Alzheimer's Disease Center at the Sanders-Brown Center on Aging

Alzheimer's Tennessee

Advances in Alzheimer's & Dementia Research (non-amyloid)

Greg Jicha, MD, PhD
McCowan Endowed Professor of Neurology
University of Kentucky ADRC




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Disclosures

(Only those related to Aβ treatments listed here)

- **Grants**
  - NIH P30 AG072946, U24 AG057437, R01 AG053798, R01 AG063689, U19 AG010483, R01 AG054029, R01 AG061848
- **Contract Research**
  - Cassava, Cyclerion, Eisai, Lilly, Vivoryon, Suven, Cognision
- **Educational Programming**
  - Medscape, CEConcepts, AAFP, Mid-America Institute on Aging and Wellness
- **Leadership Roles**
  - Alzheimer's Association ALZ-NET, ACTC, ADCS, AAN Education, ADRC Clinical Task Force

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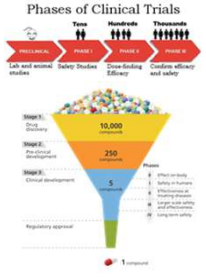
Learning Objectives

1. **Identify key targets for disease identification & modification in Alzheimer's disease**
2. **Discuss research participation with interested persons at risk for or with Alzheimer's disease**
3. **Analyze clinical trial results for new experimental medicines designed to treat Alzheimer's and related dementias**



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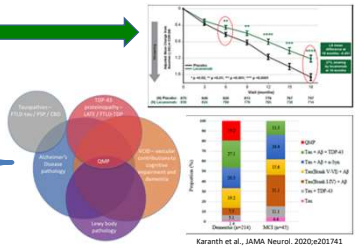
Why do we need to have targets other than Aβ?

1. Treating only Aβ only slows AD by ~30% and that is not enough
2. We are only treating the Aβ & most cases of MCI and dementia are mixed disease states
3. *"Pure" AD is only 27% to 40% of the pathology found in most MCI and or dementia cases at autopsy*



Karanth et al., JAMA Neurol. 2020;e201741

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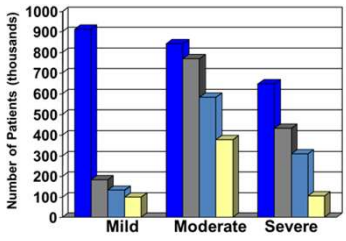
ALZHEIMER'S DISEASE PREVALENCE DIAGNOSIS & TREATMENT BY STAGE



- Far less than half of all AD patients are even treated!
- This is most true for early and late stage patients!

Prevalence (1)
Diagnosed (2)
Treated (3)
Treated w/ AChEI (4)

In part this is due to the facts that:

- Only 25% are diagnosed early
- Only 2/3 are diagnosed at the moderate stage of disease
- Only ½ are diagnosed even at the severe stage of impairment

Sources: (1) Brookmeyer et al. *AJPH*. 1998; (2) *PDDA*. 1998; (3) & (4) *Market Measures*. 1998.

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- Early diagnosis and treatment improves outcomes
- This is clear from all studies done to date
- Why do we consistently fail at even diagnosing this disease?

HOW DO WE TURN THIS AROUND AND MAKE DIAGNOSIS AN IMPORTANT PART OF OUR CARE?

A simple blood test might help?

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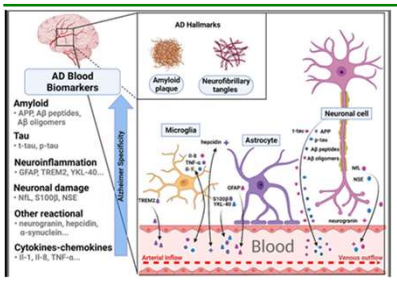
Plasma biomarkers



- Optimal detection of disease might be best achieved using a simple blood test?
- There are many proteins we can measure, but which is right?
- To date, the plasma biomarkers of Aβ & tau seem to be the most reliable for AD
- NFL is non-specific but appears highly reliable for detecting injury to the brain
- How we measure is perhaps more important than what we measure?
- Disparate data in the field is more likely due to assay than disease…

Delaby C, Hirtz C, Lehmann S. Overview of the blood biomarkers in Alzheimer's disease: Promises and challenges. Rev Neurol (Paris). 2023;179(3):161-172. doi:10.1016/j.neurol.2022.09.003

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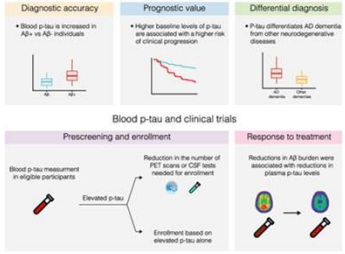

Gonzalez-Ortiz F, Kac PR, Brum WS, Zetterberg H, Blennow K, Karikari TK. Plasma phospho-tau in Alzheimer's disease: towards diagnostic and therapeutic trial applications. Mol Neurodegener. 2023 Mar 16;18(1):18. doi: 10.1186/s13024-023-00605-8. PMID: 36927491; PMCID: PMC10022272.

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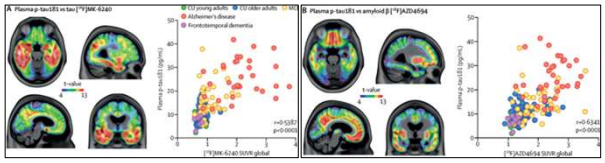
- **These show good association with FDA-approved biomarkers & are easy to implement in widespread clinical practice**
- **Some variability can be seen so they can guide, but not definitively diagnose**



Karikari et al., Lancet Neurology 2020 Vol. 19 Issue 5 Pages 422-433

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Prognostic value of 10 different assays

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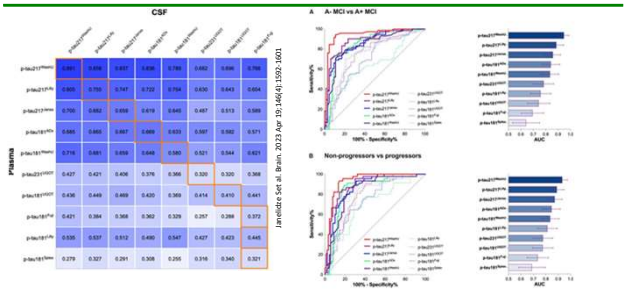
Annual Alzheimer's Disease Management & Research Symposium



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CLIA Certified Preclivity™ Test

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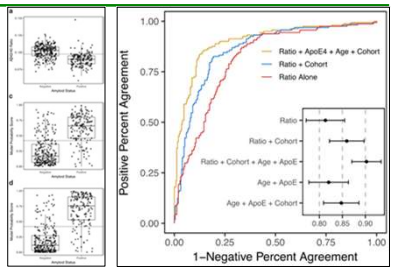
- AUC 0.90
- CLIA certified blood test available
- Accepted by FDA as indication for clinical trials in AD
- Quest diagnostics has a similar platform that is CLIA certified
- Other tests coming on-line soon
- You should know that these are likely not covered by CMS at this time
- We hope they will be covered in the future!

West et al., Molecular Neurodegeneration (2021) 16(1):30



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This section transitions to work on treatment rather than diagnosis…

It will focus on therapies in development that are not anti-amyloid antibodies as we will speak about that later today

RESEARCH ADVANCES…

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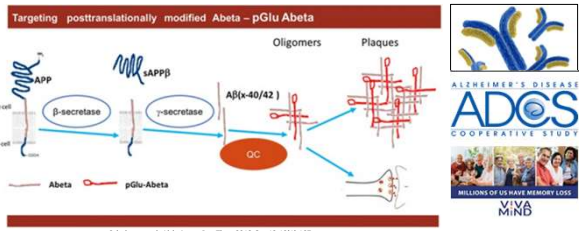
VIVA-MIND

Focused on eliminating harmful amyloid without an antibody!



Scheltens et al. Alzheimers Res Ther. 2018 Oct 12;10(1):107

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EEG, Cognition, and Biomarkers show positive effects

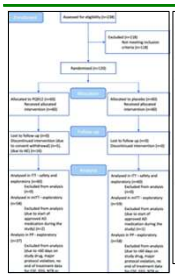

Table 4 Cohens'D Effect Size for Significant Efficacy parameters

Domain	Parameter	ITT	mITT	PP	Effect Size
NTB	One Back test	0.23*	0.23x	0.20	↓ small
CSF	QC activity	1.25***	1.28***	1.66***	↓ large
	Neurogranin	0.16x	0.20*	0.12	↓ small
	YKL40	0.16x	0.16x	0.20*	↓ small
EEG	Relative theta power	0.29**	0.32***	0.37**	↓ small-moderate
RSfMRI	MEC cunlatocc	0.58**	0.60**	0.39	↓ moderate

CSF: cerebrospinal fluid. EEG: Electro Encephalogram. ITT: Intent to Treat population. mITT: modified ITT population. MEC cunlatocc: Mean Eigen Vector centrality cuneus and lateral occipital regions. NTB: Neuropsychological Test Battery. PP: Per Protocol population. RSfMRI: Resting State functional Magnetic Resonance Imaging.
QC: glutaminyl cyclase. The arrow indicates the direction of the treatment effect.
x = $0.05 < p \leq 0.10$
* = $0.01 < p \leq 0.05$, ** = $0.001 < p \leq 0.01$, *** = $p \leq 0.001$

Scheltens et al. Alzheimers Res Ther. 2018 Oct 12;10(1):107

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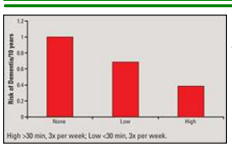
Exercise?

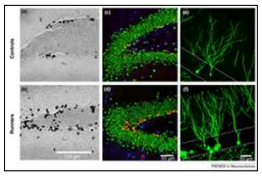


Exercise reduces risk of dementia in a dose-dependent fashion!

Cummings et al., Primary Psychiatry. 2008;15:2(suppl 1):1-24

BDNF released by exercise is like "Miracle-Grow" for your brain!

Lazarov et al, Trends Neurosci. 2010 Dec;33(12):569-79



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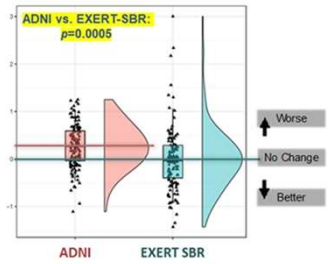
EXERT results

- This was an exercise trial for MCI to prevent AD
- Persons did either aerobic exercise or stretching/breathing exercises for 2 years
- No differences were seen between groups
- The data was then compared to ADNI and showed that stretching/breathing was most effective in warding off decline
- First off, this was a clearly negative trial
- Second, it shows that social engagement & any kind of exercise is what is really important
- It does not have to be high intensity aerobic workouts!



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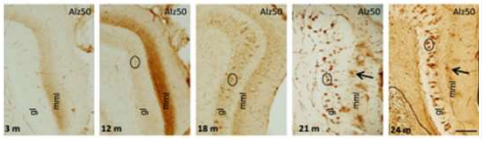
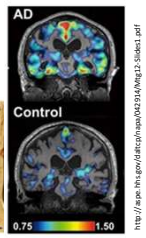
Once tangles start, they take on a life of their own!

- Tangles are most closely associated with memory problems
- Once tangles start, they take on a life of their own and are not influenced by later removal of amyloid





http://aspe.hhs.gov/daltcp/reports/042914/Mtg12-Slides1.pdf

de Calignon et al., Neuron. 2012 Feb 23;73(4):685-97
Liu et al., PLoS One. 2012;7(2):e31302.

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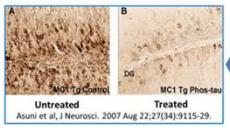
Anti-tau antibodies?



Asuni et al, J Neurosci. 2007 Aug 22;27(34):9115-29.

It works in mouseheimer's disease!

- 282 clinical trials of tau on clinical trials.gov, with 71 of these currently recruiting
- Yet several early Phase II studies have failed
  - Biogen TANGO, AbbVie AWARE, AC Immune (all n-terminal antibodies)
    - They all decreased CSF tau but no effect on tau-PET or clinical benefit
- We need to know if this is a path forward…

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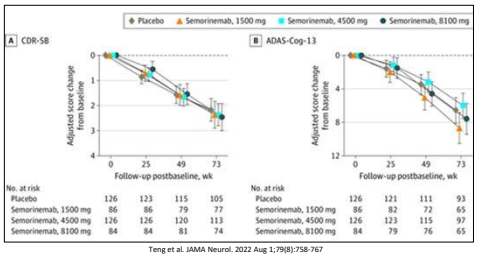
Tauriel study results…

- As with Aβ antibodies, the field is looking at unique targets
- Time will tell if this is a path forward…



Teng et al. JAMA Neurol. 2022 Aug 1;79(8):758-767

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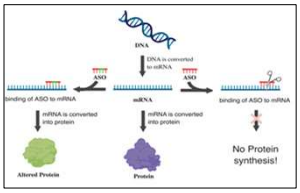
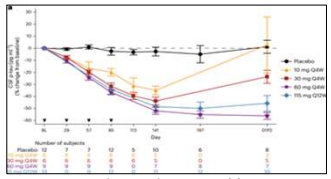
Tau antisense oligonucleotides?

- This study sought to inhibit MAPT expression with a tau-targeting antisense oligonucleotide (MAPTRx) and reduce tau levels in patients with mild AD
- A randomized, double-blind, placebo-controlled, multiple-ascending dose phase 1b trial evaluated the safety, pharmacokinetics and target engagement of MAPTRx





Mummery et al. Nat Med. 2023 Jun;29(6):1437-1447.

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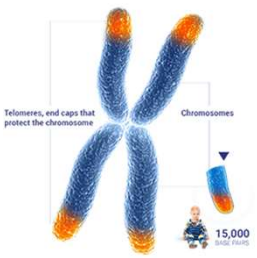
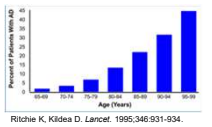
Anti-brain aging?



Advanced age is the major risk factor for the development of Alzheimer's disease and other types of neurodegenerative dementia



Ritchie K, Kildea D. *Lancet*. 1995;346:931-934.

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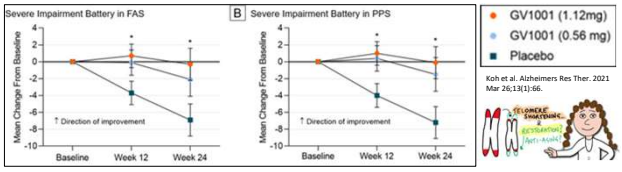
GEM-VAX

- GV1001 is a vaccine targeting telomere effects that protects neural cells against neurotoxicity, apoptosis, and reactive oxygen species (ROS) induced by Aβ and oxidative stress
- Phase 2, double-blind, parallel-group, placebo-controlled, 6-month randomized clinical trial (n=96)



Koh et al. Alzheimers Res Ther. 2021 Mar 26;13(1):66.

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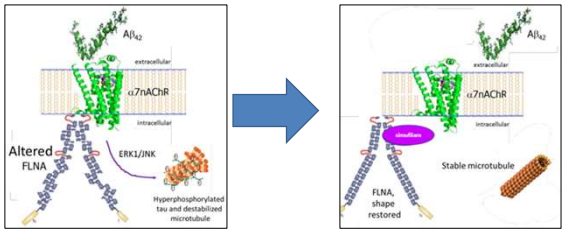
Targeting abnormal protein folding: Cassava's simufilam

Focused on correcting altered Filamin A to treat MCI/AD



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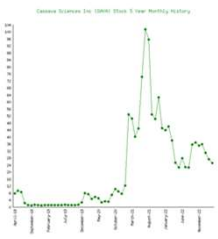
The Cassava Controversy?

- August 2021: Citizen Petition filed on behalf of a few investors who accused Cassava of manipulating Western blot data
- Links to a "short sell" financial plot have been suggested for the investors filing this petition
  - short sellers have reportedly made over $100,000,000 on this drug
- Feb 2022: FDA rejects the petition and allows the drug to move forward in clinical trials
- Legal actions and investigations continue at present…



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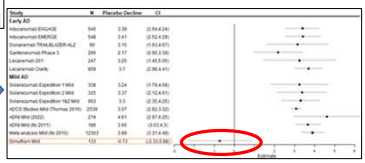
Simufilam data?

Alzheimer's Tennessee — Make Alzheimer's a Memory — 17th Annual Alzheimer's Disease Management & Research Symposium

- Phase 2 data looks promising
- Major differences seen after 24 weeks of treatment



- Phase 2 OLE data promising compared to historical data of other drugs
- No placebo group

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Metabolic malfunction?

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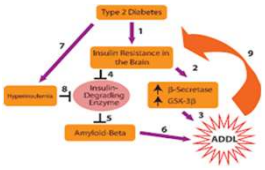
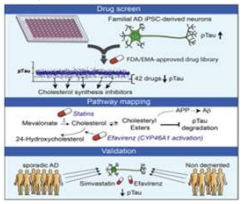


- Insulin resistance drives Aβ through negative effects on IDE (prevents clearance)
- Insulin resistance drives Aβ through activation of BACE (increases production)
- Insulin resistance drives tau pathology through GSK-3β hyperphosphorylation of tau

- Hypercholesterolemia may drive AD through dysregulation of metabolic pathways
- ApoE is the major AD risk gene for AD and functions as a regulator of lipid transport



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EVOKE & ELAD may be able to power up the brain in just 26 weeks & slow AD progression

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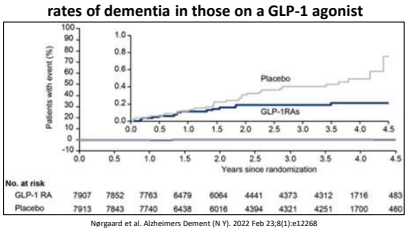
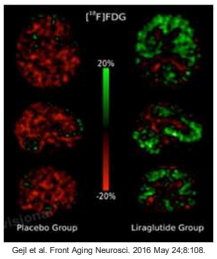
Epidemiologic data from across the globe show reduced rates of dementia in those on a GLP-1 agonist



Nørgaard et al. Alzheimers Dement (N Y). 2022 Feb 23;8(1):e12268



Gejl et al. Front Aging Neurosci. 2016 May 24;8:108.

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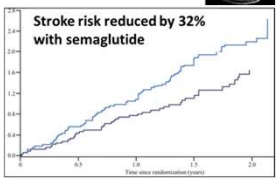
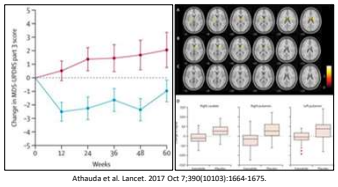
Of note, GLP-1 agonists are also being investigated for..

- **Cerebrovascular disease**



Strain et al. Stroke. 2022 Sep;53(9):2749-2757.

- **Parkinson's disease**
  - 12 week clinical trial (n=62)



Athauda et al. Lancet. 2017 Oct 7;390(10103):1664-1675.

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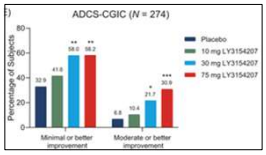
Other approaches for DLB…

PRESENCE Study (n=344)

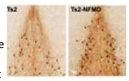
- Mevidalen (LY3154207) is a novel modulator of the dopamine D1 receptor
- While negative results were seen overall, there was a positive dose-effect relationship



Biglan et al. Mov Disord. 2022 Mar;37(3):513-524.

AscenD-LB study (n=91)

- Neflamapimod (NFMD) is a specific p38α kinase inhibitor, that can restore cholinergic function
- CDR-SB and TUGO test results suggest cognitive and motor benefit



Jiang Yet al. Nat Commun. 2022 Sep 21;13(1):5308.

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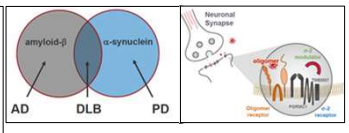
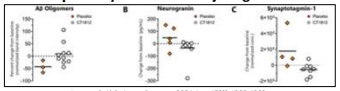
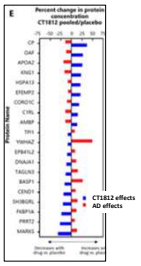
Mew approaches to the treatment of DLB: SHIMMER

- **SHIMMER is looking at a new medicine that may help slow or stop DLB**
- **This same medicine is being tested for use in slowing or stopping Alzheimer's**
- **This is a completely new way to treat these diseases!**



- **CT1812 binds to the sigma 2 receptor preventing toxic Aβ & α-synuclein from injuring nerve cells**



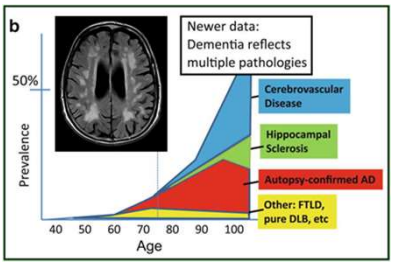


Izzo et al. Alzheimers Dement. 2021 Aug;17(8):1365-1382.

30

Vascular Cognitive Impairment & Dementia: *"Hardening of the arteries"*

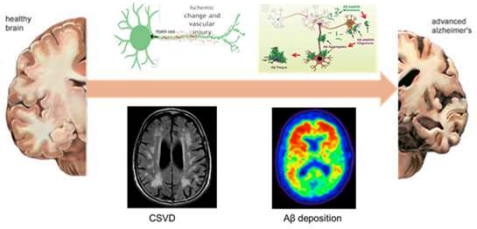
- We have been studying VCID for over 12 years
- We know that:
  - Hypertension is the #1 risk for this hardening of the arteries
  - It is just as devastating as Alzheimer's disease
- Much active work is being done to gear up for clinical trials in this area
- Let's take a look…



31

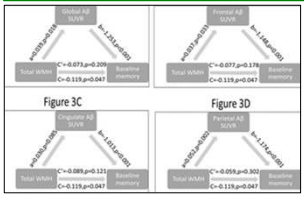
How does hardening of the arteries affect AD risk and progression?

- This remains largely unknown although links between the two are clear!

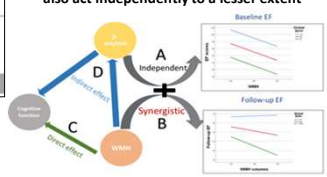


32

WMH cause/accelerate AD and not the other way around!



- WMH affect cognitive decline through an Aβ mediated pathway!
- Axonal injury appears to be associated with increased amyloid accumulation but can also act independently to a lesser extent



- WMH affect cognitive decline through an Aβ mediated pathway!

Ali et al. Brain Behav. 2023 Aug 3:e3209.

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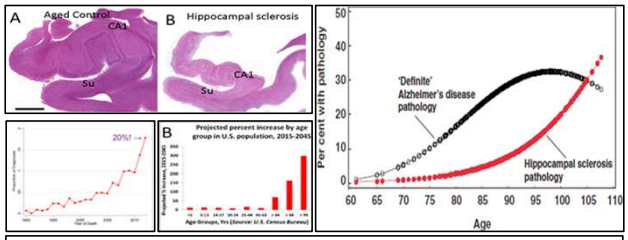
Alzheimer's Disease Center at the Sanders-Brown Center on Aging

LATE Disease What is it?



➢This is a major cause of dementia for those living to advanced ages!

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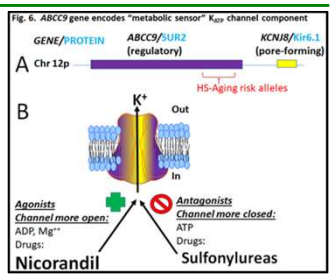
Alzheimer's Disease Center at the Sanders-Brown Center on Aging

LATE: *Limbic-associated, age-related, TDP-43 encephalopathy*

- ➢Recent consensus meeting to name disease and establish its importance
- ➢Diagnostic biomarkers sought
- ➢First ever clinical trial funded by NIA to UK ADC to try and stop this disease!
- ➢If you are 75+ years and have memory changes but do not think you have AD, you may have LATE!



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SMART-HS

Nicorandil prevents death OR 0.65 (95% CI: 0.51-0.84)

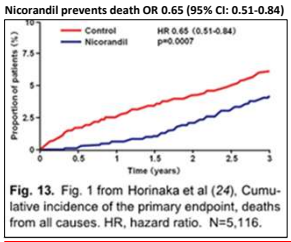
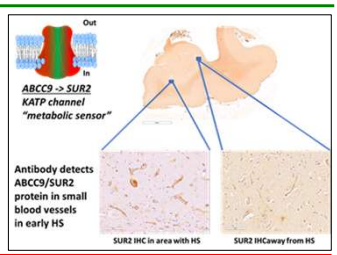


Fig. 13. Fig. 1 from Horinaka et al (*24*), Cumulative incidence of the primary endpoint, deaths from all causes. HR, hazard ratio. N=5,116.



Watch this space, upcoming major NIH clinical criteria consensus coming out now!

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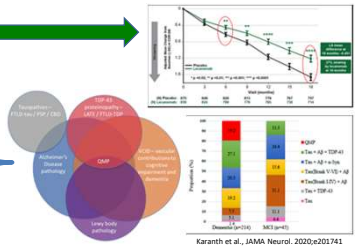
Alzheimer's Disease Center at the Sanders-Brown Center on Aging

Why do we need to have targets other than Aβ?

Alzheimer's Tennessee — Annual Alzheimer's Disease Management & Research Symposium

1. **Treating only Aβ only slows AD by ~30% and that is not enough**
2. **We are only treating the Aβ & most cases of MCI and dementia are mixed disease states**
3. ***"Pure" AD is only 27% to 40% of the pathology found in most MCI and or dementia cases at autopsy***



Karanth et al., JAMA Neurol. 2020;e201741

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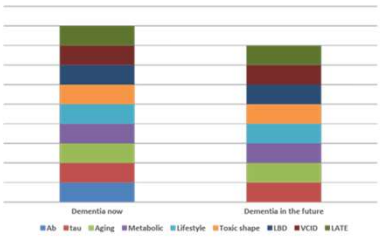
Alzheimer's Disease Center at the Sanders-Brown Center on Aging

What if we slow or stop Aβ?

Alzheimer's Tennessee — Annual Alzheimer's Disease Management & Research Symposium

If we can slow or stop:

- Aβ
- Tau
- Aging
- Metabolic dysfunction
- Lifestyle impacts
- Toxic protein shapes
- Lewy Bodies
- Cerebrovascular disease
- LATE/TDP-43



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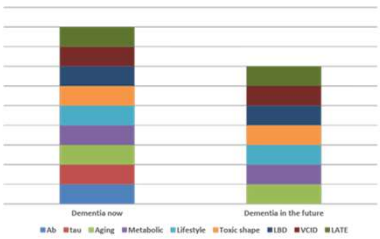
Alzheimer's Disease Center at the Sanders-Brown Center on Aging

What if we could slow or stop tau too?

Alzheimer's Tennessee — Annual Alzheimer's Disease Management & Research Symposium

If we can slow or stop:

- ~~Aβ~~
- Tau
- Aging
- Metabolic dysfunction
- Lifestyle impacts
- Toxic protein shapes
- Lewy Bodies
- Cerebrovascular disease
- LATE/TDP-43



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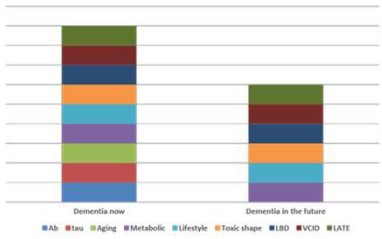
What if we could slow or stop aging too?

If we can slow or stop:

- ~~Aβ~~
- ~~Tau~~
- Aging
- Metabolic dysfunction
- Lifestyle impacts
- Toxic protein shapes
- Lewy Bodies
- Cerebrovascular disease
- LATE/TDP-43

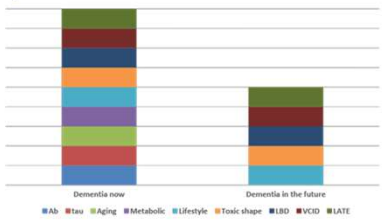


40

What if we could slow or stop metabolic dysfunction too?

If we can slow or stop:

- ~~Aβ~~
- ~~Tau~~
- ~~Aging~~
- Metabolic dysfunction
- Lifestyle impacts
- Toxic protein shapes
- Lewy Bodies
- Cerebrovascular disease
- LATE/TDP-43

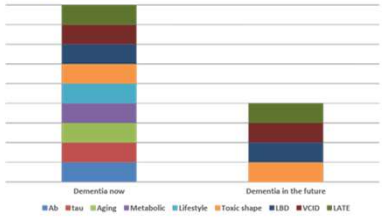


41

What if we could slow or stop negative lifestyle impacts too?

If we can slow or stop:

- ~~Aβ~~
- ~~Tau~~
- ~~Aging~~
- ~~Metabolic dysfunction~~
- Lifestyle impacts
- Toxic protein shapes
- Lewy Bodies
- Cerebrovascular disease
- LATE/TDP-43

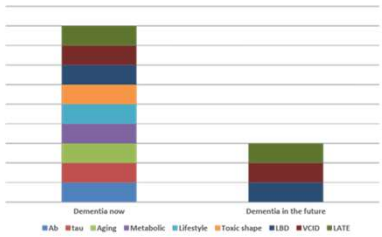


42

What if we could slow or stop toxic protein shapes too?

If we can slow or stop:

- ~~Aβ~~
- ~~Tau~~
- ~~Aging~~
- ~~Metabolic dysfunction~~
- ~~Lifestyle impacts~~
- Toxic protein shapes
- Lewy Bodies
- Cerebrovascular disease
- LATE/TDP-43

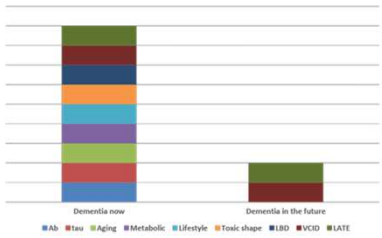


43

What if we could slow or stop Lewy bodies too?

If we can slow or stop:

- ~~Aβ~~
- ~~Tau~~
- ~~Aging~~
- ~~Metabolic dysfunction~~
- ~~Lifestyle impacts~~
- ~~Toxic protein shapes~~
- Lewy Bodies
- Cerebrovascular disease
- LATE/TDP-43

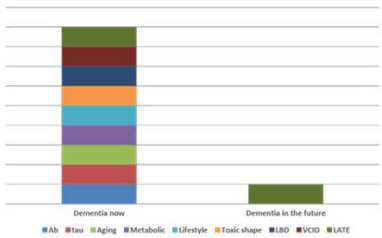


44

What if we could slow or stop VCID too?

If we can slow or stop:

- ~~Aβ~~
- ~~Tau~~
- ~~Aging~~
- ~~Metabolic dysfunction~~
- ~~Lifestyle impacts~~
- ~~Toxic protein shapes~~
- ~~Lewy Bodies~~
- Cerebrovascular disease
- LATE/TDP-43



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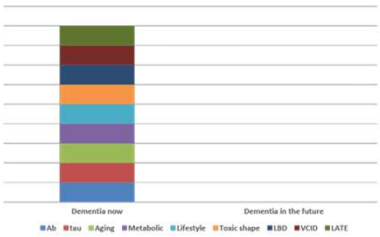
Alzheimer's Disease Center at the Sanders-Brown Center on Aging

What if we could slow or stop LATE/TDP-43 too?

Alzheimer's Tennessee — Make Alzheimer's a Memory. — 17th Annual Alzheimer's Disease Management & Research Symposium

If we can slow or stop:

- ~~Aβ~~
- ~~Tau~~
- ~~Aging~~
- ~~Metabolic dysfunction~~
- ~~Lifestyle impacts~~
- ~~Toxic protein shapes~~
- ~~Lewy Bodies~~
- ~~Cerebrovascular disease~~
- LATE/TDP-43



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Alzheimer's Disease Center at the Sanders-Brown Center on Aging

Hey wait a minute…

Alzheimer's Tennessee — Make Alzheimer's a Memory. — 17th Annual Alzheimer's Disease Management & Research Symposium

On the other hand, this is worth it!

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Alzheimer's Disease Center at the Sanders-Brown Center on Aging

What about symptomatic treatments?

Alzheimer's Tennessee — Make Alzheimer's a Memory. — 17th Annual Alzheimer's Disease Management & Research Symposium

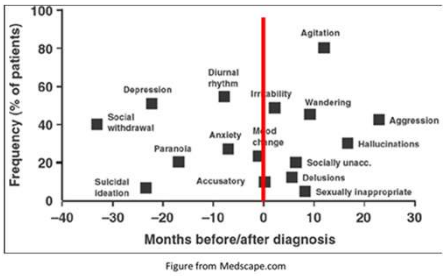
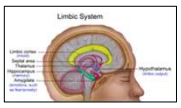


Figure from Medscape.com



- **Quality of life is also important!**
- **BPSD are major contributors to lower QOL**
- **We need to do better…**
- **What is happening in this space?**

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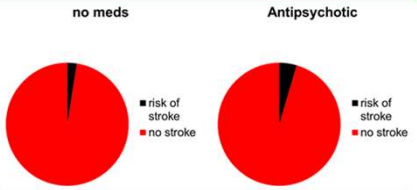
Anti-psychotics?

- We all know that these meds have risks and that we need to do better
- Do newer agents have the effectiveness needed to justify the risks?



- Sometimes, safety risks of BPSD are greater than 1.9%
- Sometimes the risk of 1 in 50 is worth bringing some peace to someone living in a never ending nightmare

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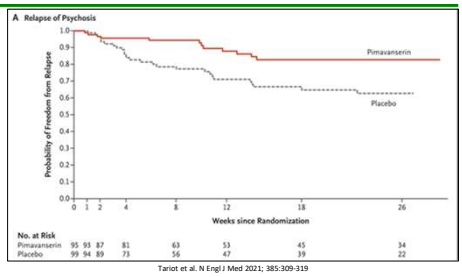
Pimavanserin: Can we do better?

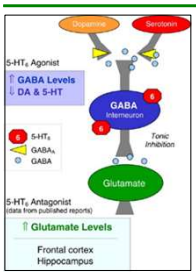
- Hazard ratio for time to relapse, 0.35; 95% confidence interval [CI], 0.17 to 0.73; P=0.005
- Risk for serious adverse events were not statistically different in the treatment group



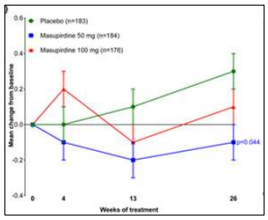
Tariot et al. N Engl J Med 2021; 385:309-319

50

Don't we have anything new? Masupirdine (SUVN-502)



- SUVN-502 is an orally available, brain-penetrant, selective antagonist of the 5-HT6 serotonin receptor



- Side effects were mostly GI including nausea & diarrhea
- Benefits were also possible in the psychosis domain of the NPI
- Phase 3 trials are underway currently!

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The end-stage of dementia…

- Joan is 82 years old and is in the end-stage of dementia
- She no longer walks, talks or engages in the world around her
- She frequently moans and grimaces as if she is in pain
- All we can do is keep her comfortable and be there for her as this disease slowly takes her life

- It's impossible to know what she is feeling…
- We can give her opiates and benzodiazepines to make her more comfortable, but then she is less aware and cannot even smile when her son gently kisses her forehead
- There must be more we can do?

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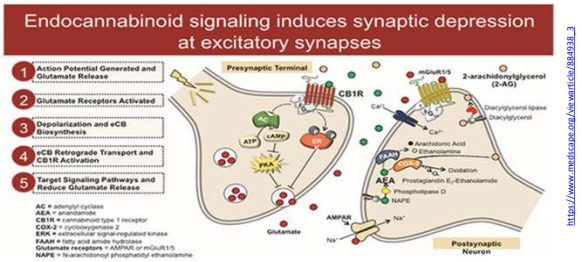
Cannabinoids?



https://www.medscape.org/viewarticle/884928_3

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LIBBY (Life's end Benefits of CannaBidol and TetrahYdrocannabinol (LiBBY) Trial)



- 12-week, phase 2, multicenter, randomized, double-blind, parallel-group, placebo-controlled study
- 150 hospice-eligible agitated AD patients over a 2-year period
- A total daily dose of 8 mg of THC and 400mg of CBD dissolved in digestible oil will be administered 3 times per day
- Following the 12-week randomized phase, all participants are eligible for a 6-month open-label extension

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Alzheimer's Disease Center at the Sanders-Brown Center on Aging

So why would you, or your patients/clients/friends/family want to get involved?

- **Most of these are still experimental**
- **There is always the chance that:**
  - They won't work…
  - That you could get the placebo…
  - That this could make things worse…

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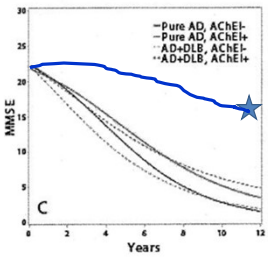
Alzheimer's Disease Center at the Sanders-Brown Center on Aging

Why indeed?

- **These medicines are based on state-of-the-art science**
- **Even in the placebo arm there is benefit of enhanced care & patients do better**
- **Safety is always first and foremost**



- **My patient X has been receiving lecanumab for 10 years now**
- **Let's look at where he is now?**
- **He did this for himself!**
- **He did this for his children!**
- **Where would he be if he had waited for drug approval?**
- **Maybe its just a fluke?**

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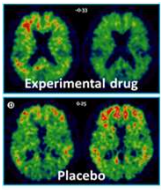
Alzheimer's Disease Center at the Sanders-Brown Center on Aging

What's next? Other experimental therapies?

- **There are over 100 potential new treatments including possible cures being investigated**
- **The UK ADC is at the leading edge of this research**
- **Right here! Right now!**
- **The time to get involved is now!**



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