

Research Blog for January 2020

Anti-amyloid antibodies clear brain amyloid, would they improve cognition?

With anti-amyloid antibody Aducanumab's resurrection driving renewed interest in anti-amyloid therapies against Alzheimer's disease, researchers at the [12th Clinical Trials on Alzheimer's Disease conference](#), held last December, have provided updates on their own. Presentations on [Gantenerumab](#), [Donanemab](#), and [BAN2401](#) reinforced previous reports that all three mop up plaques, and added more evidence that this clearance is sustained over time, even after a treatment interruption. There are hints—though that is all they are at this point in time—that amyloid clearance correlates with preserved memory, as well.

- Gantenerumab and donanemab drive plaque load to zero over time.
- Clearance with BAN2401 maintained even after a break of several years.
- Crenezumab has little effect on plaque or tangle buildup.

<https://www.alzforum.org/news/conference-coverage/amyloid-clearance-check-cognitive-benefit-um-maybe>

Exercise and Brain Health Activities Are Associated with a Slower Rate of Frontotemporal Dementia (FTD)

Persons with a genetic risk for frontotemporal dementia seem to benefit from exercise and engaging in activities associated with brain health such as, reading, games, and socializing, according to results of a longitudinal study published in January in *Alzheimer's & Dementia*.

The findings are part of the so-called ARTFL/LEFFTES study, a multicenter study following 174 families with a history of FTD. There are 105 mutation carriers (C9orf72/MAPT/GRN) and 69 non-carriers in the study.

Dr Kaitlin Casaletto, PhD, a neuropsychologist and assistant professor at the University of California, San Francisco Memory and Aging Center, and her colleagues reported that greater physical and cognitive activities led to an estimated 55 per cent slower clinical decline in those who carry a gene for FTD. Even leisure activities seemed to have a role in slowing cognitive decline. In fact, those who had tissue loss in their brain but reported

the highest activity levels performed two-fold better on a range of cognitive tests conducted annually compared with those who spent less time on these activities.

Changes in brain volume itself did not appear to be related to this effect, although the scientists said that the number of patients in the study may have been too small.

The results so far only report a correlation and does not show cause and effect. It is possible that some participants have less-active lifestyles because they have a more severe or aggressive form of FTD, impacting their ability to be active. Clinical trials that manipulate cognitive and physical activity levels in people with FTD mutations are needed to prove that lifestyle changes can alter the course of the disease.

The findings suggest that cognitive reserve may have a role in the progression of this disease—even with strong disease genes at play. It is still too early to know how long these activities will confer some protection against the biology of this disease. The scientists are now trying to understand how exercise and other lifestyle activities protect the diseased brain.

<https://journals.lww.com/neurotodayonline/blog/breakingnews/pages/post.aspx?PostID=900>

The Role that Fragmented Sleep Plays in Cognition

A new study suggests that disrupted sleep throughout older age is accompanied by rapid ageing and over-activity of brain's immune cells, potentially contributing to cognitive impairment.

Older adults who had experienced greater fragmented sleep showed higher levels of a gene signature suggestive of aged immune cells in the brain (microglia), and they performed worse on annual cognitive tests.

The findings—which were based on data from two prospective, observational, community-based studies of older persons who had donated their brains and medical records for research purposes—underscore the role that poor sleep can play in late life and cognition.

“These findings add more evidence that fragmented sleep is bad for the brain,” said Andrew S.P. Lim, MD, associate professor of neurology at University of Toronto and senior investigator of the study, published December 11 in *Science Advances*. “It means that sleep problems in older people need to be taken seriously.”

More research is needed to test whether modifying sleep can reverse these changes, and to figure out how much sleep fragmentation is enough to trigger activated microglia or other changes in the brain's innate immune cells that regulate inflammation and other immune system functions, Dr. Lim said.

There is growing evidence that microglia play a role in Alzheimer's disease (AD) and in sleep. "Understanding microglia biology could ultimately allow us to target pathways in the brain that can reverse these problems," said Dr. Lim, a sleep neurologist.

https://journals.lww.com/neurotodayonline/Fulltext/2020/01090/The_Role_that_Fragmented_Sleep_Plays_in_Cognition.5.aspx

Vascular Dysfunction Taxes Cognition, but Not Via Amyloid, AD

- Is Too Much Vitamin B12 a Health Hazard?

Vitamin B12 is a commonly used supplement and has been tested as a preventive treatment for Alzheimer's disease, but could too much of it be bad for you?

In the January 3 JAMA Network Open, scientists led by Jose Flores-Guerrero and Stephan Bakker, University of Groningen, the Netherlands, reported that people who have high levels of the vitamin in their blood are more likely to die over the next eight years. This was true after adjusting for common comorbidities. It is unclear whether the elevated levels are a marker of underlying disease or a cause, but the authors caution that the supplement should be avoided if there is no underlying deficiency.

- Scientists monitored B12 levels in 5,571 people over eight years.
- Those with highest plasma B12 were more likely to die.
- Plasma B12 may be a marker of ongoing disease.

B12 helps metabolize the neurotoxic amino acid homocysteine, which has been reported to raise the risk of dementia and Alzheimer's disease. Some studies suggest low vitamin B12 levels associate with AD, though other studies refute that claim.

In clinical trials, B12 supplements have failed to prevent cognitive decline in healthy people, or slow it in those with mild to moderate AD. One two-year clinical trial did report less degeneration in Alzheimer's disease-vulnerable brain regions in people with high levels of plasma homocysteine with a combination of B vitamins, but other trials

have found higher mortality in elderly and hospitalized patients with high blood levels of vitamin B12.

No one cause of death emerged. In fact, the authors point out that elevated B12 levels may indicate liver damage or chronic kidney disease, suggesting an effect of ongoing disease rather than a cause. Still, the authors caution against supplements when there's no deficiency.

<https://www.alzforum.org/news/research-news/too-much-vitamin-b12-health-hazard>