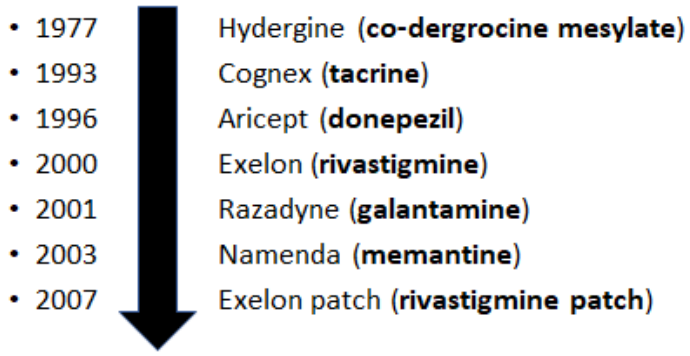
Adjourning Alzheimer's

Medical Therapies (Day 64)

As we all know, **medications** are often used in Alzheimer's. Unfortunately, while taking a tablet or wearing a patch every day is pretty easy, any benefits are usually small, and temporary. Moreover, when medications do provide benefit, it is only to "mask" the symptoms of Alzheimer's. Medications do not slow the pathological process down. Not even a little bit.

In 1977, the first medication for Alzheimer's, hydergine, was introduced. Later, several other medications made an appearance. Currently, the most widely prescribed medications for Alzheimer's today are the **"big four"** - donepezil, rivastigmine, galantamine, and memantine.



We learned earlier that the pathological hallmark of Alzheimer's is selective neuron loss within the hippocampus and cerebral cortex. Neurons in these brain structures produce high levels of two particular **neurotransmitters** (chemicals important for neuron-to-neuron communication) called acetylcholine and glutamate. Since many of the neurons that produce these neurotransmitters are lost, people with Alzheimer's have lower brain levels of acetylcholine and glutamate.

The first three of the "big four" medications - donepezil, rivastigmine, and galantamine - attempt to maintain brain acetylcholine levels by **inhibiting acetylcholinesterase**, the enzyme that normally degrades acetylcholine. This can produce improvements in cognition for people with mild to moderate Alzheimer's. However, even if improvement does occur it may come at the expense of adverse effects such as slowed heart rate, gastrointestinal upset, vivid dreams, drowsiness, and headache.

The last of the "big four" medications - memantine - **blocks glutamate** from binding its receptor, although how this effect might improve cognition is not understood. Memantine is not effective in people with mild Alzheimer's, but may have limited effectiveness in those people with moderate to severe Alzheimer's. It has a similar adverse effect profile to the acetylcholinesterase inhibitors.

It is not unreasonable for someone with Alzheimer's to try out one of the above medications; even a mild cognitive boost, in the absence of adverse effects, may be worth the minor hassle of taking a tablet or wearing a patch every day. However, large studies show that the "big four" medications collectively produce only a 3-point improvement on a 70-point cognitive scale after 6 months, which is about a **4% improvement**, with only 10% of people responding in a clinically meaningful way. Moreover, the overall duration of improvement is usually **6 to 18 months**, after which most people are "back to where they started." Thus, even if improvements do occur, they are usually slight, and transient.

As of 2019, the "big four" remain the mainstay of medical therapy for Alzheimer's. Yet other **potential medical therapies** have also been investigated for a number of years - immunotherapies, neurotrophic factors, and cell transplant therapies.

Vaccines against Alzheimer's?

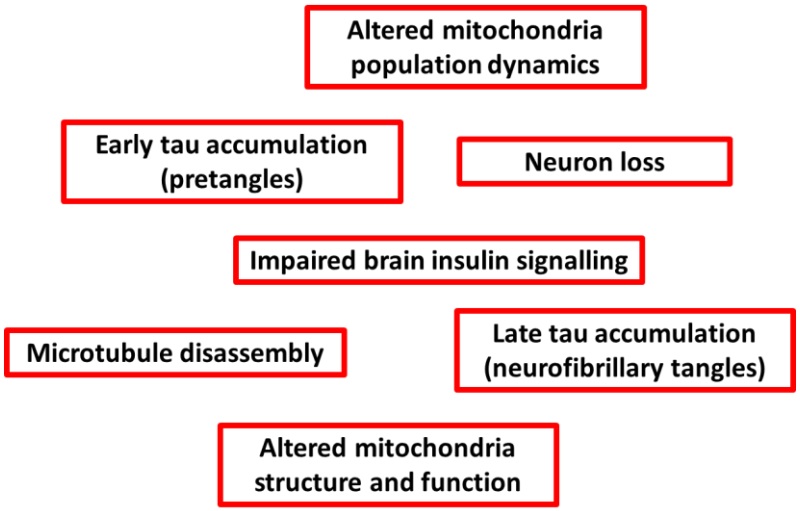
Immunotherapies aim to reduce or remove the abnormal amyloid-beta (Aβ) or tau proteins from the brain, either passively or actively. In **passive immunization**, anti-Aβ or anti-tau antibodies are injected into a person; the antibodies then seek and destroy the abnormal proteins. In **active immunization**, a vaccine containing a "mimic" of Aβ or tau is injected into a person, stimulating that person's own immune system to hunt and destroy the abnormal proteins.

Unfortunately, a number of large clinical trials have repeatedly shown that although immunotherapies can successfully destroy large amounts of Aβ and tau, the same immunotherapies **do not slow down Alzheimer's**. Given our earlier postulate that both Aβ and tau are highly unlikely to be the main culprits driving the Alzheimer's pathological process, these results may not be surprising. However, despite numerous trials showing that immunotherapies do not slow down Alzheimer's, some scientists remain convinced that immunotherapies can still work, if they could be used in early stages of Alzheimer's.

Hope also remains for neurotrophic factors and cell transplant therapies. **Neurotrophic factors** are proteins that direct and support the survival, growth, specification, and maturation of neurons. Unfortunately, after decades of research, neurotrophic facts have not shown substantial evidence of

benefit in Alzheimer's. **Cell transplant therapies,** such as stem cells, aim to replace the neurons lost in Alzheimer's with new, undifferentiated cells that can grow into new neurons. However, the long-term memories produced by an old, "experienced" neuron cannot be replaced by a new, "inexperienced" neuron - it seems highly unlikely how any approach aiming to replace neurons could be beneficial.

It is vital that we strive towards potential medical therapies that slow, stop, or reverse Alzheimer's. Yet for a therapy to be successful in this regard, surely it must address the **earliest and most central abnormalities seen in Alzheimer's** such as tau accumulation, mitochondria dysfunction, microtubule disassembly, and of course, impaired brain insulin signalling. Each of the proposed medical therapies discussed above ignores several of the most central facts about Alzheimer's; without facing these facts, it is difficult to see how any of them will ever succeed.



If we are to slow down or reverse Alzheimer's, we cannot ignore the central facts.

Let's sum up. Current medications may improve the cognitive symptoms of Alzheimer's in a minority of people, but the cognitive improvements are **small, and temporary**. Proposed future medical therapies, despite decades of research, **remain ineffective**. This is not surprising, given that all these medical therapies ignore a number of the most important facts about the Alzheimer's pathological process.

Medical therapies are easy to follow, but this apparent advantage may actually be part of the problem; **they don't take you to the edge**, the place where you challenge yourself. Medications do not help you reclaim your epigenetic power; they cannot awaken the anti-Alzheimer's genes that already exist within you, the ones we want to unleash against the pathological process in a multi-targeted manner. So, let's keep looking.

Matt (Neurologist, Waikato Hospital).

References

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