Sunday General Session

An Integrative and Molecular Approach to Better Aging

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Educational Objectives
By the end of this activity, the participant should be better able to:
1. Discuss the role of metabolic factors and mitochondria in aging.
2. Discuss the role of vitamins, micronutrients and supplements in aging.
3. Become familiar with the “MEND” protocol which use a multifaceted approach to reversing cognitive impairment and early Alzheimer’s.

Speaker Disclosure
Dr. Hausman-Cohen has disclosed that she has no actual or potential conflict of interest in relation to this topic.
Integrative Approach to Aging: A focus on the Reversal of Cognitive Decline in Alzheimer’s Disease and More

Sharon Hausman-Cohen, MD, ABIHM

With a THANK YOU to Dale E. Bredesen, MD
Professor for Neurodegenerative Disease Research,
UCLA & founder of Buck Institute

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U.S. Census 2000 by age

Alzheimer’s:

30,000,000

patients in 2012

• 3rd leading cause of death
• More prevalent than breast cancer

160,000,000

Predicted patients in 2050
Prescription Cures
But now there is a way to MEND patients

Alzheimer's Disease (AD) Therapeutic Landscape

Approved
- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Tacrine (Cognex)
- Memantine (Namenda)
- Galantamine (Razadyne)

Bapineuzumab
- Solanezumab
- Alzemed
- Flurizan
- Semagacestat
- Rosiglitazone
- Phenserine
- Dimebon
- Statins
- Antioxidant

Phase 3
- EGCG
- ELC-005

Phase 2
- NIC5-15
- PBT2
- Bryostatin-1
- EHT-0202
- BMS708163
- ABT089
- AZD3480
- PUFA
- PRX03140
- NGF
- Huperzine-A
- EVP6124
- MEM3454
- PF-04447943
- SB742457
- AL-108
- PF04360365
- ACC001
- AN1792
- CAD106

Phase 1
- GSK933776
- MABT5102A
- UB311
- R1450
- V950
- E2012
- MK0752
- CHF5074
- CTS21166
- PF-04447943
- Begacestat
- Talsaclidine
- AF102B

Clinical Trial in AD terminated

Failure Rate of New Drugs is 243 of 244

Neurons Normally have Balance Between Growth and Pruning:
Imbalance in Alzheimer’s Disease

There are MANY Factors Contributing to Brain Health and thus Many Targets for “Perfect Drug”:
- Reduce APP β-cleavage, reduce γ-cleavage, increase α-cleavage, reduce caspase-6 cleavage, reduce caspase-3 cleavage, prevent oligomerization of Aβ, increase neprilysin, increase IDE, increase microglial clearance of Aβ, increase autophagy, increase BDNF, increase NFG, increase netrin-1, increase ADNP, reduce homocysteine, increase PPARα activity, reduce phospho-tau, increase phagocytosis index, increase insulin sensitivity, improve axoplasmic transport, enhance mitochondrial function and biogenesis, reduce oxidative damage and optimize ROS production, enhance cholinergic neurotransmission, increase synaptoblastic signaling, reduce synaptoclastic signaling, improve LTP, optimize estradiol, progesterone, E2:P ratio, free T3, free T4, TSH, pregnenolone, testosterone, cortisol, DHEA, and insulin, reduce inflammation, increase resolvin, enhance detoxification, improve vascularization, increase cAMP, increase glutathione, provide synaptic components, optimize all metals, increase GABA, increase vitamin D signaling, increase SirT1, reduce NFκB, increase telomere length, reduce glial scarring, enhance repair, etc.
A Roof with 36 Holes…
Patching One Doesn’t Do Much

Work Up Of Alzheimer’s Patient (Over Simplified)

- Identify all measurable contributors to the imbalanced plasticity network (E.G.,
  - Copper:Zinc ratio > 1.3,
  - RBC Mg < 5.2,
  - hs-CRP > 1.0,
  - Homocysteine > 7,
  - Fasting insulin > 4.5
  - Free T₃ < 3.2, TSH > 2.0
- Careful History: History of mini-strokes, evidence of inflammation, mitochondrial issues, contributing diseases, Apo E4 considered, Diet considered
- Plan is personalized

CASE: 67 y.o. Woman with 2-yr History of Progressive Cognitive Decline

- Mother died with dementia, onset age 62.
- Unable to navigate on freeway.
- Could not remember what she had read.
- Unable to prepare reports for work.
- Unable to recall even 4-digit numbers.
- Retinal scan positive for amyloid
- Treated with MEND (metabolic enhancement for neurodegeneration).

55 yo Apo E 4/4 Case: Improvement on MEND (California Verbal Learning Test)

<table>
<thead>
<tr>
<th>Neurocognitive index</th>
<th>2015</th>
<th>2016 (MEND 5 mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite memory</td>
<td>1%ile</td>
<td>61%ile</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>3%ile</td>
<td>93%ile</td>
</tr>
<tr>
<td>Processing speed</td>
<td>37%ile</td>
<td>81%ile</td>
</tr>
<tr>
<td>Executive function</td>
<td>14%ile</td>
<td>58%ile</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td>16%ile</td>
<td>61%ile</td>
</tr>
</tbody>
</table>

CASE: 70 y.o. Man with 12-yr History of Accelerating Memory Loss

- ApoE4 positive (heterozygote)
- FDG-PET scan typical of AD (temporoparietal reduced Glu)
- Progressive loss: CVLT from 84%ile to 1%ile
- Unable to remember lock combination, faces, schedule
- Difficulty at work, and with numbers; Dx—early AD
- Improvement at 6 months: co-workers, schedule, faces, numbers
- Wife notes accelerated decline completely stopped.

So how does one go about developing an effective treatment for an “incurable” disease with so many contributing factors?
Dr. Bredesen’s Hypothesis:
*We may have to independently target multiple goals to design effective therapeutics.*

**Understanding Cleavage of Amyloid Precursor Protein:**

Dr. Bredesen’s work started with understanding APP. Amyloid Precursor Protein is a signaling protein

- Depending on how it is cleaved it helps to control brain plasticity.
  - It can be cleaved to signal to start a neurotrophic (synaptoblastic) cascade (nerve growth)
  - Or it can be cleaved to start a neuronal pruning cascade (synaptoclastic)

**GOAL:** Reduce APP β-cleavage, reduce γ-cleavage, increase α-cleavage and improve cognitive outcomes and feedback loops

**How Amyloid Precursor Protein is Cleaved then Triggers a Prionic Loop or Cascade of Events**

- If cleaved at the alpha site the two α peptides derived mediate neurite extension and inhibit Aβ production, caspase activation and programmed cell death
- If cleaved at the beta site Aβ, Jcasp, C31 are formed and they have been shown to mediate neurite retraction, synaptic inhibition, caspase activation and trigger programmed cell death
- In other words APP appears to function as a “molecular switch” mediating plasticity related processes and AD is associated with increase in the ratio of neurite retractive peptides to the neurite extending peptides.

**Pushing Cleavage of APP Down the Alpha Synaptoblastic Path:**

- There are many metabolic/environmental conditions and other supplements that push APP down the path to “trophic” cleavage. For example:
  - Ashwagandha and Curcumin directly effects cleavage toward trophic synapse building pathway
  - Inflammation pushes towards pruning (Beta) cleavage
- Addressing this pathway is just one step of MEND

**He also showed ApoE4 was a Transcription Factor or Promoter – Lots More Targets**
Addressing Molecular Mechanisms

- Approach: Fill as many of those holes as possible simultaneously. “MEND – metabolic enhancement for neurodegeneration”
- Alzheimer’s researchers have mapped the many molecular mechanisms of cognitive decline and AD – which were used to create treatment protocol.
- These include dozens of interventions, beginning with DESS (diet, exercise, sleep, stress), hormonal optimization, nutrients, targeted herbs, brain stimulation, drugs, etc.

Examples of Factors that Increase Autophagy and BDNF

- Exercise Increases Brain Derived Neurotrophic Factor -30-60 min a day
- Intense exercise is best
- Fasting 12 hrs minimum at night helps promote “clean up” in the brain (autophagy)
- Sleep 8 hr a night

Enhanced Mitochondrial Function and Biogenesis

- Mitochondria are the main sources of Brain ATP.
- There are a lot of mitochondrial nutrients that improve function and biogenesis
  - CoQ10
  - NAC
  - Acetyl L Carnitine
  - Alpha Lipoic Acid
  - B Vitamins
  - Minerals

Consider combination products

NADH also helps to decrease ROS

The Perfect Alzheimer’s Drug Would:

Reduce APP β-cleavage, reduce γ-cleavage, increase α-cleavage, reduce caspase-6 cleavage, reduce caspase-3 cleavage, prevent oligomerization of Aβ, increase neprilysin, increase IDE, increase microglial clearance of Aβ, increase autophagy, increase BDNF, increase NGF, increase netrin-1, increase ADNP, reduce homocysteine, increase PP2A activity, reduce phospho-tau, increase phagocytosis index, increase insulin sensitivity, improve axoplasmic transport, enhance mitochondrial function and biogenesis, reduce oxidative damage and optimize ROS production, enhance cholinergic neurotransmission, increase synaptoblastic signaling, reduce synaptoclastic signaling, improve LTP, optimize estradiol, progesterone, E2:P ratio, free T3, free T4, TSH, pregnenolone, testosterone, cortisol, DHEA, and insulin, reduce inflammation, increase resolvins, enhance detoxification, improve vascularization, increase CAMP, increase glutathione, provide synaptic components, optimize all metals, increase GABA, increase vitamin D signaling, increase SirT1, reduce NFκβ, increase telomere length, reduce glial scarring, enhance repair, etc.

Increase Insulin Sensitivity, HgA1c <5.5, Insulin <7- Important in Decreasing Inflammation

- Low Carbohydrate diet can help with this
- Weight loss
- Weight loss
- Weight loss
- Weight loss
- Metformin
- Berberine

Addressing Cortisol – Ashwagandha

- Decreases cortisol levels significantly (24% reduction) p = .0006
- BONUS: Significant reduction (P<0.0001) in scores on all the stress-assessment scales on Day 60, relative to the placebo group.
- We also know that meditation and yoga reduce cortisol and help cognition
- Usual dose is 500 mg twice a day
- With max 1000 bid
- Also increases blood flow
Ashwagandha and APP Cleavage

- Ashwagandha is from Withania Somnifera plant
- Has been shown to improve memory in adults in their 40s and 50s (with mild memory symptoms)
- Trophic Amyloid cleavage
- Ashwagandha to increase receptor-mediated clearance of amyloid-β
- Caution with blood thinners (mild anti-platelet), can lower BP


Ashwagandha In Vivo Rat Studies (Done in Japan):

- Rats were pretreated with injection of Aβ25–35 (in to the ventricles) which caused densities of axons and synapses in the parietal cortex to be reduced, and spatial memory of the mice was diminished
- Consecutive oral administration of withanolide A, withanoside IV, or withanoside VI for 12 d increased the densities of axons and synapses in the parietal cortex and improved spatial memory deficit.


Address Inflammation: Curcumin

- Potent anti-inflammatory (benefits in Arthritis and anti cancer properties/ studies)
- Decreases hs-CRP
- Also Promotes Alpha pathway of APP- not Aβ cleavage
- Usual dose 500 mg twice a day
- Use an activated form such as Meriva, C3 or a micronized curcumin for better absorption (500 bid)

References:

Reduce Inflammation: hs-CRP (Goal <1)

- Intense exercise helps to lower CRP
- Curcumin lowers CRP by 6.4 mg/l (p= .004) in a meta-analysis of individuals with elevated CRP. * Usual dose is 500 mg twice a day
- bioavailable forms include Curcumin-phosphatidyl choline and C3
- Quercetin 500 mg with Vitamin C 250 mg lowered CRP in those with mild elevation (1.4 to .8). Had to take together.
- N-acetyl cysteine (NAC) 600 mg twice a day can have a huge effect on hs-crp (24 baseline, 5.2 treatment in dialysis patients), other studies in non renal patients. (NAC also helps with detox/glutathione)
- EGCG (Green Tea Extract) can lower CRP from inflammation
  - Minerals decrease absorption (calcium/potassium)
  - Take with food as can otherwise cause stomach upset

References:
  http://www.lifeextension.com/magazine/2014/5/Testing-For-C-reactive-Protein-May-Save-Your-Life/Page-01

MORE CRP LOWERING OPTIONS

- Omega 3 fatty acids; Lowered hs-CRP and depression scores in shift workers and low omega 3s correlate with higher CRP in PAD patients
- Ginger reduced hs-crp in diabetic adults
- Other Correlations:
  - Higher magnesium levels correlate with lower CRP in overweight middle aged women
  - Probiotics lowered CRP in diabetics
  - Vitamin E, Zinc, mixture of resveratrol, pterostilbene, quercetin, delta tocotrienol and nicotinic acid reduced CRP 29% in healthy seniors

References:
  http://www.lifeextension.com/magazine/2014/5/Testing-For-C-reactive-Protein-May-Save-Your-Life/Page-01
Improve Synaptogenesis: Citicoline or CDP-Choline

• Has been shown to help with synaptogenesis after strokes or other damage and with cognition.
• Usual dose 250-500 mg -2 times a day

References/Mechanisms on Citicoline (Action in Post Stroke)

<table>
<thead>
<tr>
<th>Enzyme cascade level</th>
<th>Citicoline putative mode of action</th>
<th>Main effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytidine kinase</td>
<td>Synaptogenesis is the final stage of neural development and refers to the formation of the synapse.</td>
<td>Between neurons</td>
<td>Brain Sci. 2013, 3</td>
</tr>
<tr>
<td></td>
<td>1. between neurons</td>
<td>Between neurons and muscle cells</td>
<td></td>
</tr>
</tbody>
</table>

Improve Synaptic Integrity: Citicoline or CDP-Choline

• Usual dose 250-500 mg -2 times a day
• Other actions of citicoline with cognition:
  - Enhance the processes of inhibition of apoptosis
  - Neurogenesis
  - Angiogenesis
  - Nerve sheath regeneration
  - Modulation of neurotransmitters

Notice that all these effects are similar to those induced by stem cells.

Increase Vitamin D Signaling: Vitamin D is Needed for Making Neurotransmitters

Vitamin D deficiency accelerates aging

Vitamin D and K2

• Goal: 25-OH-D3 50-80ng/ml, with vit K2.
• Lower vitamin D concentrations are associated with poorer cognitive function and a higher risk of AD.
• Vit D Associated with the synthesis of serotonin and neurotransmitters
• Vitamin K2 essential for the synthesis of sphingolipids. Present in high concentrations in brain cell membranes, sphingolipids are now known to possess important cell signaling functions in addition to their structural role. In the past 20 y, additional support for vitamin K functions in the nervous system has come from the discovery and characterization of vitamin K–dependent proteins that are now known to play key roles in the central and peripheral nervous systems. Notably, protein Gas6 has been shown to be actively involved in cell survival, chemotaxis, mitogenesis, and cell growth of neurons and glial cells.
Activating Sirtuins (SIRT Genes)

- Sirtuins are “anti-aging” genes
- Promote not only younger healthier brain but also organs (autopsy studies on rats)
- Resveratrol and Pterostilbene activate these genes
- NADH/NAD helps

Pterostilbene Other Mechanisms

- Inflammation:
  - Pterostilbene was shown to reduce both iNOS and COX2 expression
  - Pterostilbene lowered the production of inflammatory cytokines TNFα, IL-1β and IL-4
- Metabolic:
  - Lowers blood glucose levels (stimulates PPAR-alpha pathway)
  - Lowers cholesterol (LDL) levels
- Improved working memory
- Anti-oxidant: Pterostilbene protected against the decrease in dopamine release following oxidative stressor.
- Also Activate Sirtuin gene (anti-aging gene) …as discussed


Review: Basic Concepts of MEND 3.0 LIFESTYLE

<table>
<thead>
<tr>
<th>Goal</th>
<th>Approach</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimize diet: Minimize simple CHO, minimize inflammation</td>
<td>Choice of several low glycemic index, low inflammatory, low grain diets</td>
<td>Minimize inflammation, minimize insulin resistance</td>
</tr>
<tr>
<td>Enhance autophagy, ketogenesis</td>
<td>Fast 12 hrs each night including 3 hrs before bed</td>
<td>Reduce insulin, Reduce A beta</td>
</tr>
<tr>
<td>Reduce Stress</td>
<td>Yoga, meditation, music etc.</td>
<td>Reduce cortisol, CRF, stress axis</td>
</tr>
<tr>
<td>Optimize Sleep</td>
<td>8 hrs of sleep per night, melatonin 5 mg qhs, Trp 500 mg po qhs 3x/week if awakening, n’t sleep apnea</td>
<td>BDNP production</td>
</tr>
<tr>
<td>Exercise</td>
<td>30-60 min/day 4-6 days a week</td>
<td></td>
</tr>
<tr>
<td>Brain Stimulation</td>
<td>Posit, or related</td>
<td></td>
</tr>
</tbody>
</table>

Basic MEND 3.0 Vitamin/Metabolic

<table>
<thead>
<tr>
<th>Goal</th>
<th>Approach</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum B12 &gt;500</td>
<td>Methyl B12</td>
<td>30% less progression MCI AD</td>
</tr>
<tr>
<td>Fasting insulin &lt;7</td>
<td>Diet as above (meds if needed)</td>
<td>Type 2 DM-AD relationship</td>
</tr>
<tr>
<td>Homocysteine &gt;7</td>
<td>Me-B12, MTHF, PSP, TMG if necessary</td>
<td></td>
</tr>
<tr>
<td>Vitamin D (25-OH) 50-100 ng/ml</td>
<td>Vitamin D3, Vitamin K2</td>
<td>Neurotransmitter synth and memb</td>
</tr>
<tr>
<td>CRP &lt;1.0 A0&lt;1.5</td>
<td>Anti-inflammatory diet, curcumin, DHA/EPA, optimize hygiene, other supplements</td>
<td>Inflammation is bad</td>
</tr>
<tr>
<td>Optimize Zn/Cu ratio</td>
<td>Depends on values obtained Goal Cu:Zn&lt;1.3</td>
<td></td>
</tr>
<tr>
<td>Hormone Balance (thyroid and sex hormones)</td>
<td>Optimize FT3, FT4, E2, T, progesterone, pregnenolone, cortisol</td>
<td>Trophic nature of hormones</td>
</tr>
</tbody>
</table>

Basic MEND 3.0 Mitochondria, SirT1, Neuronal

<table>
<thead>
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<th>Approach</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Reduction of A-Beta</td>
<td>Curcumin, Ashwagandha</td>
<td></td>
</tr>
<tr>
<td>Cognitive Enhancement</td>
<td>Bacopa monniera, MgT</td>
<td></td>
</tr>
<tr>
<td>*Provide Synaptic Structural components</td>
<td>Choline, DHA, resolvins</td>
<td></td>
</tr>
<tr>
<td>Optimize anti-oxidants</td>
<td>Mixed tocopherols and tocotrienols, Se, blueberries, NAC, Vit C, ALA</td>
<td></td>
</tr>
<tr>
<td>*Optimize Mitochondrial function</td>
<td>CoQ10 or ubiquinol, ALA, PDO, NAC, ALCAR, Se, Zn, resveratrol, Vit C, thiamine</td>
<td></td>
</tr>
<tr>
<td>Increase SirT1 function</td>
<td>Resveratrol, Pterostilbene</td>
<td></td>
</tr>
<tr>
<td>Exclude heavy metal toxicity</td>
<td>Evaluate Hg, Pd, CD; chelate if indicated</td>
<td>CNS effects of heavy metals</td>
</tr>
</tbody>
</table>
Treating Cognitive Impairment and Alzheimer’s will Take an Integrative Approach

MEND 3.0: Want to Learn More

• Website of Dr. Bredesen’s research for patients and physicians: MPIcognition.com
• Review Article: Protocol Published in Aging, September 2014, Vol 6 No. 9
• There is lots of research on his website and trainings for those interested in learning more!

Basic Concepts of MEND 3.0 (cont’d)
• A key component of the program is that it addresses many targets.
• Drugs can be used in conjunction but are not the main solution.
• The earlier you treat, the greater your chance for reversal. TEST with SLUMS or MoCCA
• As the metabolic parameters improve, so goes the cognition.
• You do not usually need to do every step. – Use patient history to guide you as to which are most likely contributing factors

Characteristics of Success
• Diligence with program
• Attention to detail
• Improvement in lab values
• Supportive spouse or significant other
• Follow-up
• Repeated optimization
• Helpful physician

Characteristics of Reduced Success
• Lack of diligence with program
• Lack of attention to detail
• Lack of improvement in lab values
• Delay in starting program until late in the illness
• Lack of follow-up
• Assuming the first phase is the final plan
• Unhelpful physician (i.e.; if you don’t feel comfortable helping patients with this protocol consider referring)

Alzheimer’s Barriers to Care
• PATIENTS do not tend to seek medical care early
  • Fear loss of driver’s license or independence
  • Been told there is nothing that can be done
  • Stigma of a diagnosis
  • inability to obtain long-term care
• PHYSICIANS options have been limited:
  • Neuropsychological testing
  • Expensive imaging
  • Little or nothing to offer therapeutically
  • Patients treated with acetylcholinesterase inhibitors but minimal improvement at best.
“We build too many walls and not enough bridges.”

–Sir Isaac Newton

Thank You!