New Alternative and Complementary Treatment Options & Strategies for Alzheimer’s Disease

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Disclaimer

• There are positive and negative findings for every treatment option & risk factor for AD.

• We are discussing some research-based treatments & approaches that may still be under investigation and/or may not have received FDA approval.

• Dr. Nejtek is a Cognitive & Behavioral Neuroscientist working as a Clinical Researcher – not a treating clinician.
Goals of the Talk

✓ Discuss the role of alternative & complementary treatment options for Alzheimer’s Disease (AD):
   A paradigm shift in treatment research

✓ Identify prevention, intervention, and integrative treatment strategies to discuss with your physician:
   A life history approach

✓ To provide information for you to better understand the impact of daily living creating undue risks for AD:
   It’s not all genetic!
AD – a irreversible (so far) and progressive brain disease with horrific short-term memory loss + devastating decision-making impairments.

- 5 million Americans with AD diagnosis
- 40 million world-wide
- 6th leading cause of death in the US
- 10 million Americans with AD expected in 20-years
- 28 million Baby Boomers with AD expected by 2050
- 115 million world-wide with AD expected by 2050
1993:
The 1st cholinesterase inhibitor with FDA-approval - Cognex (tacrine) – mild to moderate AD

2013:
FDA withdrew Cognex in US –
Adverse Side Effects, Safety concern – liver toxicity
In the last 20-years, FDA has approved 5 drugs - the most recent in 2003!

Drugs developed as an *intervention* – when the disease had already caused damage

when symptoms were clearly present

Temporarily treats symptoms
Does not stop the underlying mechanism of the disease

– which is still under investigation
The 5 Current FDA-approved Medications for AD

**Cholinesterase inhibitors – mild to moderate AD**

1. Razadyne (galantamine)
2. Exelon (rivastigmine)
3. Aricept (donepezil)

**N-methyl D-aspartate (NMDA) antagonist – moderate to severe AD**

4. Namenda (memantine)

**Cholinesterase + NMDA Combination**

5. Namzaric *(memantine extended release + donepezil)*
So why aren’t more medications available?
PRE-CLINICAL

Drug Sponsor’s Discovery and Screening Phase

1. **Drug Developed**
   - Drug sponsor develops a new drug compound and seeks to have it approved by FDA for sale in the United States.

2. **IND Application**
   - The sponsor submits an Investigational New Drug (IND) application to FDA based on the results from initial testing that include the drug’s composition and manufacturing, and develops a plan for testing the drug on humans.

Animals Tested
- Sponsor must test new drug on animals for toxicity. Multiple species are used to gather basic information on the safety and efficacy of the compound being investigated/researched.

**IND REVIEW**
- FDA reviews the IND to assure that the proposed studies, generally referred to as clinical trials, do not place human subjects at unreasonable risk of harm. FDA also verifies that there are adequate informed consent and human subject protections.

CLINICAL

Drug Sponsor’s Clinical Studies/Trials

3. **Phase 1**
   - The typical number of healthy volunteers used in Phase 1; this phase emphasizes safety. The goal here is to determine what the drug’s most frequent side effects are and, often, how the drug is metabolized and excreted.

4. **Phase 2**
   - The typical number of patients used in Phase 2; this phase emphasizes effectiveness. This goal is to obtain preliminary data on whether the drug works in people who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment—usually a placebo, or a different drug. Safety continues to be evaluated, and short-term side effects are studied.

   At the end of Phase 2, FDA and sponsors discuss how large-scale studies in Phase 3 will be done.

5. **Phase 3**
   - The typical number of patients used in Phase 3. These studies gather more information about safety and effectiveness, study different populations and different dosages, and uses the drug in combination with other drugs.

6. **Phase 4**
   - Post-marketing surveillance trials that occur after a drug has been approved and is on the market.

**FDA’s Center for Drug Evaluation and Research (CDER)** evaluates new drugs before they can be sold.

The center’s evaluation not only prevents quackery, but also provides doctors and patients the information they need to use medicines wisely. CDER ensures that drugs, both brand-name and generic, are effective and their health benefits outweigh their known risks.
**NDA REVIEW**

**Drug Labeling**
FDA reviews the drug's professional labeling and ensures appropriate information is communicated to healthcare professionals and consumers.

**Application Reviewed**
After an NDA is received, FDA has 60 days to decide whether to file it so it can be reviewed. If FDA files the NDA, the FDA Review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness.

**NDA Application**
The drug sponsor formally asks FDA to approve a drug for marketing in the United States by submitting an NDA. An NDA includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured.

**Review Meeting**
FDA meets with a drug sponsor prior to submission of a New Drug Application.

**Facility Inspection**
FDA inspects the facilities where the drug will be manufactured.

**Drug Approval**
FDA reviewers will approve the application or issue a response letter.

**FASTER APPROVALS**
The Accelerated Approval program allows earlier approval of drugs that treat serious diseases and that fill an unmet medical need. The approval is faster because FDA can base the drug's effectiveness on a "surrogate endpoint" such as a biomarker or an efficacy measure, rather than waiting for results from a clinical trial.

**Drug Approval**
FDA reviews the drug's safety and effectiveness. Once FDA approves a drug, the post-marketing monitoring stage begins. The sponsor (typically the manufacturer) is required to submit periodic safety updates to FDA.

**PDUFA**
Prescription Drug User Fee Act
Since the PDUFA was passed in 1992, more than 1,000 drugs and biologics have come to the market, including new medicines to treat cancer, AIDS, cardiovascular disease, and life-threatening infections.

**POST-MARKETING**

**FDA's Post-Approval Risk Assessment Systems**
Because it's not possible to predict all of a drug's effects during clinical trials, monitoring safety issues after drugs get on the market is critical. The role of FDA's post-marketing safety system is to detect serious, unexpected adverse events and take definitive action when needed.

**MedWatch**
FDA's MedWatch voluntary system makes it easier for physicians and consumers to report adverse events. Usually, when important new risks are uncovered, the risks are added to the drug's labeling and the public is informed of the new information through letters, public health advisories, and other education. In some cases, the use of the drug must be substantially limited. And in rare cases, the drug needs to be withdrawn from the market.

* The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be $2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

FDA Approval Process

Drug Discovery, Development, Approval

It takes ~12-20-years from bench to bedside

Only 5 out of 5000 compounds tested in animals will be tested in humans

Only 1 out of 5 drugs receives FDA-approval
Clinicaltrials.gov

Alzheimer’s Disease Research –

93 agents in drug development (phase I, II, III)

Most target amyloid or tau mechanisms but…

Eli Lilly’s Experimental Alzheimer’s Drug Fails in Large Trial - July, 2016

The A4 Study:
Anti-Amyloid Treatment in Asymptomatic Alzheimer’s

Solanezumab – targeted amyloid plaques – the presumed hallmark characteristic of AD in mild or moderate AD

No benefit in moderate AD, but may benefit mild AD
Many other clinical trial failures or falters based on amyloid hypothesis

As of August 2014, out of 16 different drug trials, 7 have been discontinued or terminated

Morris, Clark, and Vissel, 2014
Alzheimer’s Drug LMTX Falters in Final Stage of Trials - July, 2016

Targeting Tau Microtubule Tangles:

TauRx: LMTX results - (15% of 891 subjects benefited)

Others Targeting Tau
Genentech/Roche: Crenezumab
Axon Neuroscience SE: AADvac1
AC Immune AG: ACI-35
Hoffmann-La Roche: RG7345

Panza et al, 2016
Clues from *Cognitively Normal Elderly* -

**Study 1:** Up to 40% have some type of neural pathology meeting criteria for AD

**Study 2:** 10-30% have amyloid-positive brain scans

**Study 3:** Some non-demented elderly have same plaque build-up as demented patients

**Study 4:** Neurodegeneration can occur w/o plaque build-up

**Study 5:** Up to 50% AD cases have mixed neural pathologies

*Morris et al, 2014*
“Whenever a theory appears to you as the only possible one, take this as a sign that you have neither understood the theory nor the problem which it was intended to solve”

-- Karl Popper
Complementary –
pairing conventional medicine with another type of treatment / therapy (*non-traditional*)

Integrative –
combining several treatments / therapies to comprehensively heal the whole body (*lifestyle*)
"Health is a state of complete physical, mental, & social well-being and not merely the absence of disease or infirmity"

--- World Health Organization
Hundreds of studies are now testing alternative hypotheses involving a variety of proteins, mutations, neural, & physiological mechanisms associated with neurodegeneration, cognitive decline, and other AD pathologies…

Alternative Hypotheses

Inflammation

- Inflammatory Cytokines –
  - may precede amyloid and tau
  - dysregulates glial cell functioning & plasticity

Blood sugar metabolism

- Insulin Resistance –
  - abnormal response to glucose
  - neural synaptic dysfunction in memory brain areas

Morris et al, 2014; De Felice et al, 2014; Rubio-Perez & Morillas-Ruiz, 2012
Alternative Hypotheses

Some ‘off-label’ research shows

- Non-steroidal anti-inflammatory drugs (NSAIDs) may reduce amyloid plaque
- Insulin resistance drugs may protect synaptic brain tissue & functioning

Morris et al, 2014; De Felice et al, 2014; Rubio-Perez & Morillas-Ruiz, 2012
Using insulin to treat AD????

Study of Nasal Insulin to Fight Forgetfulness (SNIFF)

Clinical Trial Protocol ID: 13090401
Clinical Trial Investigator Name: Neelum T. Aggarwal, MD
Rush University Medical Center

Clinical Trial Protocol Description:

18-month study is to determine whether a type of insulin, when administered as a nasal spray, improves memory in adults with mild cognitive impairment or AD.
Alternative Hypotheses
Lithium ‘Off-label’ Use

One study –
lithium reduced dementia in 87% of patients w/ mood disorders compared to patients on other medications

Three randomized placebo trials –
lithium reversed severity of AD symptoms

Two in-vitro studies –
lithium increased brain-derived neurotropic factor blocks harmful proteins that create tau protein

Mauer et al., 2014; Leeds et al., 2014; Yu et al., 2012; Hampel et al., 2009; Hooper et al., 2008, Angst et al., 2007
Hypotheses about the gut-brain axis

Gut microbes can produce neurotransmitters:
These neurotransmitters might signal the brain via the vagus nerve.

Gut microbes can stimulate immune cells to produce cytokines:
These cytokines might travel to the brain via blood vessels of the circulatory system.

Gut microbes can produce metabolites:
These metabolites might travel to the brain via blood vessels or stimulate gut epithelial cells to produce neurotransmitters that activate the vagus nerve.
Hypothesis

The Bidirectional Gut-Brain Axis

The ability of the brain to influence the intestinal microbiota

Perturbation of your normal habitat via stress-induced changes in gastrointestinal:
- Physiology
- Epithelial function
- Mucin production
- EE cell function
- Motility
- Release of Neurotransmitters

The ability of the microbiota to influence brain, behavior, and mood

Activation of neural pathways to the brain

Activation of mucosal immune responses

Production of metabolites that directly affect the CNS


- Neuroendocrine
- Food Absorption
- Metabolism
- Pain Perception
- Stress Response
- BDNF
- Omega 3 PUFAs
Most common bacteria that fulfill the microbiota

The Firmicutes are the largest phylum include:

- Lactobacillus
- Mycoplasma
- Bacillus and Clostridium

Actino-bacteria

Bacteroides

Mycoplasma

http://www.slideshare.net/SauravDas4/gut-microbiota-27829610?next_slideshow=2
• Over **200** species live on you daily.
• Most are in your **digestive** tract.
• They stimulate the **immune** system, aid in bodily processes, some make **vitamins**, some inhibit and kill other bad **bacteria**.
Bacterial Diversity is Affected by Aging

Ottmann N et al. Front Cell Infect Microb 2012
Flavonoids, Polyphenols

Believed to reduce neural degeneration, inflammation, oxidative stress, and reduce risks for AD

Where do you find flavonoids?

Green tea  Broccoli
Soy         Celery
Berries     Chocolate
Citrus fruits  Tomatoes
Onions      Leeks

--- just to name a few

Baptista et al., 2013; Hu, Wang, and Jin, 2016
Where do you find polyphenols?

<table>
<thead>
<tr>
<th>Coffee</th>
<th>Cocoa Powder</th>
<th>Fruits/Berries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinach</td>
<td>Cloves</td>
<td>Oregano</td>
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<tr>
<td>Rosemary</td>
<td>Coconut Flour</td>
<td>Thyme</td>
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<tr>
<td>Peppermint</td>
<td>Spearmint</td>
<td>Basil</td>
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<tr>
<td>Pecans</td>
<td>Almonds</td>
<td>Beans</td>
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</tbody>
</table>

...just to name a few

Hu, Wang, and Jin, 2016
Ginkgo Biloba –

a centuries old plant extract
antioxidant and anti-inflammatory properties
cell membrane protection
regulator or neurotransmitter functioning

Used in traditional Chinese medicine for a variety of ailments
Used in Europe for cognitive problems

Literature shows mixed results –

Kelley and Knopman, 2008
NIH Funded - Large, multicenter Phase 3 clinical trial

The \textbf{Ginkgo Evaluation and Memory (GEM) Study} –

Randomized, placebo control

3,000 individuals, 75-years or older, no signs of dementia or had MCI

Placebo versus 120 milligrams of daily ginkgo biloba extract

Followed up every 6-months for 6-years

Ginkgo was no better than a placebo in preventing or delaying AD

DeKosky et al., 2006
Ginkgo biloba versus Donepezil Study:

Double-blind, randomized, placebo controlled trial
60 Patients, 50-80-years old, mild to moderate dementia
Longitudinal, 24-weeks
Ginkgo (160mg) vs. Donepezil (5 mg) vs. Placebo

Ginkgo performed similarly to Donepezil (no significant differences)

Ginkgo and Donepezil performed better than placebo

Caveat- very small sample size

Mazza, Capuano, Bria and Mazza, 2006
Acetyl-L-carnitine –

Study 1: Double-blind, randomized, placebo controlled trial
12-months, 431 ‘probable’ AD patients
No improvements – EXCEPT in younger patients

Study 2: Double-blind, randomized, placebo controlled trial
12-months, 197 early-onset AD, 45-65 years old
No improvements

Study 3: Meta-analyses of 21 randomized, placebo control trials
3-12-months each trial, 1204 mild AD or MCI
Significant improvements

Kelley and Knopman, 2008
Lecithin –

Meta-analysis: 10 clinical trials – no info on study design
265 patients with AD – no info on severity
No improvements

Huperzine A –

Meta-analysis: 10 randomized, placebo control clinical trials,
12-24-weeks, 92 vascular dementia patients,
60-85-years old
8-24 weeks, 733 AD patients, 50-90-years old

Questionable improvements due to large variability in illness severity among the trials for each disease

Huperzine A

The Alzheimer's Disease Cooperative Study

Conducted 1st large-scale U.S. clinical trial

Treatment for mild to moderate AD

No greater benefit than placebo
Curcumin - a natural polyphenol product derived from the rhizome of the Indian spice turmeric (Curcuma longa)

Bench and Animal studies suggest curcumin:

- has antioxidant properties
- inhibits amyloid beta (Aβ) production and tau-regulation
- facilitates neuroprotection particularly dopamine neurons
- promotes neural growth, connectivity
- facilitates spatial memory

Tiwari et al., 2013
Curcumin - Clinical Trial NCT00099710

- Double-blind, randomized, placebo controlled trial
- First 24-weeks – placebo, 2 grams / day, 4 grams / day
- Second 24-48-weeks - open –label extension
- 73-years old, 36 patients with mild to moderate AD

No differences among treatment groups – no improvements

Caveat – small sample size and mix of AD severity levels

Ringman et al., 2012
Caprylic acid (clinically tested as Ketasyn [AC-1202] and marketed as a “medical food” called Axona® & coconut oil

Two primary theories behind Axona –

Alternative energy source for brain cells that have lost their ability to use glucose (sugar) in AD

Reduced glucose found in brain regions affected by AD

Phase II clinical trial – 152 patients with mild to moderate AD
Allowed adjunctive FDA-approved AD drugs

**Axona reports:**

Ketasyn resulted in better memory and overall functioning than placebo

Effectiveness, safety, purity ???
Can have serious interactions with current medications
“Coral” calcium supplements
Heavily marketed as a cure for Alzheimer’s disease
Federal Trade Commission (FTC) and FDA have filed formal complaints

Coenzyme Q10 (idebenone)
An endogenous antioxidant needed for normal cell reactions
Tested in AD, but showed no benefits
Vitamins & Supplements

**Vitamin E** - from food (rather than supplements) reduces AD risk

**Niacin** - from (food & supplements) associated w/ fewer incidents of AD [after adjusting for age, sex, education, & APOE-4]

**B12 & Folate** - low levels are associated w/ increased AD risk

Engelhart et al. 2002; Martin & Mayer, 2003; McCabe et al. 1994; Morris et al. 2003, 2005; Young & Ma, 1999; Khachaturian et al. 2006; Wang et al. 2001
Exercise Is Medicine
move to prevent diabetes, heart disease, arthritis
and to Reduce Risks for Alzheimer’s Disease!!
How Much Exercise?
You need to get your heart pumping!!!

General Findings:

Regular physical activity / exercise decreases risks for AD

Minimum - 15-min / day x 3-days / week
Optimal - 30-min / day x 6-days / week

increase cellular functioning

Walking, Biking, Aerobics, Calisthenics, Swimming, Golfing, etc.

Larson et al. 2006; Laurin et al. 2001; Podewils et al. 2005; Wang et al. 2002
EXERT study: Building Memories Through Exercise

Clinical Trial Protocol ID: 16052408
Clinical Trial Investigator Name: Neelum T. Aggarwal, MD

Clinical Trial Protocol Description: 18-month trial
Tests whether exercise improved memory and thinking abilities in older adults with mild memory loss.

Random assignment to aerobic exercise versus stretching / balance / range of motion exercise program
Social Connection
well-being | community engagement

and Reduces Risks for Alzheimer’s Disease!!
What Kind of Social Connection?

**PAQUID study:**
Traveling, Visiting friends / family, Playing parlor games, Gardening, Knitting, Quilting / Sewing, Crocheting

**Kungsholmen study:**
Reading, Writing, Crosswords, Painting/Drawing, Cooking, Theater, Concerts, Art Exhibitions, Part-time jobs, or Volunteering

Fabrigoule et al. 1995; Lindstrom et al. 2005; Wang et al. 2002
The Social Connection & Cognitive Functioning

The Religious Orders Longitudinal Study:

40 Groups in U.S. = >800 nuns, priests, brothers age 65-yrs & older

Cognitive activity = listening to radio, reading, playing games, and going to museums.

Created summed 5-point scale on frequency of events

Derived an average mean number of events during past year

- 5 pts = every day or about every day;
- 4 pts = several times per week
- 3 pts = several times per month
- 2 pts = several times per year
- 1 pt = once / year or less.

Wilson et al. 2002
The relative risk of developing AD decreased by 33% for each 1-point increase in composite measure of cognitive activity!!
Another study found that for every hour of increased TV viewing in middle-adulthood during the lifetime corresponded to a **1.3 times elevated risk of AD!!**

**Mr. Potato Head strikes again...**

Lindstrom et al, 2005
MUSIC & THE BRAIN

Healing Powers
Listening to music can decrease anxiety, speed healing, increase optimism and decrease pain.

Incredible Memory for Sounds
Alzheimer’s patients can recall and sing songs long after they’ve stopped recognizing names and faces. There is growing evidence that listening to music can help stimulate seemingly lost memories and even help restore some cognitive function.

Creativity Boost
Music boosts creative energies through the production of alpha and theta waves. Large influxes of alpha waves induce states of enhanced creativity while theta waves are associated with dreaming, learning and relaxing.

The key for boosting creative energies is to listen to the type of music you enjoy the most. If you want more inspiration in language and mathematics, it would make sense to listen to music with singing, while music without words stimulates more artistic and visual senses.

Music Taps Into Primal Fear
There are certain sounds that humans automatically associate with death because they tap into our evolutionary fear of the screams of other animals (and other human beings). Scientists have dubbed these “discordant noises.” Any noise that makes you feel very unpleasant falls into this category.

We know if we hear other living things making those discordant noises that we have to react because something bad is going to happen. Movie directors know this and make good use of it when deciding on the score for a film.

Babies Know Happy From Sad Songs
Babies as young as 5 months can distinguish an upbeat tune, such as “Ode to Joy” from Beethoven’s Ninth Symphony, from a lineup of gloomy tunes.

The Mozart Effect
It’s been thought that listening to classical music, particularly Mozart, enhances performance on cognitive tests. However, recent findings show that listening to any music that is personally enjoyable has positive effects on cognition.

“Sound is a nutrient for the nervous system. Love your ears...they are much more important than you ever realized.”
Prof. Dr. Alfred Tomati

https://www.youtube.com/watch?v=IaB5Egej0TQ
Predicting the Future of AD Treatments is Impossible, But…

You Should Now Have a Better Understanding About…

- New Alternative Hypotheses Being Tested
- Complementary & Integrative Treatments
- Health Benefits of an AD-related Diet
- Importance of Being Physically Active
- Advantages of Social Connections
- Avoiding Undue Risks for AD Onset
- Where to Find Clinical Trials & Results
The NCCIH Clearinghouse provides information on NCCIH and complementary and integrative health approaches, including publications and searches of Federal databases of scientific and medical literature.
Toll-free in the U.S.: 1-888-644-6226
TTY (for deaf and hard-of-hearing callers): 1-866-464-3615
Web site: nccih.nih.gov
E-mail: info@nccih.nih.gov

National Institute on Aging (NIA)
NIA is the NIH institute that focuses on supporting and conducting high-quality research on aging processes, age-related diseases, and special problems and needs of the aged. NIA publications include Hormones and Menopause: Tips from the National Institute on Aging.
Web site: www.nia.nih.gov

Office of Dietary Supplements (ODS), National Institutes of Health (NIH)
ODS seeks to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, supporting research, sharing research results, and educating the public. Web site: ods.od.nih.gov
E-mail: ods@nih.gov
There Are No Miracles in a Bottle…yet

Be An Informed Health Consumer

Be Bold in Talking to Your Doctor About the Newest Research & Treatment Options

Don’t Be Gullible or Naïve About Marketing Claims

Take Care of Your Brain by Nurturing Your Mind, Body, & Spirit
WONDERFUL EFFECT OF MORRISON'S VEGETABLE PILLS

They told me if I took 1000 pills at night I should be quite another thing in the morning.