I can’t find the keys: Neurocognitive Disorders and Medication Management

Rodney Sepich, M.D., C.M.D.
Medical Director, Foxdale Village
State College, PA
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.
Blood column diameter, centerline blood speed, and retinal blood flow rate were reliably measured in a major temporal retinal vein of each subject using a Canon laser Doppler retinal blood flow instrument in Alzheimer’s Disease patients, Mild Cognitive Impairment patients, and normal controls.

Retinal blood flow in MCI is intermediate between what is measured in control subjects and in AD patients. Our findings suggest that blood flow abnormalities may precede the neurodegeneration in AD.

Alzheimers: I see it in your eyes?

Association of Preclinical Alzheimer Disease With Optical Coherence Tomographic Angiography Findings

- Bliss Elizabeth O’Bryhim, MD, PhD; Rajendra S. Apte, MD, PhD; Nathan Kung, MD;
- Dean Coble, PhD; Gregory P. Van Stavern, MD
Case-control study included 32 participants recruited from the Charles F. and Joanne Knight Alzheimer Disease Research Center, Washington University in St Louis, St Louis, Missouri. Results of extensive neuropsychometric testing determined that all participants were cognitively normal.

Alzheimers: I see it in your eyes?

- Participants underwent positron emission tomography and/or cerebral spinal fluid testing to determine biomarker status.
- Individuals with prior ophthalmic disease, media opacity, diabetes, or uncontrolled hypertension were excluded.

Automated measurements of retinal nerve fiber layer thickness, ganglion cell layer thickness, inner and outer foveal thickness, vascular density, macular volume, and foveal avascular zone were collected using an OCTA system from both eyes of all participants.

Fourteen participants had biomarkers positive for AD and thus a diagnosis of preclinical AD (mean [SD] age, 73.5 [4.7] years).

Sixteen participants without biomarkers served as a control group (mean [SD] age, 75.4 [6.6] years).
The foveal avascular zone was increased in the biomarker-positive group compared with controls (mean [SD], 0.364 [0.095] vs 0.275 [0.060] mm²; P = .002).

Mean (SD) inner foveal thickness was decreased in the biomarker-positive group (66.0 [9.9] vs 75.4 [10.6] μm; P = .03).

*JAMA Ophthalmol.* 2018 Nov 1;136(11):1242-1248
Figure 1. Foveal Avascular Zone (FAZ) Measurements

A Individual with biomarker-positive findings

B Individual with biomarker-negative findings

Measurements were obtained using optical coherence tomography (OCT) angiography (Avanti OptoVue; OptoVue). Top images depict the angiogram with nonflow areas of 0.212 mm² (A) and 0.311 mm² (B); bottom images, OCT scans.
Figure 2. Foveal Thickness and Foveal Avascular Zone (FAZ) Measurements

Data are shown as box and whisker plots, where whiskers represent 1.5 times the interquartile range. A, Positron emission tomography (PET) imaging results are shown for fluorine 18–labeled fluorodeoxyglucose compound testing. Open circles indicate outliers. B, Cerebrospinal fluid (CSF) analysis results are shown for β-amyloid 42 and t protein biomarkers. C and D, Participants with negative findings for all biomarkers (PET and/or CSF) were compared with those with positive findings for at least 1 test.
This study suggests that cognitively healthy individuals with preclinical AD have retinal microvascular abnormalities in addition to architectural alterations and that these changes occur at earlier stages of AD than has previously been demonstrated.

Alzheimers: I see it in your eyes?

- Researchers at Duke University used OCTA to compare the retinas of Alzheimer’s patients with those of people with mild cognitive impairment, as well as healthy people.

- 122nd Annual Meeting of the American Academy of Ophthalmology, October 2018
Seventy eyes from 39 AD participants, 72 eyes from 37 MCI participants, and 254 eyes from 133 control participants were enrolled.

Alzheimer’s participants showed significantly reduced macular vessel density, perfusion density, and ganglion cell–inner plexiform layer thickness compared with MCI and controls.
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
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).
Dementia etiologies and NCD

- Any cause of dementia can also produce mild NCD.
- For example, both major and mild NCD due to Alzheimer's disease are diagnosable conditions.
In case you are not confused yet:

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
- Vascular disease
- Lewy body disease
- Frontotemporal lobar degeneration
- 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

"I WISH I NEVER KNEW THAT...."
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 Alzheimers 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
Neurocognitive Disorder due to Alzheimer's Disease

Prevalence of AD Through 2030

Alzheimer's Disease Prevalence

Year


Affected Individuals

0 1,000,000 2,000,000 3,000,000 4,000,000 5,000,000 6,000,000 7,000,000 8,000,000 9,000,000 10,000,000

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)
73 Y/P MALE, PTSD, MMS = 30 (ECD)
### 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
# Parkinson’s, Lewy Body, Alzheimer’s

<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>
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 OVERTIME

SCORE

AVERAGE TIME OF ILLNESS (years)
Vascular Dementia
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

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)
Neuropsychological Testing

Specifically designed tasks used to measure a psychological function known to be linked to a particular brain structure or pathway
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)
On average, stopping acetylcholinesterase inhibitors may have a deleterious effect on cognition and behaviors. (J Clin Psychiatry 2015;76(11):e1424–e1431)

In institutionalized Alzheimer’s 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)
- Ginkgo Biloba not supported by evidence at this time  
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

Donepezil 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)
Prevention of NCD

- Mid life hypertension increases risk of NCD.
- 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?”
Concepts of brain reserve

Neurology 53, 1942–1947
Alcohol: Often overlooked
Alcohol

- 19% of older adults that take medications that may interact with alcohol, report that they use alcohol.  

- 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
Antiarrythmics:

- 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
- Prednison
- 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)
Insomnia medications

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!
Atherosclerosis

- Vascular is a key mechanism that triggers neurocognitive disorders.
Prevention of atherosclerosis

Focus on improved endothelial function by:

- Exercise
- BP control
- Nutrition/cholesterol
Eye doctors roles:

- Eye doctors have a unique way to look directly at blood vessels, and to know when atherosclerosis is occurring.
- It will take teamwork to get patients to focus on improving vascular health.
ED = Endothelial Dysfunction
Endothelial cells

- Endothelial cells form the lining of all blood and lymphatic vessels within the vascular tree. The adult human body contains at least one trillion endothelial cells, which weigh more than 100 g and cover a surface area of more than 3000 square meters. They therefore constitute a distributed organ that forms a dynamic interface with all other organs in the body.

Endothelial dysfunction

- The loss of the endothelium's ability to regulate vascular resistance.
Endothelial Dysfunction

- The endothelium modulates tone, growth, hemostasis, and inflammation throughout the circulatory system.

- **Endothelial vasodilator dysfunction** is an initial step in atherosclerosis and is felt to be caused principally by loss of endothelium-derived nitric oxide.

How artery blockage occurs:

1. **NORMAL**
   - Adventitia
   - Media
   - Intima

2. **Atherosclerosis**
   - Lipids
   - Atherosclerotic plaque

3. **FIXED CORONARY OBSTRUCTION (Typical angina)**
   - Platelet aggregate

4. **PLAQUE DISRUPTION**
   - Thrombus

5. **SEVERE FIXED CORONARY OBSTRUCTION (Chronic ischemic heart disease)**
   - Thrombus

Healing occurs between the plaque disruption and severe fixed coronary obstruction.
Nitric Oxide

L-Arginine + O₂ → Nitric Oxide Synthase → Nitric Oxide

L-Citrulline

Inhibits platelet adherence

Inhibits leukocyte chemotaxis

Vasorelaxes

Inhibits SMC proliferation and migration

Promotes endothelial regrowth
Figure 2 | The entero-salivary circulation of nitrate in humans. Ingested inorganic nitrate and nitrite from food are converted to nitrite in the oral cavity by bacteria. Nitrite is then absorbed in the intestine and transported to the blood. An active uptake of nitrate from the blood occurs in the salivary glands. Nitrate in blood originates from the food and systemic NO production. In the gastric acidic milieu, a non-enzymatic reduction of nitrite to NO occurs. Nitrate is excreted by the kidneys.
Exercise

1. Among patients with dementia or mild cognitive impairment, randomized controlled trials (RCTs) documented better cognitive scores after 6 to 12 months of exercise compared with sedentary controls.

2. Meta-analyses of RCTs of aerobic exercise in healthy adults were also associated with significantly improved cognitive scores.

3. One year of aerobic exercise in a large RCT of seniors was associated with significantly larger hippocampal volumes and better spatial memory; other RCTs in seniors documented attenuation of age-related gray matter volume loss with aerobic exercise.

Exercise and ED:

4. Cross-sectional studies similarly reported significantly larger hippocampal or gray matter volumes among physically fit seniors compared with unfit seniors.

5. Brain cognitive networks studied with functional magnetic resonance imaging display improved connectivity after 6 to 12 months of exercise.

6. Besides a brain neuroprotective effect, physical exercise may also attenuate cognitive decline via mitigation of cerebrovascular risk, including the contribution of small vessel disease to dementia.

Hypertension: SPRINT MIND Trial

- SPRINT Memory and Cognition IN Decreased Hypertension (SPRINT-MIND) is examining whether treating to the lower blood pressure target reduces the risk of developing dementia, slows the decline in cognitive function, and results in less small vessel disease in the brain as shown by magnetic resonance imaging (MRI).
Hypertension: SPRINT MIND Trial

- Randomized Patients with cardiovascular risk factors into two groups:
  - First Group Target Systolic BP to less than 120.
  - Second Group Target Systolic BP to less than 140.

- Alzheimer’s Association International Conference in Chicago on July 25
Hypertension: SPRINT MIND Trial after 3.2 years:

- Goal SBP less than 120:
  - Seen q month x3, then q 3 months.
  - At 1 year mean sbp 121.4
  - Same brain volume as less intensive group, but 18% less white matter lesions on 4 year MRI.

- Goal SBP less than 140:
  - Seen q month x3, then q 3 months.
  - At 1 year mean sbp 136.2
Hypertension: SPRINT MIND Trial after 3.2 years:

- Goal SBP less than 120:
  - Lowered risk of Mild Cognitive Impairment by 19%
  - Lowered risk of all cause dementia by 17%
  - 18% less white matter lesions on MRI (marker of small blood vessel cerebrovascular disease).
  - 30% reduction in cardiovascular events, stroke and cardiovascular death.

- Goal SBP less than 140:
  - Higher rates of MCI
  - Higher rates of Dementia
  - Higher rates of stroke
  - More cardiovascular deaths

(9,361 patients over 50 years old, mean 68 yo, 28% over 75 yo)
Hypertension: SPRINT MIND Trial

- Brand name drugs no better than generics.
- No drug has ever produced this effect.
- Equal benefit of men and women, and all races.
- Worked as well for those over 75 as those younger!
Hypertension

Hypertension can be positively and progressively related to the risk for stroke and coronary heart disease. In some age groups, the risk of cardiovascular disease doubles for each incremental increase of 20/10 mmHg of blood pressure, starting as low as 115/75.

JAMA, 2003, 289:2560–2572
51 yo male presents with sbp 134.  

Individuals who had a systolic blood pressure of 130 millimeters of mercury (mm Hg) or over as they reached the age of 50 had a 45 percent higher risk of dementia than people with the same age and a lower systolic blood pressure.

*European Heart Journal*, Volume 39, Issue 33, 1 September 2018, Pages 3119–3125
Nutrition intervention in 51 yo

- Eliminate animal protein, including dairy products
- Increase vegetable and fruit intake
- Avoid processed grains and simple sugars
- Add milled flax seed 2 tablespoons daily

**Results at 3 months:**
- Fasting sugar decreased from 99 to 74
- Weight decreased 8.8%
- Average SBP decreased 134 to 117.
- Side effects: psoriasis disappeared, 90% reduction in migraines, energy levels increased.
Blood pressure over 3 months
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.

  Can Pharm J (Ott). 2015 May; 148(3): 150–155
Second-hand tobacco smoke. Let’s keep a sense of perspective.

Almost every day, it seems that one thing or another has been discovered to be some kind of health risk.

And this review puts the risk of lung cancer from second-hand tobacco smoke at a level well below the risk reported by other studies.
Contact

- r.sepich@nittanyvalleymed.com
- 814-574-1414