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Clinical and biological effects of long-term lithium treatment in older adults with amnestic mild cognitive impairment: randomised clinical trial

Orestes V. Forlenza, Márcia Radanovic, Leda L. Talib and Wagner F. Gattaz

Why lithium for AD?

Rationale

1) Evidence of neurotrophic & neuroprotective effects of lithium replicated in multiple experimental models

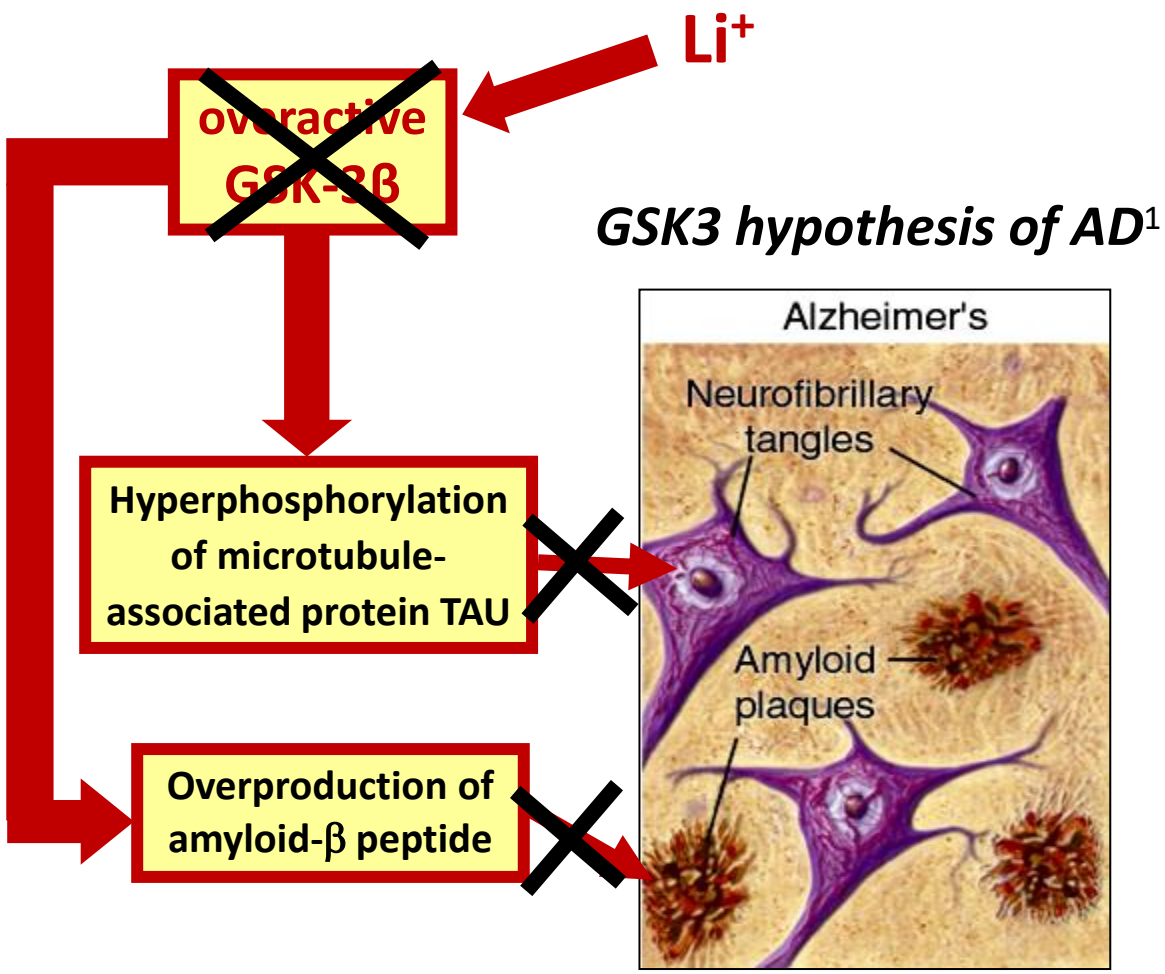
2) Extrapolations from neuroimaging in bipolar disorder and epidemiological studies

3) Rather pessimistic perspective in AD drug development pipeline towards disease modification, particularly regarding anti-amyloid immunotherapy

   – *repurposed drugs*: 43% of pharmacological compounds in current phase 1, 2 and 3 trials (52 drugs)[1]

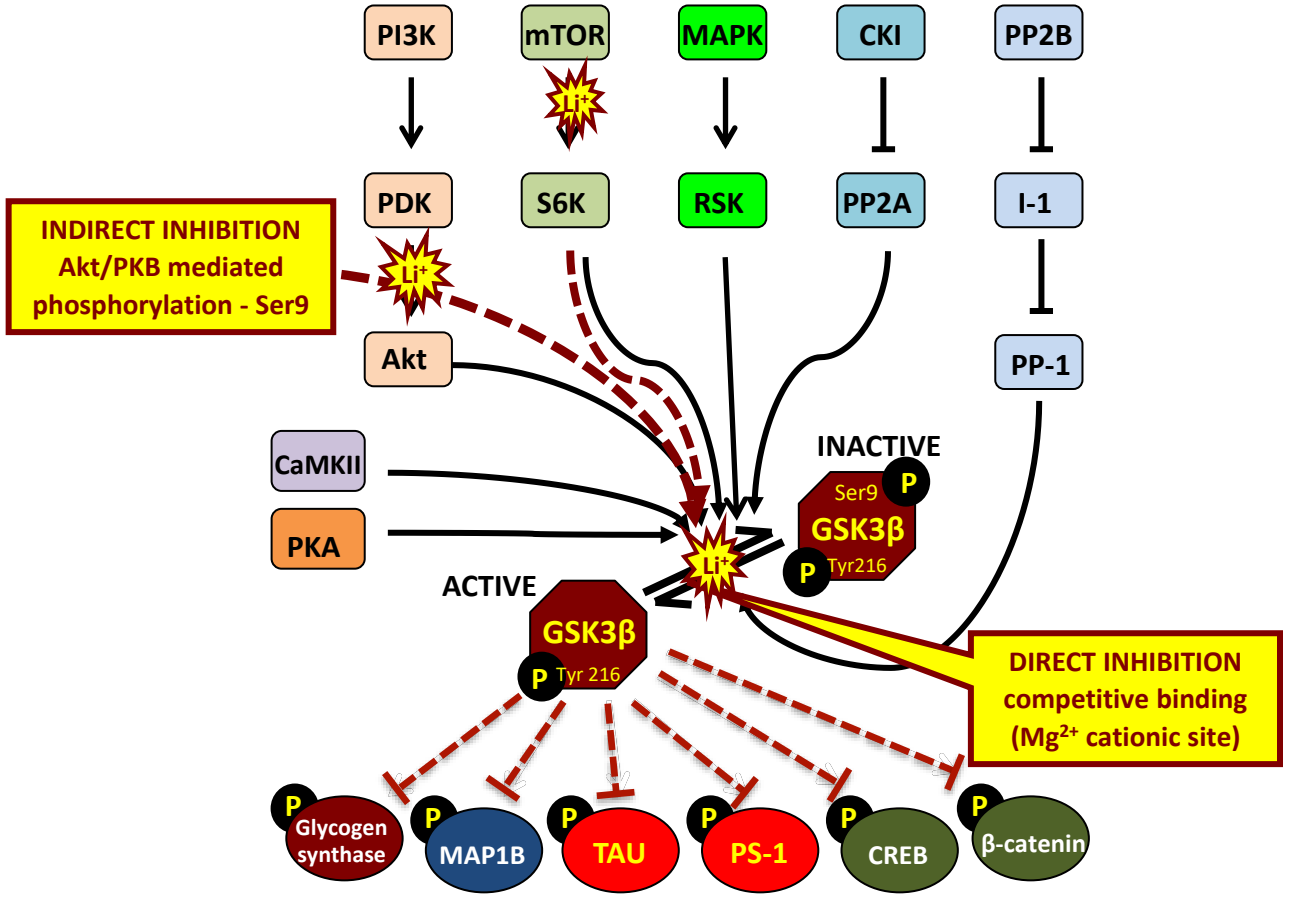
[1] Cummings et al. Alzheimer's disease drug development pipeline 2020. *Alzheimers Dement TRCI* 2020.

Biological assumption



GSK3 hypothesis of AD[1]

Lithium is a potent, dual inhibitor of GSK-3β



[1] Hooper et al. The GSK3 hypothesis of Alzheimer's disease. *J Neurochem* 2008;104(6):1433-1439

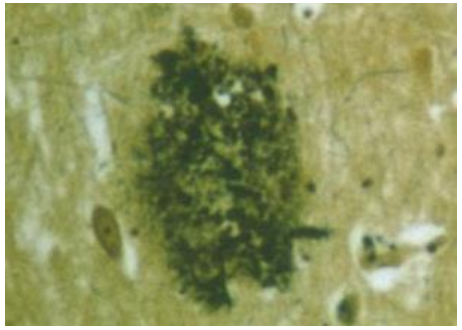
Beyond plaques & tangles

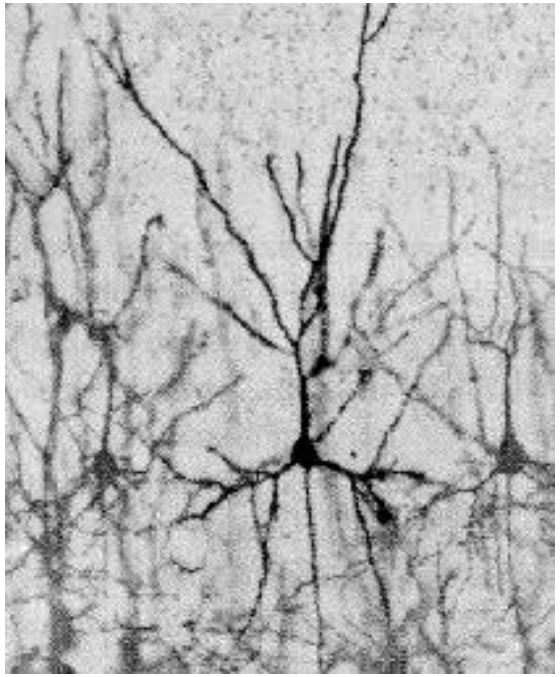
Lithium may protect neurons against AD-specific and -unspecific insults

Amyloid-β

↓

Neuritic plaques

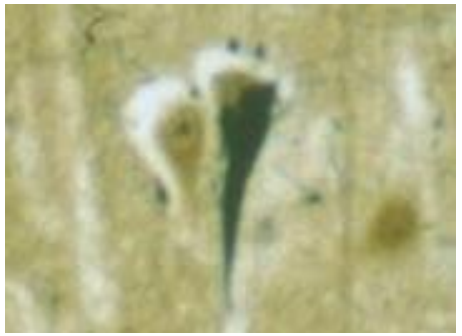




Phospho-TAU

↓

Neurofibrillary tangles



Neurogenesis
Synaptic plasticity
Neurotrophic support
Structural remodeling

- **Gene regulation**
- **Response to injury**
- **Mitochondrial function**
- **Apoptosis and autophagy**

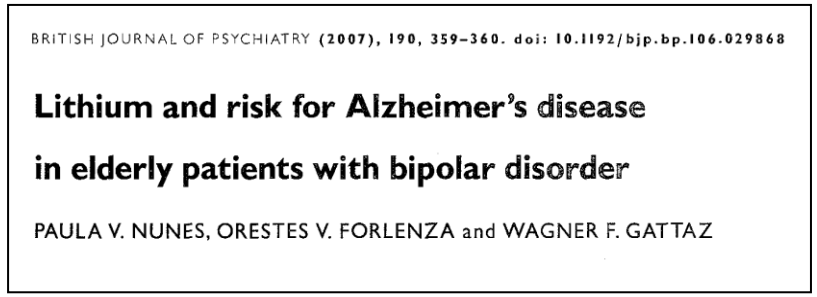
Klein & Melton. A molecular mechanism for the effect of lithium on development. *PNAS* 1996;93:8455-9

Background (i)

Chronic lithium use is associated with lower prevalence of dementia

Chronic lithium use prevents dementia in BD

- **Lithium and risk for AD in elderly patients with bipolar disorder.**
  Nunes et al. *Br J Psychiatry* 2007;190:359-60.
  - Overall dementia rate: 21.4% (vs. 5-7% estimated)
    Lithium: 5%; non-lithium: 33% (p<0.001)
  - Older age: positive association with dementia (p=0.02)
    Lithium use: negative association with dementia (p<0.001)


BRITISH JOURNAL OF PSYCHIATRY (2007), 190, 359–360. doi: 10.1192/bjp.bp.106.029868

Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorder

PAULA V. NUNES, ORESTES V. FORLENZA and WAGNER F. GATTAZ

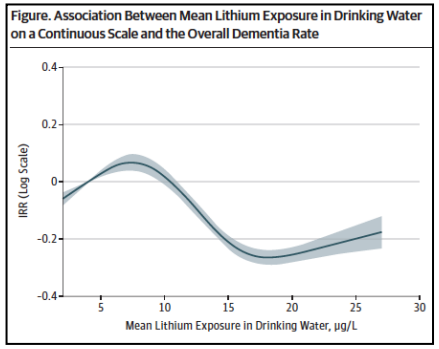
- **Lithium treatment and risk of dementia.**
  Kessing et al. *Arch Gen Psychiatry* 2008;65(11):1331-35.
  - At least one purchase of lithium (presumably BD): higher dementia rate;
    Multiple purchases (i.e. continued use): progressive reduction in dementia rate

Long-term exposure to trace lithium lowers dementia rates

- **Association of lithium in drinking water with incidence of dementia.**

  Kessing et al. *JAMA Psychiatry* 2017;74(10):1005-10

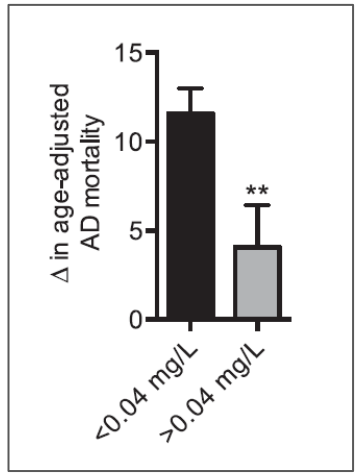
  - Non-linear effect: 5-10µg/L: increase; **>10-27µg/L: decrease in IRR** (incidence rate ratio for overall dementia, AD and VD)



- **Examining the relationship between trace lithium in drinking water and the rising rates of age-adjusted Alzheimer's disease mortality in Texas.**

  Fajardo et al. *J Alzheimers Dis* 2018;61(1):425-34

  - **Trace lithium in water was negatively associated with AD mortality** (also with obesity and type-2 diabetes)



Background (ii)

Lithium treatment also delivers neurotrophic effects

MRI studies in BD

- **Lithium-induced increase in human brain grey matter.**
  Moore et al. *Lancet* 2000;356(9237):1241-2
  - Grey-matter volume increases after 4 weeks of treatment: **neurotrophic effect**

- **Large positive effect of lithium on prefrontal cortex N-acetylaspartate in patients with bipolar disorder: 2-centre study.**
  Hajek et al. *J Psychiatry Neurosci* 2012;37(3):185-92
  - Li-treated patients with similar illness burden had **prefrontal NAA levels similar to controls**

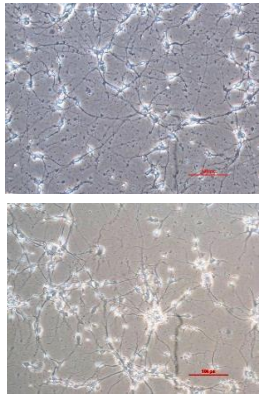
- **Brain age in bipolar disorders: effects of lithium treatment.**
  Van Gestel et al. *Aust N Z J Psychiatry* 2019;53(11):1179-88
  - Machine-learning MRI algorithm to estimate *BrainAGE* (vs. chronological age) in 504 controls; 84 BD (lithium vs. non-lithium): **Lithium users have 'younger' brains**

Lithium upregulates BDNF

- **Long-term lithium treatment increases intracellular and extracellular BDNF in cortical and hippocampal neurons at subtherapeutic concentrations.**

  De Paula et al. *Bipolar Disord* 2016;18(8):692-695.

  - Chronic, low-dose lithium treatment (0.02/0.2mM) up-regulates BDNF production in primary neuronal cell culture



- **Lithium increases plasma brain-derived neurotrophic factor in acute bipolar mania: a preliminary 4-week study.**

  De Sousa et al. *Neurosci Lett* 2011;494(1):54-6.

- **Increase of BDNF serum concentration in lithium treated patients with early Alzheimer's disease.**

  Leyhe et al. *J Alzheimers Dis* 2009;16(3):649-56.

Research question

Is lithium a candidate drug for disease modification in AD?

Clinical evidence

- **4 clinical trials of lithium in AD continuum**
  - UK, single blinded, therapeutic concentrations, 12 months moderate AD (n=22) (Macdonald et al 2008)[1]
  - German-EU, single-blinded, therapeutic (0.5-0.8mM), 10 weeks, mild AD (n=71) (Hampel et al 2009)[2]
  - **BR, double-blinded (2 yrs) + extension, amnestic MCI (n=61) sub-therapeutic doses (Forlenza et al 2011; 2019)**[3,4]
  - BR, single-blinded, microdoses (300µg/day), moderate AD, 18 months (Nunes et al 2013)[5]
- **1 meta-analysis (of studies 2-4)**[6]

[1]Macdonald et al. A feasibility and tolerability study of lithium in AD. *Int J Geriatr Psychiatry* 2008; [2]Hampel et al. Lithium trial in AD: a randomized, single-blind, placebo-controlled, multicenter 10-week study. *J Clin Psychiatry* 2009; [3]**Forlenza et al. Disease-modifying properties of lithium treatment for aMCI: randomised controlled trial. *Br J Psychiatry* 2011**; [5] Nunes et al. Microdose lithium treatment stabilized cognitive impairment in patients with Alzheimer's disease. *Curr Alzheimer Res* 2013; [6] Matsunaga et al. Lithium as a treatment for AD: a systematic review and meta-analysis. *J Alzheimers Dis* 2015

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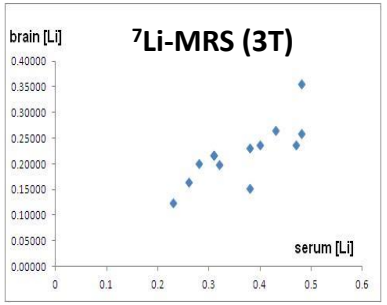
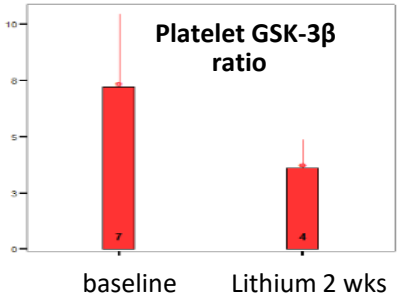
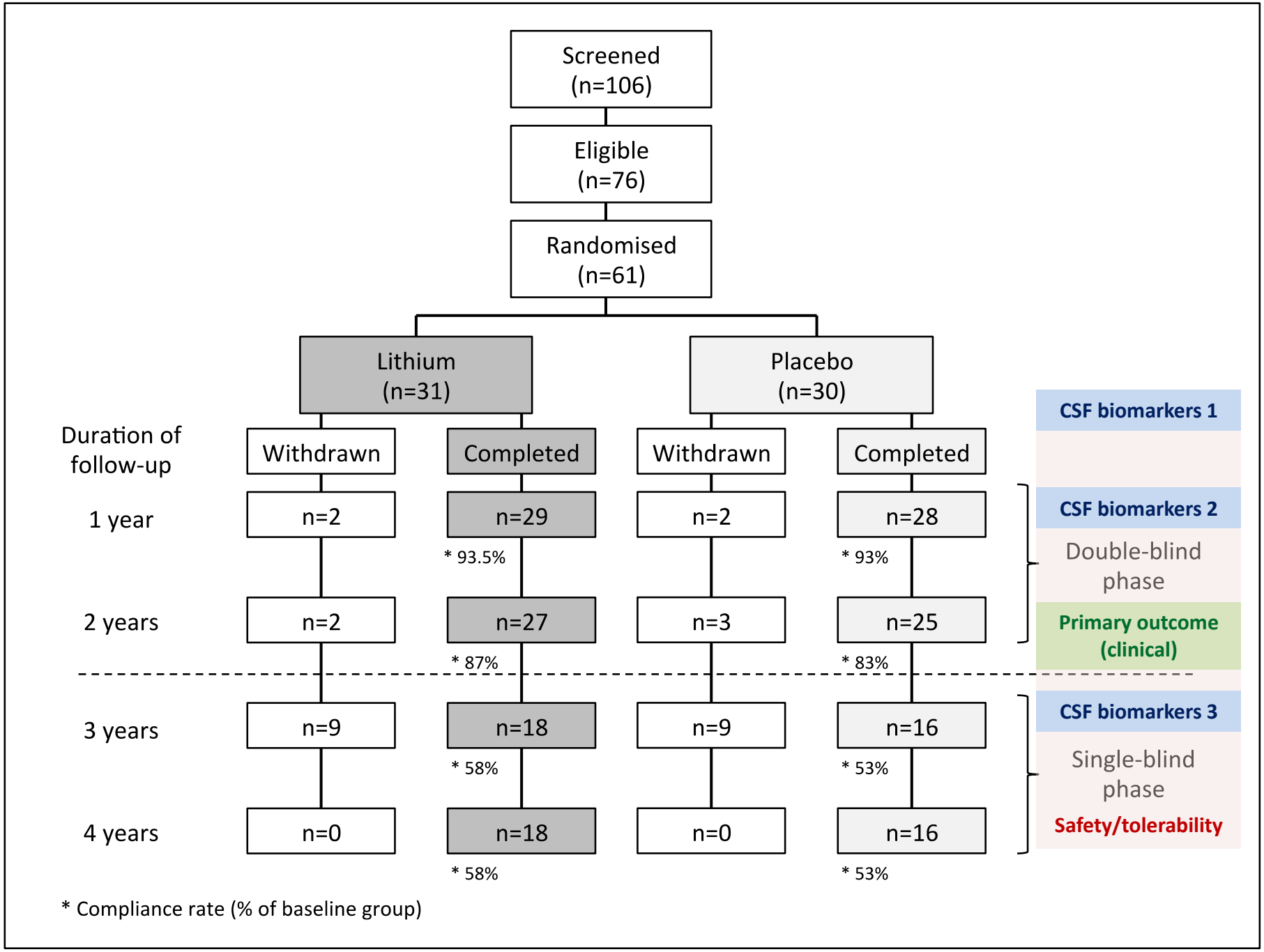
- **double-blind, placebo-controlled (2 yrs.)**
- **single-blinded extension (+2 yrs.)**
- **older adults with amnestic MCI** (104 ➔ 61)
- **sub-therapeutic lithium doses**
  0.25-0.5mEq/L
- **outcome variables:**
  - conversion (MCI-AD)
  - functional status (CDR-SoB)
  - cognition (ADAS-Cog, neuropsychological tests)
  - peripheral markers (not shown)
  - CSF $A\beta_{1\text{-}42}$, total TAU, p-TAU (0, 12, 36 months)






Screened (n=106)
Eligible (n=76)
Randomised (n=61)
Lithium (n=31)
Placebo (n=30)
Duration of follow-up
Withdrawn
Completed
Withdrawn
Completed
1 year
n=2
n=29
n=2
n=28
* 93.5%
* 93%
2 years
n=2
n=27
n=3
n=25
* 87%
* 83%
3 years
n=9
n=18
n=9
n=16
* 58%
* 53%
4 years
n=0
n=18
n=0
n=16
* 58%
* 53%
CSF biomarkers 1
CSF biomarkers 2
Double-blind phase
Primary outcome (clinical)
CSF biomarkers 3
Single-blind phase
Safety/tolerability
* Compliance rate (% of baseline group)

Safety / tolerability

1. **Good compliance**
   - 1 year: 93% (total sample = subgroups)
   - 2 years: 85% (similar dropout rates)
   - 3-4th yrs: PBO 53% (16/30); Li 58% (18/31)

2. **Good safety/tolerability profile**
   - low incidence of adverse events (Li > PBO)
   - NS changes critical parameters

Safety & tolerability

- **Long-term, low-dose lithium treatment does not impair renal function in the elderly: a 2-year randomized, placebo-controlled trial followed by single-blind extension.**
  Aprahamian et al. *J Clin Psychiatry* 2014;75(7):e672-8.

Clinical message:

- **Low-dose lithium appears to be safe, especially regarding renal function in an older population**
- **Older adults on low-dose lithium present mild impairments in daily activities due to side-effects**
- **Periodic evaluation of at least endocrine and renal functions is important to avoid organic lesions**

Lithium vs. placebo:

- ↑ neutrophil count
- ↑ serum TSH
  within normal limits
  interaction: N.S.
- ↑ body weight
  n=5; 25%; mean 5.5kg
- more overall AE's
  generally mild
  severe AE's: N.S.
  incident cases DM, arrhitmia

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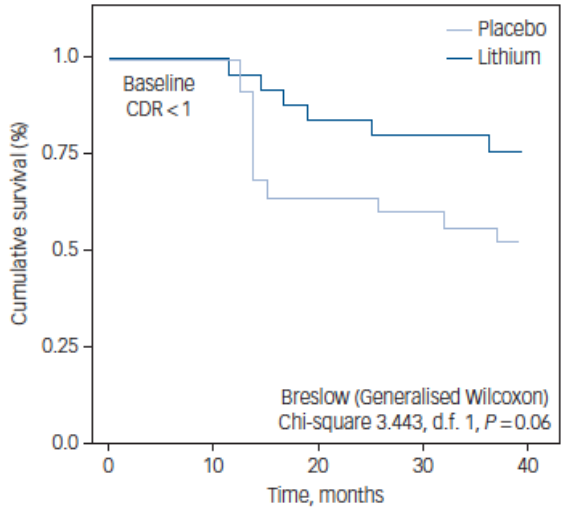
Cognitive and functional outcome after 2 years
(double-blind endpoint)

— Placebo
— **Lithium**

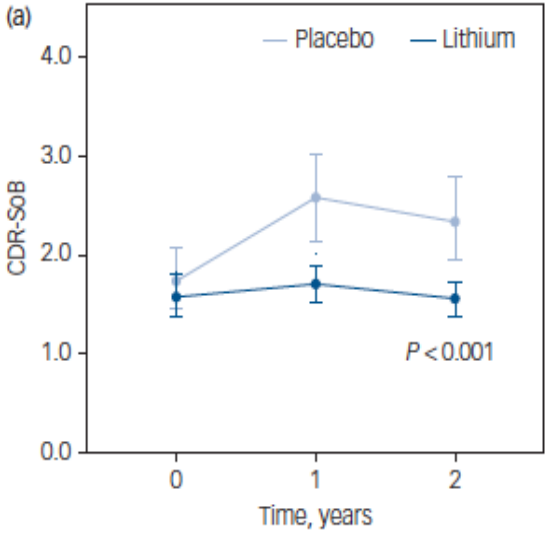
Conversion (MCI-AD)



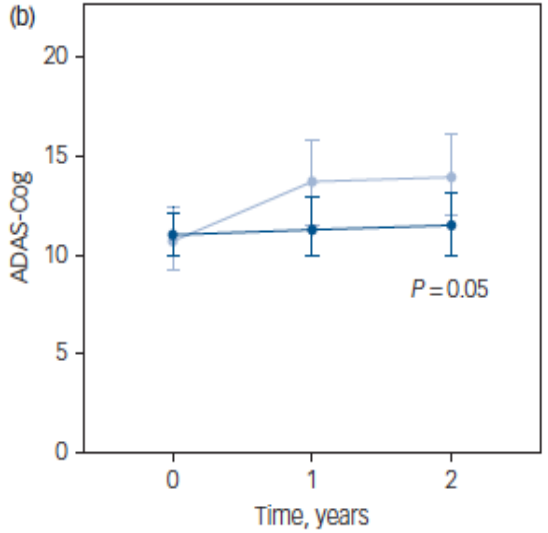
Converters:
Lithium, n=5
Placebo, n=9

Attrition:
1st year, n=4
2nd year, n'=5
(Li vs. Pbo, N.S.)

Functional state (CDR-SoB)



Global cognitive state (ADAS-Cog)



Delayed recall

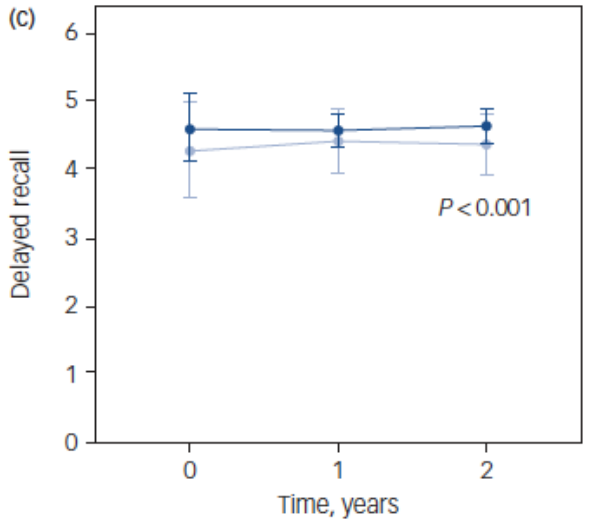
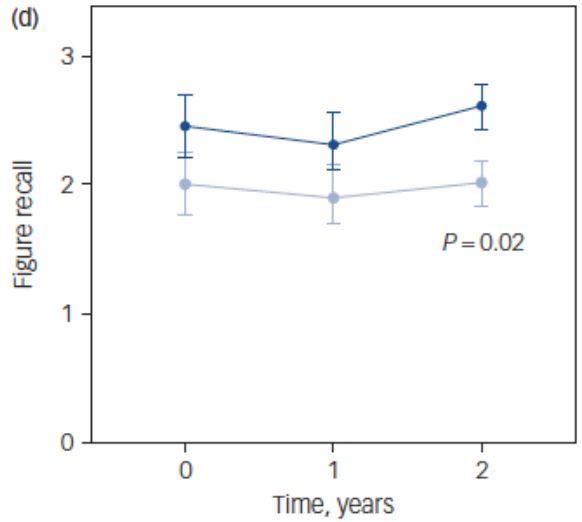


Figure recall



Linear mixed effects model

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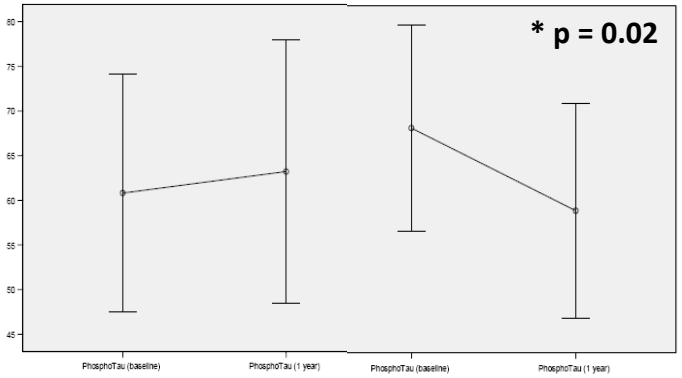
Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial†

Orestes V. Forlenza, Breno S. Diniz, Márcia Radanovic, Franklin S. Santos, Leda L. Talib and Wagner F. Gattaz

Lithium: reduction in CSF p-Tau

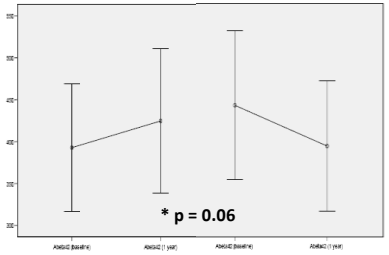
(interim analysis, T0 vs. 12 months)

Phosphorylated Tau^{181}



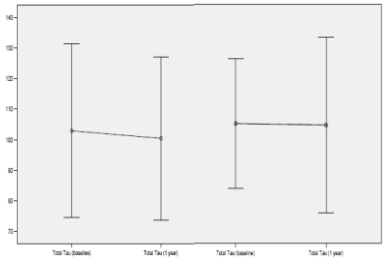
Placebo **Lithium**

Amyloid-β42



Placebo **Lithium**

Total Tau



Placebo **Lithium**

'AD-signature':
- ↓ $A\beta_{1\text{-}42}$
- ↑ total TAU
- ↑ p-TAU

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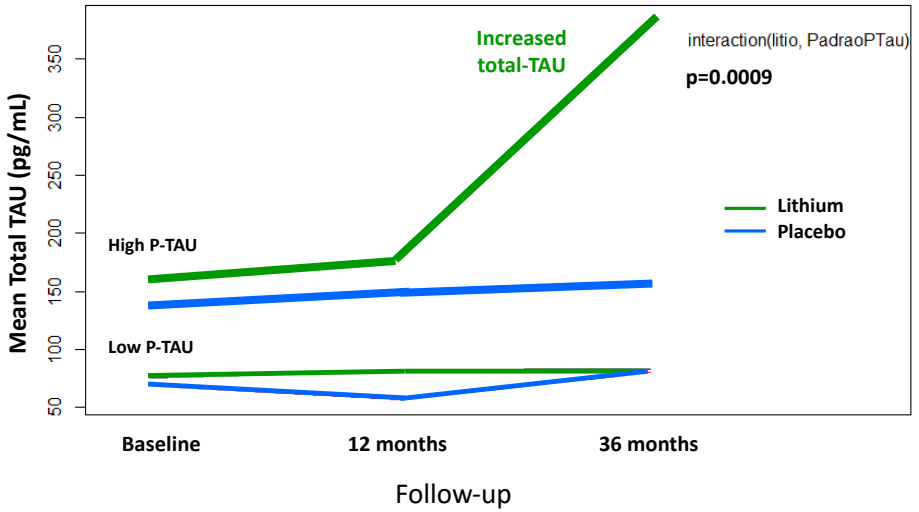
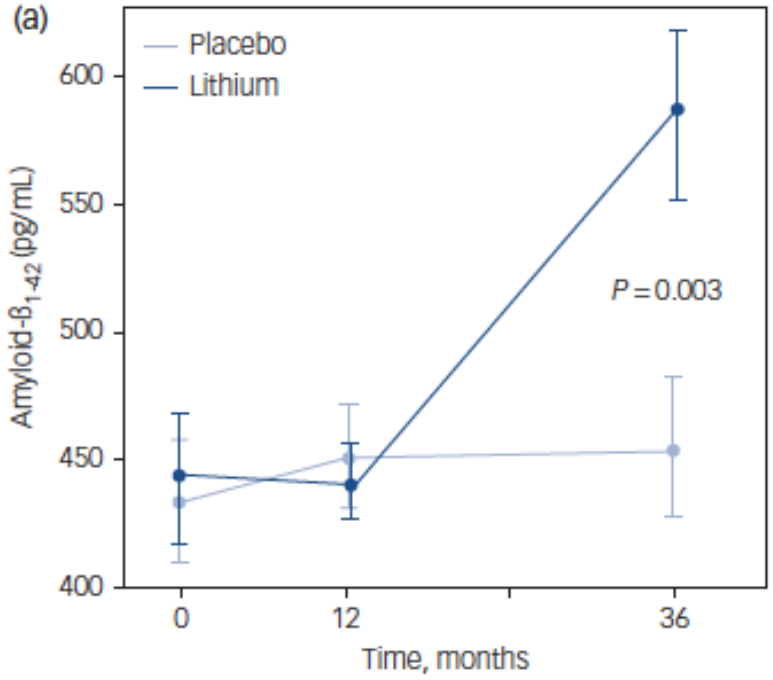
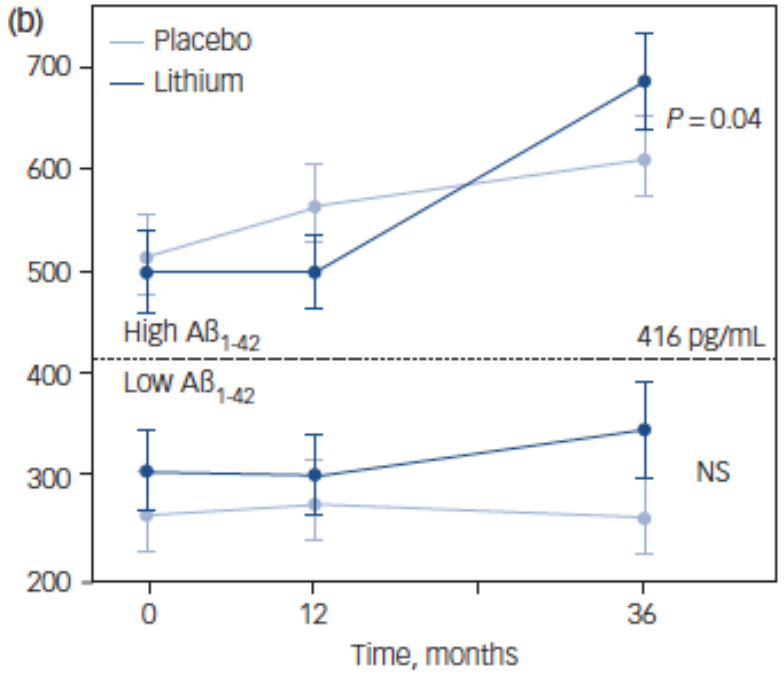
Lithium: increase in CSF $A\beta_{1-42}$ (T0 vs. 36 months)

'AD-signature':
- ↓ $A\beta_{1-42}$
- ↑ total TAU
- ↑ p-TAU







- Increase in CSF T-Tau but not p-Tau: suggestive of neurogenesis
- Greater effect among cases of 'late-stage MCI' (i.e., higher baseline CSF p-Tau)

- Increase in CSF $A\beta_{1-42}$: suggestive of amyloid clearance from the brain
- Greater effect among cases of 'early-stage MCI' (i.e., higher baseline CSF $A\beta_{1-42}$)

Conclusions

1. **Lithium-treated patients: cognitive and functionally stable over 2 years**
   - ADAS-Cog, CDR-SoB and memory scores

2. **Reduction in CSF phospho-Tau (1 year)**
   Increase in CSF $A\beta_{42}$ (3 years)

Evidence of disease-modification?

Discussion

1. **Long-term lithium: cognitive/functional benefits**
   - AD-specific? When to start? How long? Doses?
2. **Modification of AD-related CSF pattern**
   - Dephosphorylation of Tau (1 year)
   - Long-term lithium: amyloid clearance
   - Increased T-Tau *but not P-Tau* after 3 yrs: neurogenesis?
3. **Effect partially mediated by GSK-3B**
   - Tissue-specific; short duration; therapeutic window
4. **Other mediators of the lithium effect:**
   - BDNF, Tau, PLA_2, cytokines, mitochondria, mTOR (etc…)

Disease modification in AD

- *After 20 years of extensive (and expensive) experimentation, no DMT compound has yet been approved for clinical use;*
- *Meta-analyses also failed to support significant benefits.*

What went wrong with anti-amyloid therapy?

1. **Methodological (RCT design) → → Short duration? Start at preclinical?** Li
2. **Efficacy vs. Effectiveness → → Too late to clear Aβ? Wrong Aβ peptides?**
3. **Molecular target (Aβ peptides) → → Refine Aβ? other/multiple targets?** Li
4. **Disease model (Aβ hypothesis) → → EOAD/FAD; DS-AD / Non-amyloid?**
5. **Intervention reach → anti-AD or antiDEMENTIA? Multimodal approach?** Li

Thank you!

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