Dementia are pathologically indistinguishable
- Location versus Timing

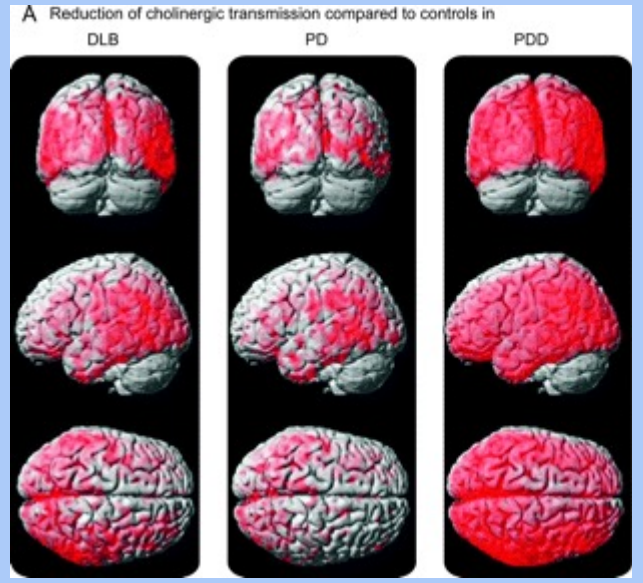


Ref 16 – Silver stain identifying tangles and plaques

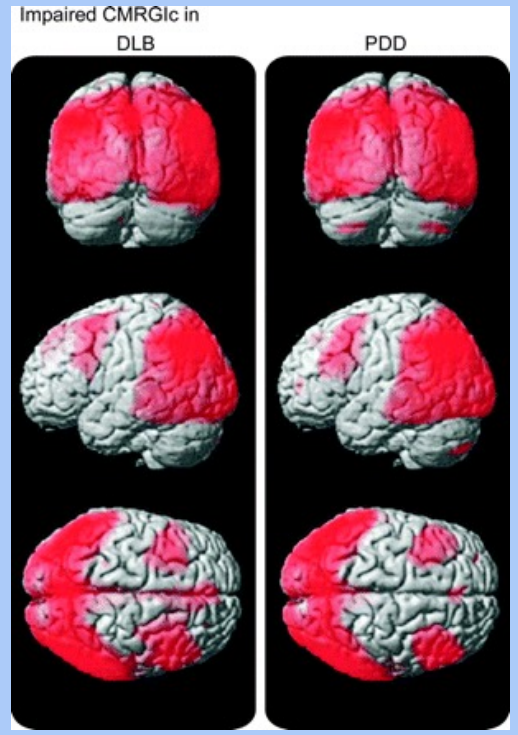
PET SCAN DATA COMPARING DLB, PD, PDD



Reduction in ^{18}flourodopa uptake
In Dopaminergic system



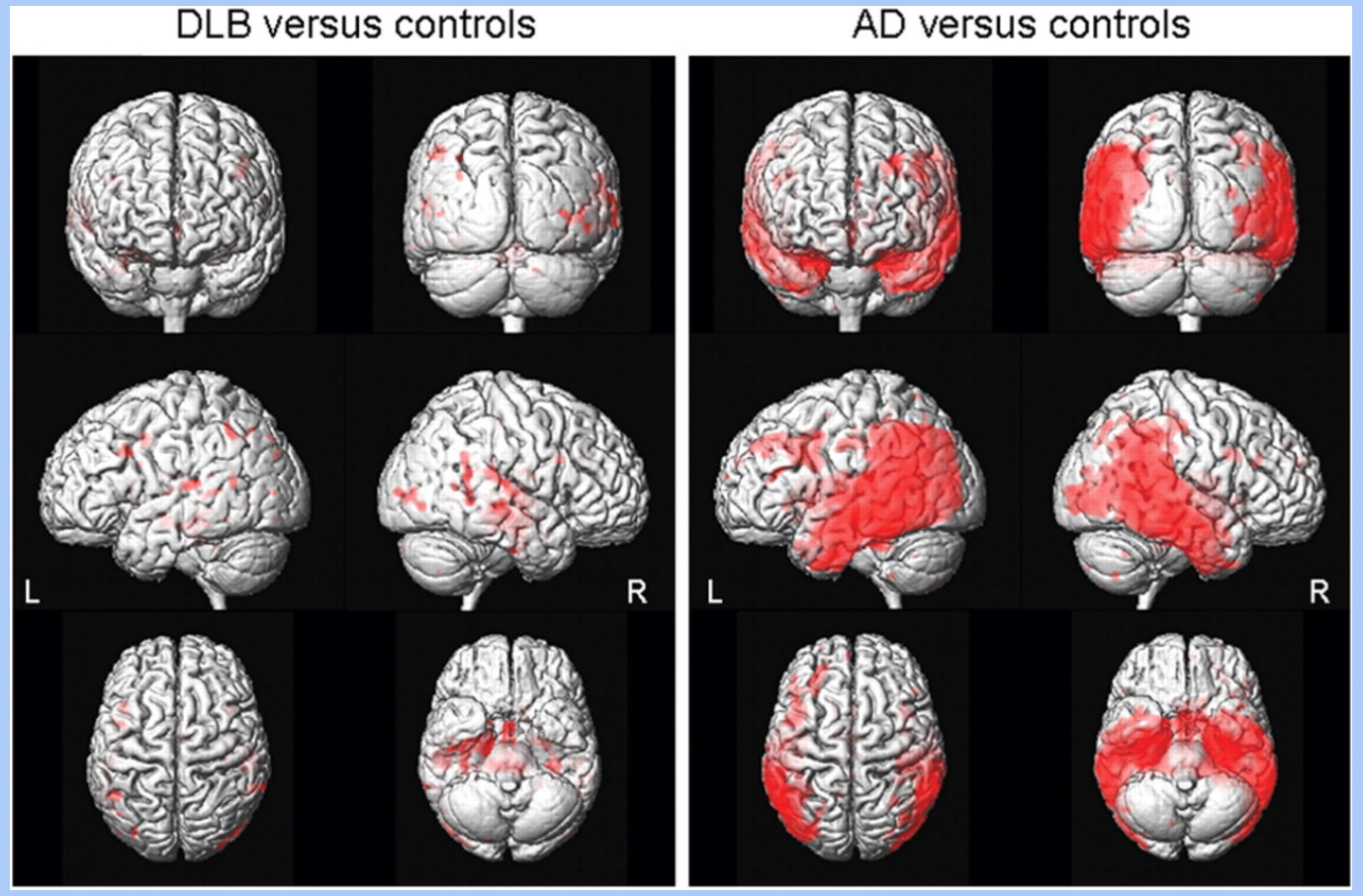
Reduction in
Cholinergic transmission



Reduction in FDG uptake
Decreased Glucose metabolism

Ref 2

GREY MATTER LOSS: LBD VS ALZHEIMER'S



Cortical grey matter loss

Ref 15

TREATMENT

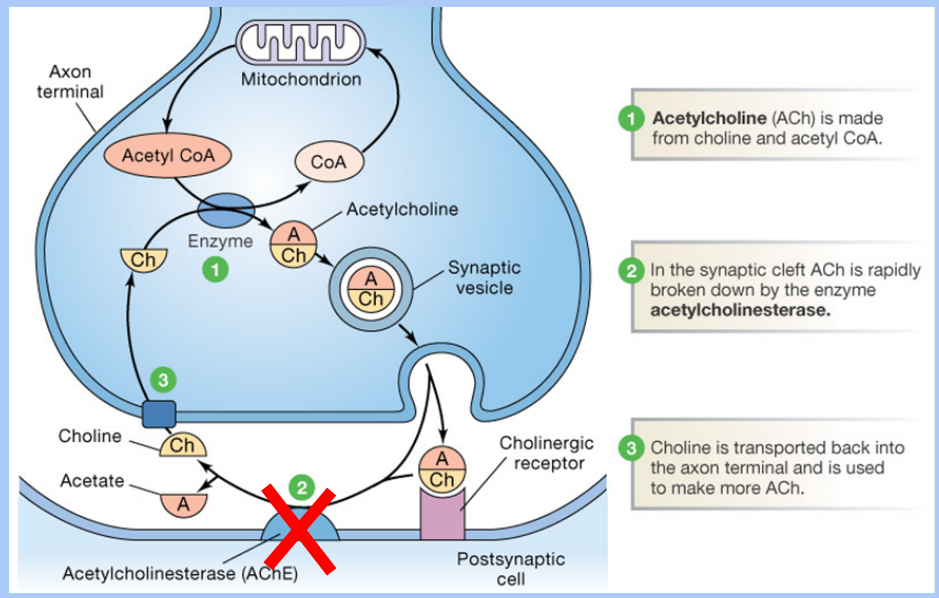
- Cognitive impairment from a number of reasons, including:
  - Initial reduction in Acetylcholine
  - Later overexpression of glutamate damages cells

↑↑↑ Acetylcholine, ↓↓↓ glutamate (through NMDA)

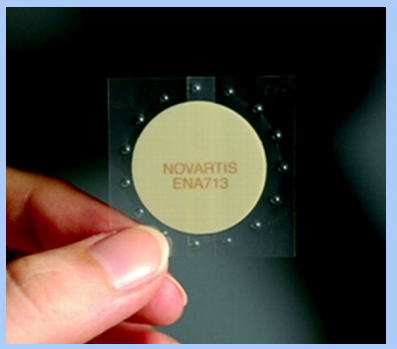
Enhanced cognition AND reduction in hallucinations

ACETYLCHOLINESTERASE INHIBITORS

- Block breakdown of Acetylcholine → Stays around cell longer → Improves function
  - Donepezil (Aricept®) – inhibits acetylcholinesterase
  - Rivastigmine (Exelon®) – inhibits butyrylcholinesterase and acetylcholinesterase
- Exelon is only FDA approved for Parkinson's Dementia
  - Patch form, reduces risk of nausea/vomiting
- Because nucleus problem and not receptor problem, patients respond better than those with Alzheimer's[8]

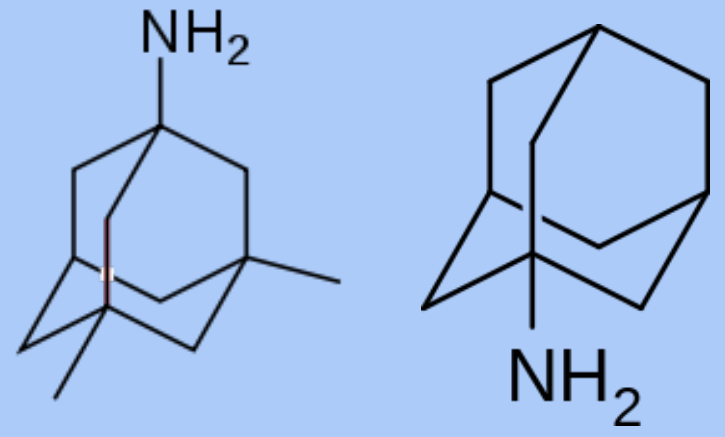


http://peaknootropics.com/wp-content/uploads/2013/08/acetylcholine-metabolism.png



NMDA BLOCKADE

- With LBD and PDD, acetylcholine is reduced
  - Triggers an increase in glutamate to compensate for the impaired functioning.
  - Overstimulation with glutamate causes neuronal hyper excitability and Nerve cell death.
- Memantine (Namenda®)
  - Blocks glutaminergic NMDA receptors
    - Reduces glutamate activity
- Corrects overexpression of glutamate
- No benefit in early dementia[9]
- Structurally similar to **Amantadine** → reduction in dyskinesias and other PD side-effects.

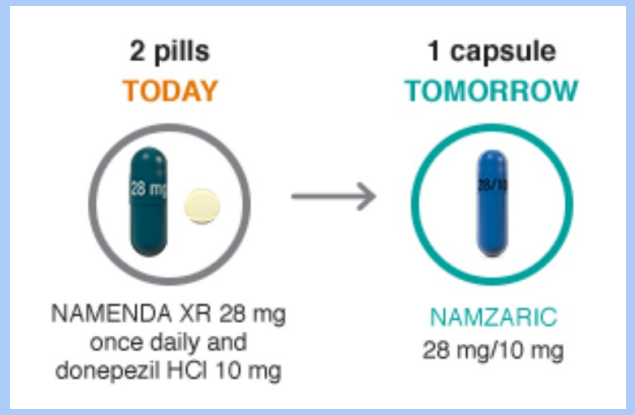


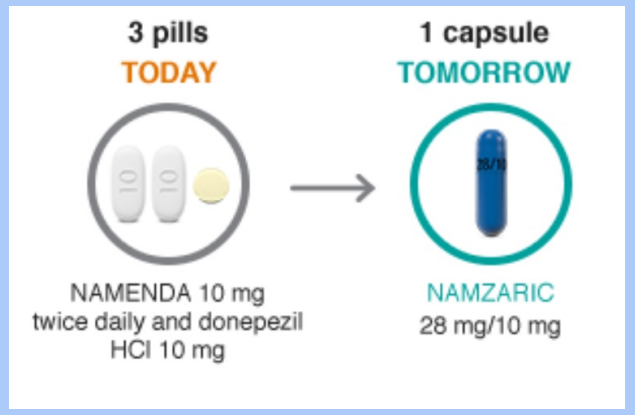
COMBINATION

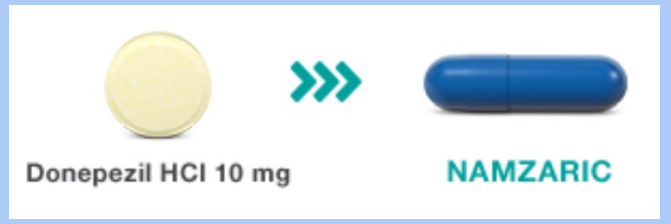
Namzaric™ (Donepezil + Memantine)

- Once a day combination of the two agents
- Moderate disease to severe.
- Can be opened and sprinkled to administer.

Namzaric™
(memantine HCl and donepezil HCl)
extended-release capsules
7/10 mg, 14/10 mg, 21/10 mg,
28/10 mg





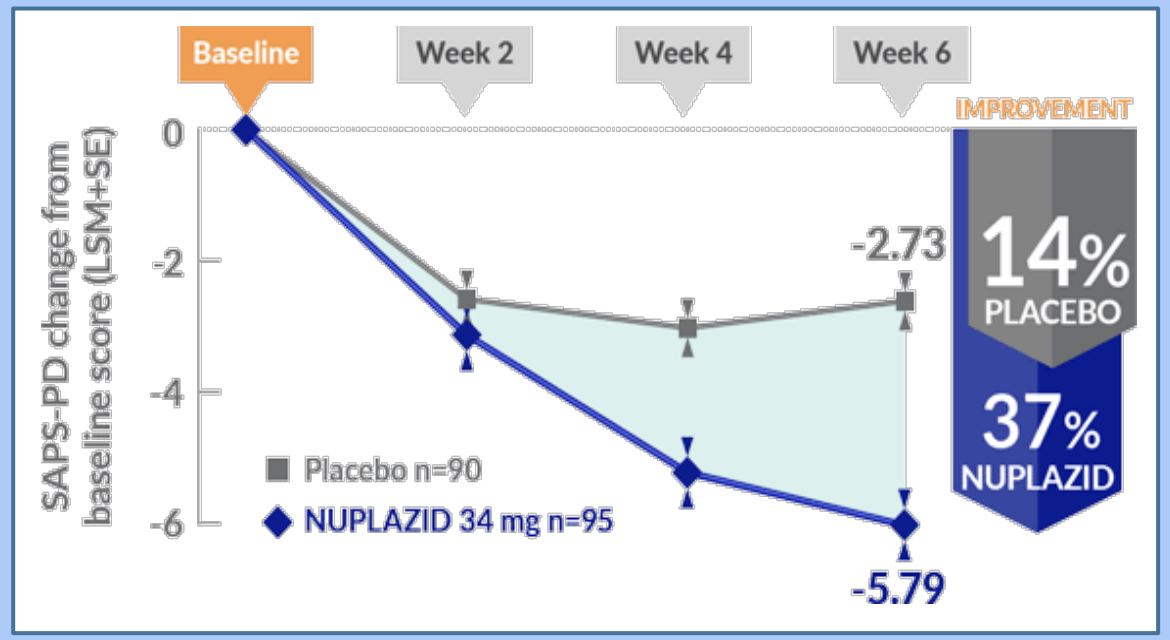


HALLUCINATIONS AND PSYCHOSIS

Nuplazid (Pimavanserin)™

- First antipsychotic medication specifically designed for hallucinations and ‘psychosis’ associated with Parkinson’s Dementia and Lewy Body Dementia.
- Serotonin Agonist with no impact on dopamine receptors
- + SAPS-PD improvement with no change in UPDRS

NUPLAZID™
(pimavanserin) tablets

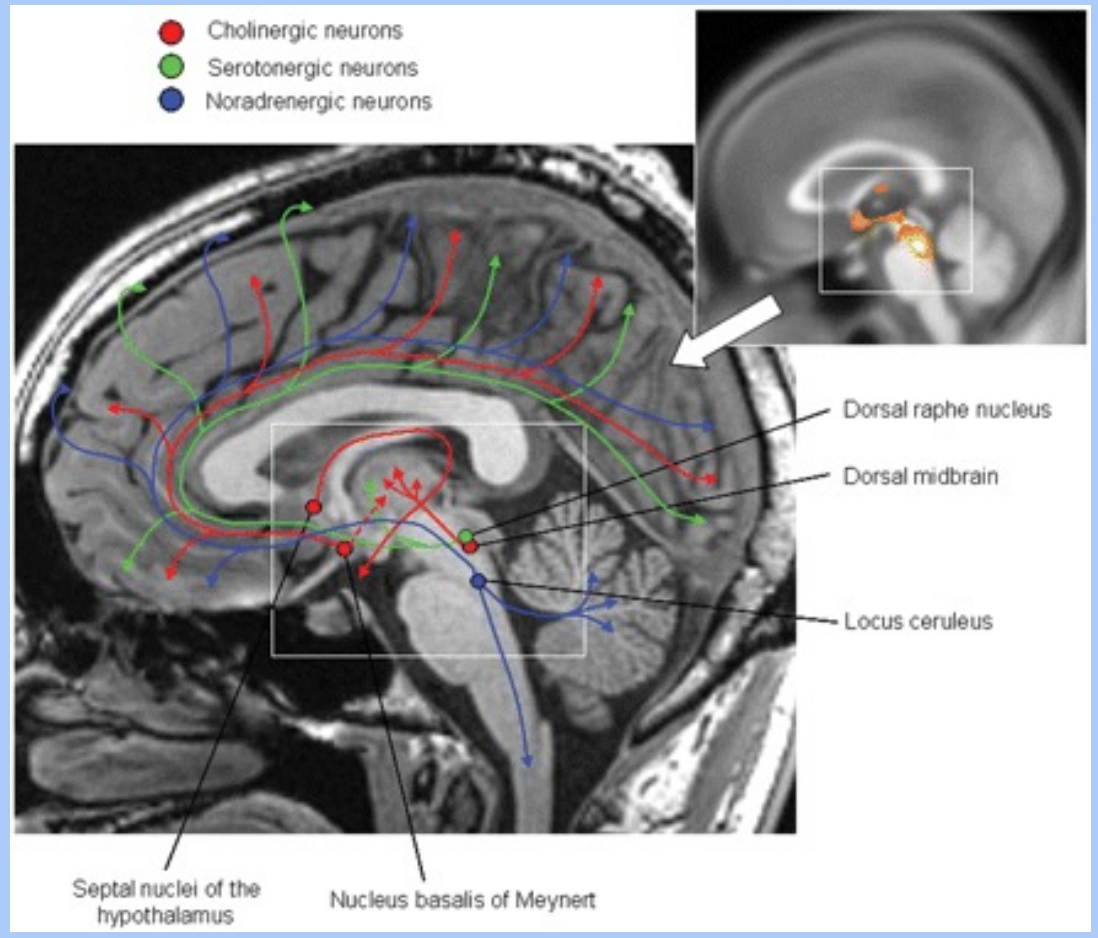


Hacksell, Uli et al. “On the Discovery and Development of Pimavanserin: A Novel Drug Candidate for Parkinson’s Psychosis.” *Neurochemical Research*39.10 (2014): 2008–2017. *PMC*. Web. 4 June 2015.

AVOID

- Avoid medications that block dopamine or acetylcholine
  - Neuroleptics
  - Benzodiazepines or Sedatives
  - Anti-cholinergics
    - Cold medications
    - OTC Sleep Aids
    - Anti-emetics
    - Some Meds for Over-Active Bladder
  - Older Parkinson's medications such as Artane or Cogentin
  - Alcohol?

IMPACT ON NEUROTRANSMITTER NUCLEI



Ref 15 – Location of Grey Matter loss in Lewy Body Dementia

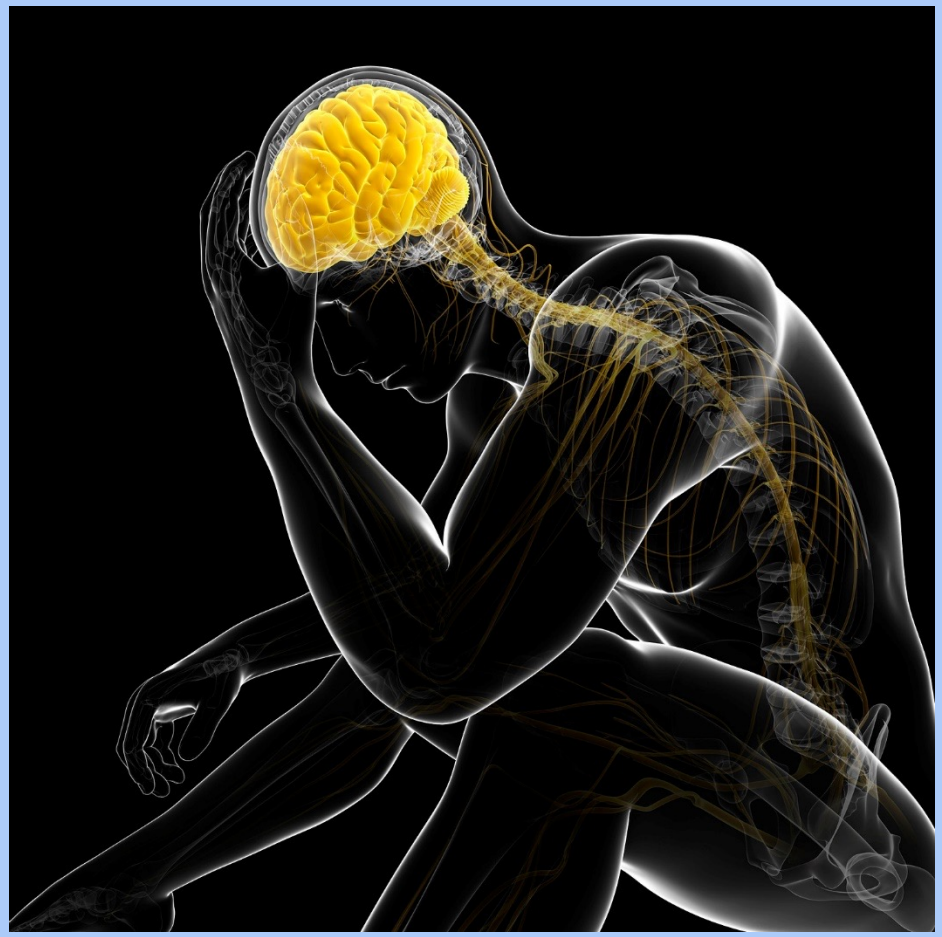
DEPRESSION AND ANXIETY'S ROLE

- Serotonin, Norepinephrine and Dopamine all significantly reduced in Parkinson's
  - Sleep, focus, mood, attention, etc.
- Depression, Anxiety and Fatigue missed by Neurologists up to 50% of the time[11]
- Treatment with SNRI or SSRI can significantly improve cognitive function in some patients

Depression masquerading as Dementia in the Parkinson's community.

YOU ARE NOT ALONE

- Depression is estimated to occur in up to 50% of patients
- Anxiety in up to 40% of patients
- Apathy in up to 40% of patients



DEPRESSION

Diagnostic Criteria:

- **Depressed Mood: Most of the day, nearly every day**

And/or

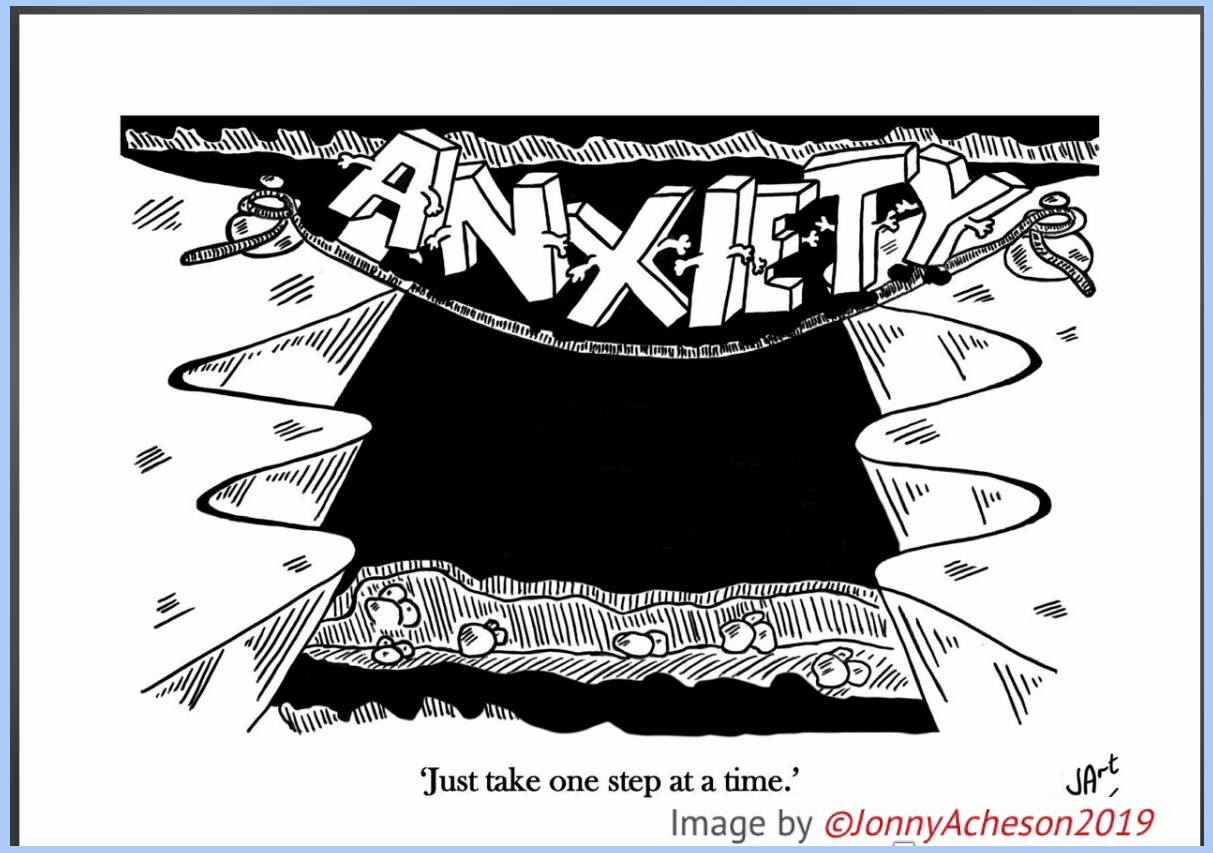
- **Diminished interest or loss of pleasure in almost all activities**

Plus: 3 to 4 of the following:

- **Weight or appetite change**
- **Increased or decreased sleep**
- **Slowing down of thought or movement**
- **Fatigue or lack of energy**
- **Feelings of worthlessness**
- **Diminished ability to think/concentrate**
- **Recurrent thoughts of death, suicidal ideation**

Image by ©JonnyAcheson2019

ANXIETY



Diagnostic Criteria:

Excessive worry or anxiety that is difficult to control occurring on more days than not, about a number of events or activities. For at least 6 months.

Also 3 (or more) of the following

- Restlessness, feeling keyed up or on edge.
- Being easily fatigued.
- Difficulty concentrating (mind going blank)
- Irritability
- Muscle tension
- Difficulty falling or staying asleep, or bad sleep

APATHY

"I don't know, I don't care, and it doesn't make any difference!" -Jack Kerouac, 1922-1969, American novelist

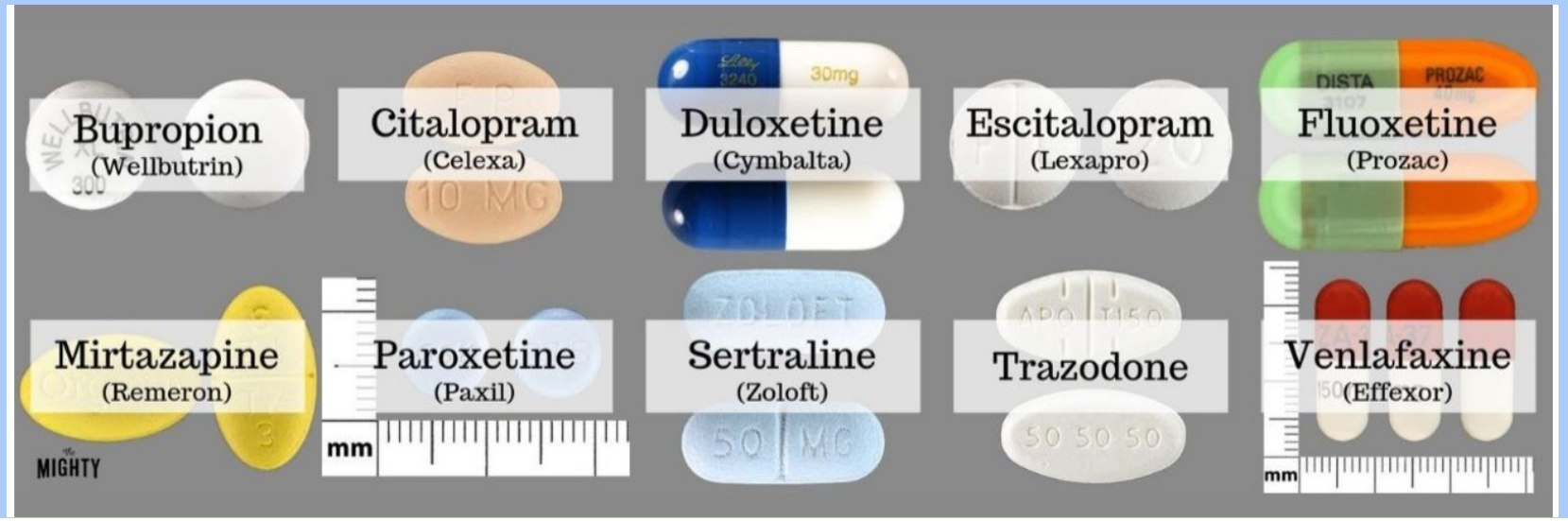
Image by ©JonnyAcheson2019

Important: Apathy is a non-motor symptom of PD and the person with PD does not have control of this.

- ★ Make a schedule! A non-negotiable schedule, and have people encourage you to stick to it.
- ★ Focus on small goals!
- ★ Even if you don't feel like it, do it!
- ★ Therapy may be helpful to work on motivation and develop a strategy to promote a positive attitude.
- ★ Traditional medications for depression may help

MEDICATION CAN HELP!

- Yes! There are medications to help! But there's so much more too!
  - There are a variety of medication options available, you should speak to your doctor about options that may be suitable for you. Not every medication works for every person the same, so it can be a bit of trial & error to find the medication that is best for you.
  - Sometimes your neurologist will manage this, sometimes your Primary Doctor, and sometimes your psychiatrist

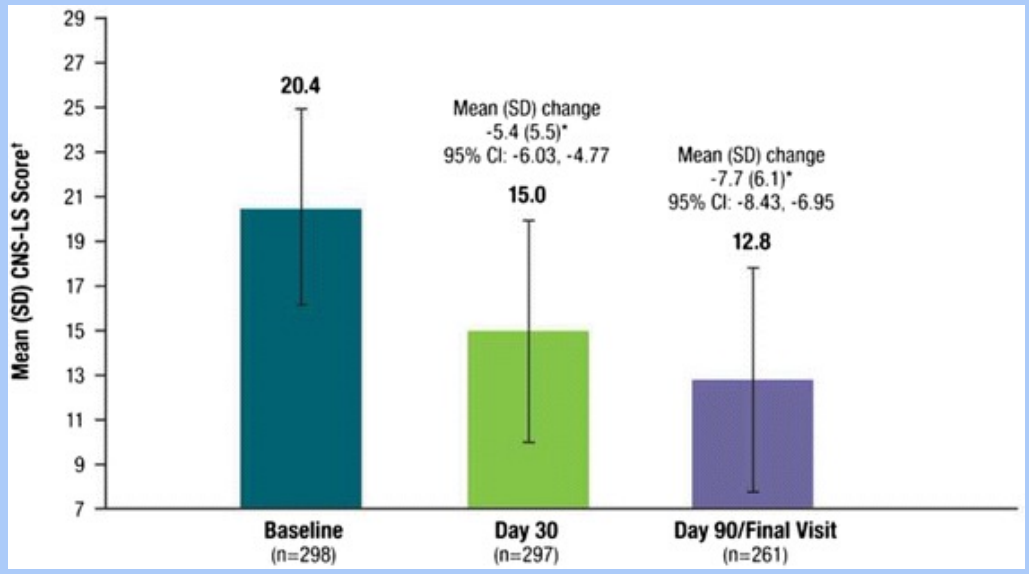


PSEUDOBULBAR AFFECT

Nuedexta

- "Uncontrollable episodes of crying and/or laughing, or other emotional displays."
- Disconnect between emotion and display, or inappropriate display
- PRISM study – 26%, though up to 40% in PD
- Estimated between 10%-40% in AD
- CNS-LS Screening reflects symptoms
- **Reduction in episodes at 90 days was 72.3%.**

NUEDEXTA®
(dextromethorphan HBr and quinidine sulfate) capsules 20 mg 10 mg



NON-MEDICATION TREATMENT

- Counseling—and the first counselor you meet, might not be ”the one”
- Exercise has been shown to be a therapeutic option in treatment of mood.
  - Exercise! Good for PD!! Good for Mood! The best exercise is the exercise you’ll do!!
- Emotional Support Animal (if appropriate)
- Mindfulness techniques!
  - Mindful breathing https://www.drweil.com/videos-features/videos/breathing-exercises-4-7-8-breath/
  - Progressive muscle relaxation
  - Meditation
  - Youtube: Search: Mindful Meditation, breathing, muscle relaxation

TREATMENT

It is Not EITHER/OR

It is BOTH/AND!!

WHAT ELSE CAN I DO?

- Activity!!
  - Physical and Mental
  - Exercise can slow progression
  - Cognitive Therapy
- Healthy Diet and lifestyle
  - Heart health is similar to Brain health
  - Cholesterol, blood pressure, diabetes
  - Cut back or stop Alcohol and tobacco
- No strong evidence for any particular diet or supplements
  - Vitamin E?
  - Omega-3?
  - B complex?
  - Ginkgo Biloba?
  - Prevagen???

LIFESTYLE IMPROVEMENTS

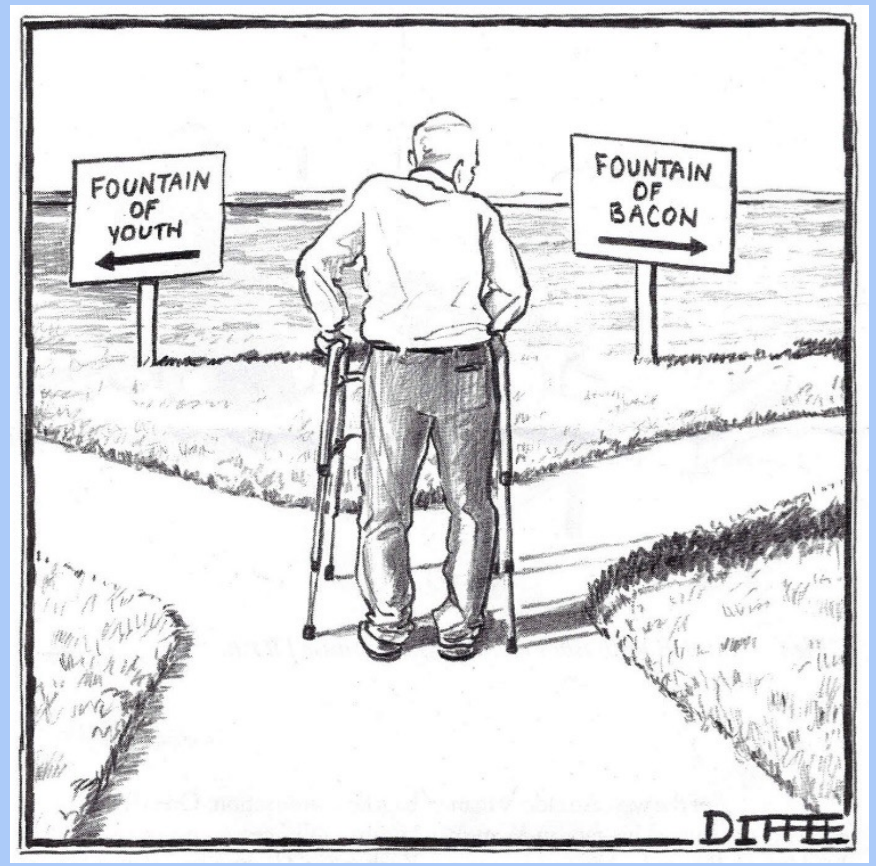
- **EXERCISE**
  - Naturally produces excess neurotransmitters, including Dopamine, Serotonin, Norepinephrine and NEUROTROPHIC FACTORS.
  - Increasing executive functioning and even reduction in the age expected decline of white and grey tissue density with increased fitness.
  - Recent study – 10-20 year reduction in 'cognitive age' with regular exercise.

- **CONTROL RISK FACTORS AND DON'T SMOKE**

Ageing, fitness and neurocognitive function.*Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, Chason J, Vakil E, Bardell L, Boileau RA, Colcombe A Nature. 1999 Jul 29; 400(6743):418-9.*
http://www.neurology.org/content/86/20/1897

LIFESTYLE IMPROVEMENT

- **DIET**
  - Higher in energy (fat/calories) lower in antioxidants – increased risk
  - Fish and seafood consumption inversely related to stroke risk
  - Low alcohol intake may:
    - reduce cardiovascular risk
    - stimulate hippocampal activity
    - In 4 studies, alcohol showed a U or J shaped curve
      - moderate to heavy drinkers disadvantaged whereas light to moderate drinkers show reduced WML, infarcts, and even dementia.
  - "Listen to your mother" diet choices



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CONCLUSIONS

- Memory, cognitive functioning and mood are directly linked to Acetylcholine and Dopamine.
  - Treatment is complicated d/t balance of treating motor and non-motor symptoms, incorporating different neurotransmitter circuits to give benefit without side-effects
- Proper diagnosis is key, as treatment is different
  - Parkinson's vs
  - Lewy Body dementia vs
  - Parkinson's dementia vs
  - Parkinson's plus syndromes
  - +/- Depression, Anxiety or Apathy
- Integrating a Movement Disorders Specialist into your treatment team

SO WHAT DOES THIS MEAN?

- Cognitive change is a normal part of aging.
- Talk to your doctor about memory changes, confusion, hallucinations and delusions.
- There are medications that can help!
- Depression and anxiety happen… we need to acknowledge it and treat it.
- Consider a psychiatrist as part of your treatment team
- Stay physically and mentally active, eat healthy and live life!

INOVA®
Parkinson's and
Movement Disorders Center

THANK YOU!

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Join our newsletter!

Stay up to date on all
of our center's offerings!

Sonia.Gow@inova.org

www.inova.org/move

703-375-9987

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