Neurocognitive Disorders and Medication Management

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Overview of Goals

- Review Causes of Dementia
- Review Medical Workup of Dementia
- Review Treatments of Dementia including Medications
- Review Medications that may worsen or cause Dementia symptoms.
- .......or is that a neurocognitive disorder.
The section entitled delirium, dementia and amnestic and other cognitive disorders in the fourth edition and subsequent text revision (DSM-IV\textsuperscript{6} and DSM-IV-TR\textsuperscript{7}) is now “neurocognitive disorders,” or NCDs
Are these people demented?, or do they have NCD’s?
Part 1: Neurocognitive Disorders
Mild Cognitive Impairment?

- In the new system, cognitive impairments that do not reach the threshold for a diagnosis of dementia are termed mild NCDs, whereas the dementias constitute nearly all of the major NC

(Note: all slides about DSM5 NCD are referenced from: J Am Acad Psychiatric Law 42:2: 159-164 (June 2014))
Diagnostic criteria for mild NCD include:

- Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition) based on:
  1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
Diagnostic criteria for mild NCD include:

2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
The concept of a continuum between mild and major NCDs is explicitly noted. “Major and mild NCDs exist on a spectrum of cognitive and functional impairment” (DSM5, p 607).
"The distinction between major and mild NCD is inherently arbitrary, and the disorders exist along a continuum. Precise thresholds are therefore difficult to determine" (DSM5, p 608).
It is noted that standardized testing is particularly important when evaluating patients with suspected mild NCD, and suggested cutoffs are provided: “For major NCD, performance is typically 2 or more standard deviations below appropriate norms (3rd percentile or below). For mild NCD, performance typically lies in the 1–2 standard deviation range (between the 3rd and 16th percentiles)” (DSM5, p 607).
Any cause of dementia can also produce mild NCD.

For example, both major and mild NCD due to Alzheimer's disease are diagnosable conditions.
A patient can have mild NCD (not a dementia)......which can progress to:

1. Mild major NCD.....then
2. Moderate major NCD.....then
3. Severe major NCD

(these latter three are all dementias)
In the new system, memory impairment is no longer a requirement in the diagnosis of a major NCD. Impairment in only one cognitive domain is enough to qualify for a diagnosis of a major NCD, except in the case of major NCD due to Alzheimer's disease, where two domains are still required, one of which must be memory impairment.
1. Complex attention
2. executive function,
3. learning and memory,
4. language,
5. perceptual motor
6. social cognition
Causes of Major NCD

- Alzheimer’s disease
- Frontotemporal lobar degeneration
- Lewy body disease
- Vascular disease
- Traumatic brain injury
- Substance/medication use
- HIV infection
Causes of Major NCD

- Prion disease
- Parkinson’s disease
- Huntington’s disease
- Another medical condition
- Multiple etiologies
- Unspecified
HOW FAST YOU WALK IN MIDDLE AGE MAY PREDICT DEMENTIA RISK

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I wish I never knew that....
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PUGH
Causes of major NCD

- Alzheimer’s Disease
Neurocognitive Disorder due to Alzheimer's Disease

- Most common dementia (64%)
- Affects twice as many women as men.
- Strikes at any age
- 10% of cases have genetic link
Neurocognitive Disorder due to Alzheimer’s Disease

- Lose many neurons and neuronal connections
- Neuritic plaques in brains cells on autopsy. Plaques made of amyloid protein. Does the amyloid kill the cells?
- Acetylcholine neurotransmitter decreased in alzheimer’s patients.
Neurocognitive Disorder due to Alzheimer's Disease

Amyloid Plaque

Farlow et al., 1994
Cognition peaks on average at age 25.
Alzheimer’s Disease Screening

1. Recent memory loss affecting job
2. Difficulty performing familiar tasks
3. Problems with language
4. Disorientation to time or place
5. Poor or decreased judgment

(Alzheimer’s Association)
Alzheimer’s Disease Screening

6. Problems with abstract thinking
7. Misplacing things
8. Changes in mood or behavior
9. Changes in personality
10. Loss of initiative

(Alzheimer’s Association)
Alzheimer’s Disease

How did your memory improvement class go last night?

I completely forgot about it!!
Neurocognitive Disorder due to Alzheimer’s Disease

“I’m stumped. We’ll have to wait for the autopsy.”
73 Y/P MALE, PTSD, MMS = 30 (ECD)
PROBABLE AD, VERY LATE STAGE
Lewy body versus Parkinson's

<table>
<thead>
<tr>
<th>Disease name</th>
<th>Location in brain</th>
<th>Function controlled</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBD</td>
<td>Cerebral cortex</td>
<td>Cognition (memory, thinking)</td>
<td>Dementia</td>
</tr>
<tr>
<td>PD</td>
<td>Substantia nigra</td>
<td>Motor</td>
<td>Movement problems</td>
</tr>
<tr>
<td>PDD</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
</tbody>
</table>

© 2007, The Lewy Body Dementia Association
<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>DLB</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dementia</strong></td>
<td>Later onset, usually 1 year after parkinsonism onset. Less prominent than DLB &amp; AD</td>
<td>Earlier compared to PD, less than a year after parkinsonism. Compared to AD, visuospatial and visual memory more severe.</td>
<td>Prominent features</td>
</tr>
<tr>
<td><strong>Fluctuation of cognitive impairment</strong></td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Visual Hallucination</strong></td>
<td>Not common</td>
<td>Common, usually non-threatening and insight remain.</td>
<td>Not common</td>
</tr>
<tr>
<td><strong>Parkinsonism</strong></td>
<td>Prominent features</td>
<td>Relatively mild, rarely asymmetry, tremor not prominent</td>
<td>Rarely present</td>
</tr>
</tbody>
</table>
Lewy Body Dementia DSM5

- The individual meets criteria for major or minor neurocognitive disorder and meets a combination of core diagnostic features and suggested diagnostic features of Lewy body dementia.
- The individual experiences insidious onset and gradual progression.
- The symptoms are not better attributed to cerebrovascular disease, as evident on focal neurologic signs or on brain imaging.
- The symptoms are not better attributed to another physical illness or brain disorder.
- Providers must specify whether major or minor neurocognitive disorder is due to probable Lewy body dementia (requiring two core features or one suggestive feature with one or more core features) or possible Lewy body dementia (requiring one core feature or one or more suggestive features).
- Core diagnostic features of Lewy body dementia include the following:
  - Fluctuating cognition with pronounced variations in attention and alertness;
  - Recurrent visual hallucinations that are typically well formed and detailed; and
  - Spontaneous features of Parkinsonism with onset at least one year later than the cognitive impairment.
- Suggestive diagnostic features of Lewy body dementia include the following:
  - Rapid eye movement sleep behavior disorder;
  - Severe neuroleptic sensitivity; and
  - Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging.
Lewy Body Dementia

Four symptoms reliably distinguish Lewy Body dementia from Alzheimer’s:

1. Daytime drowsiness and lethargy despite sufficient sleep the night before
2. Napping two or more hours during the day;
3. Staring into space for long periods
4. Episodes of disorganized, incoherent speech

(Journal of Neurology, Jan 27, 2004)
Lewy Body Dementia

- Deposits in brain cells called Lewy Bodies.
- Lewy Body deposits made of protein called alpha-synuclein (this protein also has been linked to Parkinson’s)
- May account for up to 20% of total dementia cases. (Annals Int Med 1 Apr 2008)
Lewy Body Dementia

- Visual hallucinations common
- Many times have similar symptoms to Parkinson’s (rigidity, bradykinesia, shuffling gait, tremor)
- Often have fluctuating cognition
- No specific treatment
- Limitations of antiparkinson or antipsychotic drugs.
Lewy Body Dementia
Vascular Dementia

Vascular Dementia Change on the Mini-Mental State Exam Over Time

Average Time of Illness (years)

Score

-5 0 5 10

Event

Event

Event
Vascular Dementia
“THE COMPUTER SAYS I NEED TO UPGRADE MY BRAIN TO BE COMPATIBLE WITH ITS NEW SOFTWARE.”
Frontotemporal Lobar Degeneration

- Onset often before age 60
- Language difficulties common.
- Prominent personality changes, behavioral disturbances, like hyperphagia, aggression, or prominent apathy. Memory may be preserved early
- Functional MRI with decreased activity in frontal and temporal lobes. (Annul Int med 1 Apr. 2008)
Causes of NCD

- Degenerative diseases (MS)
- Normal Pressure Hydrocephalus
Causes of NCD

- Tumors

![Image: Cystic Brain Metastases - uterine CA]
Causes of NCD

- Tumors
Causes of NCD

- Trauma
Diagnostic evaluation

- History (Trauma, Stroke, Drugs, Alcohol)
- Physical
- Labs: B12, Thyroid, Complete Metabolic Panel, CBC, Urinalysis, Sed Rate, RPR
Diagnostic Evaluation

- Consider CT scan of brain (or MRI). Most helpful if less than 3 years duration, early age of onset, rapid progression, focal neurologic deficits, atypical symptoms or know vascular risk factors.

- Consider HIV, Toxicology, Heavy metals, Folate, Chest x-ray, Urinalysis

(Annals of Int Med 1 Apr 2008)
Diagnostic Evaluation

- Neuropsychological Testing
  - Specifically designed tasks used to measure a psychological function known to be linked to a particular brain structure or pathway
Maybe they are stubborn
Part 2: Medications.....
Medications to treat NCD

- Alzheimer's Disease
- Lewy Body Disease
- Parkinson's Disease
- Vascular Disease
Alzheimers Medications

- Cholinesterase Inhibitors: Aricept, Exelon, Razadyne
- Cholinesterase inhibitors work by decreasing breakdown of acetylcholine, which is neurotransmitter thought to be important for alertness, memory, thought, and judgment
- Most common side effects: nausea, diarrhea, urinary incontinence
Do acetylcholinesterase inhibitors work?

- Most studies are short term (6 months or less) and show modest benefits on cognition, behaviors, and ADL’s.
- Longer term studies are benefits may last for a few years, but these studies were open label: more prone to bias.
- Higher doses statistically better than lower doses.

(BCMJ, Vol. 53, No. 8, October 2011, page(s) 404-408)
Do acetylcholinesterase inhibitors work?

- Adverse events are significant: nausea, vomiting, diarrhea, anorexia, weight loss, dizziness, bradycardia, myalgias, and insomnia.
- Adverse events more likely at higher dosages.
- Minimize adverse events by starting low and slowly titrating dose higher.

(BCMJ, Vol. 53, No. 8, October 2011, page(s) 404-408)
Stop Alzheimer’s meds

- On average, stopping acetylcholinesterase inhibitors may have a deleterious effect on cognition and behaviors.
  (J Clin Psychiatry 2015;76(11):e1424–e1431)

- In institutionalized Alzheimers patients who do not have hallucinations or delusions, it is safe to stop these medicines.
  (J Am Med Dir Assoc. 2016 Feb;17(2):142-7.)
Memantine (Namenda)

- Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist that is believed to decrease excitotoxicity associated with glutamate in the central nervous system. The efficacy of memantine for treating moderate to severe Alzheimer dementia has been evaluated in several trials and is statistically positive.

(BCMJ, Vol. 53, No. 8, October 2011, page(s) 404-408)
Combination therapy only showed the benefit on neuropsychiatric symptoms and behavioral problems in moderate-to-severe AD, but no other superiority in terms of cognitive function, activities of daily living, and global changes.

(JAMDA, Volume 17, Issue 9, Pages 863.e1–863.e8)
Alzheimer’s Medications

- Vitamin E not helpful and may increase mortality. (NEJM 1997;336:1216-22)
- Ginko Biloba not supported by evidence at this time (Curr Alzheimer Res 2005;2:541-551)
Acetylcholinesterase inhibitors in other diseases.

AchI may be effective in the treatment of cognitive impairment in patients with PDD, but do not affect risk of falls. The choice of treatment has to be balanced considering the increased tremor.

(J Neurol Neurosurg Psychiatry 2015;86:767-773)

Rivastigmine may be especially helpful in Parkinson’s Dementia

Vascular Dementia

- Donepazil and Galantamine may have limited positive effects on cognition.
- Studies with rivastigmine are limited.

(Eur Neurol 2016;75:132-141)
Treating multiinfarct dementia

- *Hypertension Research* (2011) 34, 74–78; doi:10.1038/hr.2010.179; published online 23 September 2010

- High plasma aldosterone concentration is a novel risk factor of cognitive impairment in patients with hypertension. Role of potassium-sparing diuretics.
Meds In Lewy Body

- Meta-analyses indicated improvements with donepezil and rivastigmine for cognition, hallucinations, delusions, and activities of daily living (without worsening motor symptoms of parkinsonism) but with adverse events.

- Memantine appears to be well tolerated but provides few benefits to patients.

(Am J Psychiatry 172:8, August 2015)
Meds for Lewy Body

- For olanzapine and quetiapine, reductions in psychiatric symptoms appear to be limited by high levels of adverse events. Citalopram, piracetam, and risperidone do not appear to be beneficial.

- There was weak evidence for potential efficacy of levodopa, clonazepam, gabapentin, duloxetine, escitalopram, trazodone, and clozapine. These studies did not include controls.

(Am J Psychiatry 172:8, August 2015)
Prevention of NCD

- Mid life hypertension increases risk of NCD.
- Hypotension may increase Alzheimer’s
- Later life hypertension may increase risk, but not as drastic as midlife.
- Treating hypertension likely has benefit on reduction of NCD. ARB may be most beneficial.
Prevention of NCD

- Taking statins reduces NCD risk 29% (Mayo Clinic Proceedings, 10/1/2013)
- Fish Oil may be helpful to prevent NCD (J Alzheimers Dis. 2011;24(3):485-93. doi: 10.3233/JAD-2011-101524.)
Prevention of NCD

- Avoid trauma
- Avoid cigarettes (vascular health)
- Coffee may be helpful
  (J Alzheimers Dis. 2010;20 Suppl 1:S187-204)
- Exercise, but avoid head trauma
  (Journal of Aging Research Volume 2013 (2013), Article ID 657508, 8 pages)
“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”

exercis
Medications that affect cognition
Concepts of brain reserve

Neurology 53, 1942–1947
Alcohol: Often overlooked
19% of older adults that take medications that may interact with alcohol, report that they use alcohol. (J Am Geriatr Soc 2005;53:1930-6.)

The term *Wernicke encephalopathy* is used to describe the clinical triad of confusion, ataxia, and nystagmus.

Treatment is thiamine early in the disease. Later, changes can be permanent. (Lancet Neurol 2007;6:442-55)
Alcohol

- Moderate to high alcohol consumption is one of the risk factors for development of dementia prior to age 65
  (Dement Geriatr Cogn Disord 2006;21:59-64)
- Alcohol related NCD improves with abstinence, but is unlikely to resolve.
Marijuana acutely decreases attention and short term memory…..but some of the these effects actually last long term.

(Pharmacol Biochem Behav 2005;81:319-30.)
ANTICHOLINERGIC SIDE EFFECTS

- Hot as a hare
- Dry as a bone
- Blind as a bat
- Red as a beet
- Mad as a hatter
Anticholinergic

- Anticholinergic: inhibiting the physiological action of acetylcholine, especially as a neurotransmitter.
- Side effects of anticholinergic drugs:
- Blurred vision, Constipation, Decreased sweating, Dizziness, Dry mouth, Slowing down of urination, confusion.
Anticholinergic medicines

- Short and long term use may affect memory and is linked to NCD.
- Taking an anticholinergic for the equivalent of three years or more was associated with a 54% higher dementia risk than taking the same dose for three months or less.

(JAMA Intern Med. 2015;175(3):401-407)
TYLENOL PM

- Tylenol pm = Tylenol plus Benadryl
- Benadryl = Diphenhydramine = Anticholinergic
Antihistamines

- Chlorpheniramine - Chlor-Trimeton®
- Clemastine - Tavist®
- Diphenhydramine - Tylenol PM®, Sominex®, Benadryl®
- Hydroxyzine - Atarax®, Vistaril®
- Promethazine - Phenergan®
- Meclizine-Bonine®, Antivert®
Antiparkinson Agents:

- Benztropine - Cogentin®
- Biperiden - Akineton®
- Procyclidine - Kemadrin®
- Trihexyphenidyl - Artane®
- Amantadine-Symmetrel
Antipsychotics:

- Chlorpromazine - Thorazine®
- Clozapine - Clozaril®
- Olanzapine - Zyprexa®
- Quetiapine - Seroquel®
- Thioridazine - Mellaril®
Antispasmodotics:

- Atropine - Sal-Tropine®
- Belladonna alkaloids - Donnatal®
- Dicyclomine - Antispas®, Bentyl®
- Flavoxate - Urispas®
- Hyoscyamine - Levbid®, Levsin/SL®
- Scopolamine
Antiarythmics:

- Disopyramide - Norpace®
- Procainamide - Pronestyl®
- Quinidine - Quinaglute®, Quinidex®
Tricyclic antidepressants:

- Amitriptyline - Elavil®
- Desipramine - Norpramin®
- Doxepin - Sinequan®
- Imipramine - Tofranil®
- Nortriptyline - Pamelor®
Muscle relaxants

- cyclobenzaprine
Possible anticholinergic effect

- Furosemide (Lasix)
- Digoxin
- Captopril
- Ranitidine
- Warfarin
- Prednisone
- Hydrochlorothiazide
- Atenolol
Urinary incontinence drugs

- Most are anticholinergic
- Oxybutynin (Ditropan XL, Oxytrol)
- Tolterodine (Detrol)
- Darifenacin (Enablex)
- Solifenacin (Vesicare)
- Trospium (Sanctura)
- Fesoterodine (Toviaz)
Both acute and chronic opioid use is associated with neuropsychological deficits in executive functions, attention, concentration, recall, visuospatial skills, and psychomotor speed.

(Neuropsychol Rev 2007;17:299-315.)
Opiates

- **Side effects:**
  - Anticholinergic

- **Long-term effects can include:**
  - Nausea and vomiting, Abdominal distention and bloating, Constipation, Brain damage due to hypoxia, Development of tolerance.

- Limited proof of long term efficacy. Few studies have attempted to study effects over one year or more of use.

  (Ann Intern Med. 2015;162:276-286)
I saw patient with known microvascular disease with SLUMS score of 21 out of 30.

- Stopped Ambien given by another physician
- Score on SLUMS increased to 27 out of 30.
“Sleeping pills”

- zolpidem (Ambien)
- eszopiclone (Lunesta)
- zaleplon (Sonata)
Benzodiazepines

Figure 1: Percent of population with any benzodiazepine use by sex and age, United States, 2008

Data Source: IMS LifeLink® Information Assets-LRx Longitudinal Prescription Database, 2008, IMS Health Incorporated.
Long term cognitive decline

- There is an association between benzodiazepine use in older people and increased risk of Alzheimer’s disease. The association was stronger with increasing length of use; the risk was nearly doubled for those using benzodiazepines for more than 180 days.

BMJ. 2014 Sep 9;349
Benzodiazepine use in elderly

- Doubles the risk of fall with age >80.
  
  **Drugs Aging.** 2008;25(1):61-70

- Risk of falls increased most with long acting Benzodiazepines

And now, for some good news.

Good News, Everyone!
Statins

- Despite some case reports of statin-induced memory loss and confusion, statins do not appear to be associated with an increased risk of cognitive impairment.

- If cognitive impairment is suspected in a patient taking a statin, look for other medications that may be contributing.

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Can Pharm J (Ott). 2015 May; 148(3): 150–155
Sunrise or Sunset?