Parkinson Disease

Parkinson's is a disease difficult to treat, unlike Alzheimer's where we only need to solve the dementia problem by giving acetylcholine esterase inhibitors with a centrally acting activity like Scopolamine. Now Parkinson's is also a neurodegenerative disease where the dopaminergic activity is being lost. So multiple mechanisms, mainly for increasing dopamine levels, are being used, with paying attention to 2 major problems :-

1. Dopamine is binding nonspecifically.
2. This disease is associated with degeneration of dopaminergic neurons.
   Thus, the normal inhibitory influence of dopamine on the cholinergic neurons is significantly diminished, which result in the overproduction of ACT. This trigger abnormal signaling, resulting in loss of muscles movement.

Parkinson is characterized by tremors, muscular rigidity, bradykinasia (slow in the voluntary movements) where most patient are over 65 years old. The cause is unknown for most patients, rare to be secondary to viral encephalitis. Therapy aimed to restore dopamine and antagonizing the excitatory effect of cholinergic neurons, this restore the balance between dopamine/ACT in CNS.

I. Levodopa + carbidopa

Dopamine in the periphery causes nausea, hypertension, hyper- or hypothermia.
Levodopa is a prodrug that needs to be metabolized to dopamine. Giving it orally is ineffective because it's metabolized fast before reaching the blood (the problem isn't that Levodopa doesn't cross the BBB but that it gets metabolized before absorption into the blood at the first place). So now we know why Carbidopa is given besides the Levodopa; to make it available centrally and to inhibit the metabolism of it peripherally and thus reduce the side effects. This combination is found in one tablet.

We have one important issue though; the wearing off problem (the on-off problem) :-
It means that after being responsive for 2-3 years, the patient will deteriorate and this is because of the pathology of the disease; degenerating neurons until the patient is incapable of taking up Levodopa and convert it to dopamine.
Solutions : Increase the frequency or dose of administration (up to 5 times a day; In early stages it's about 3 times) but here the continuous stimulation of D2 receptors will cause dyskinesia. Another solution is the usage of COMT inhibitors.

II. COMT inhibitors (Entacapone)

The previously given carbidopa will not only inhibit the peripheral metabolism of Levodopa, it will also increase the levels of 3-O-methyldopa which competes with the transport of Levodopa to the central nervous system and the role of COMT inhibitors is clear now; they

decrease the plasma concentration of 3-O-methyldopa thus increase the central reuptake of dopamine.

Note : the dyskinesia side effect is less severe after taking COMT inhibitors than after increasing the frequency or dose of administration.

III. Selegiline

This is the next option in early-stage treatment of Parkinson's after Levodopa/carbidopa.
It's a selective inhibitor of central metabolism of dopamine; selective against MAO type B (Remember it's used in atypical depression by inhibiting MAO type A).

Selegiline exhibits little therapeutic benefit when used independently, but Enhances the action of Levodopa and when administered together, Selegiline substantially reduce the required dose of Levodopa.

Note : It causes hypertension in high doses because selectivity is lost.

IV. Dopamine agonists

This group includes

1. Two older agents (Bromocriptine and Pergolide) --> NOT important.
2. Two newer agents (Ropinirole and Pramipexole).

These agents has longer duration of action than that of Levodopa, thus have been effective in patients exhibiting fluctuation in their response to Levodopa.

Initial therapy with the newer agents is associated particularly with less risk of developing dyskinesia and motor fluctuations in compare to Levodopa (so they're NOT as effective as Levodopa). Also these agents are ineffective in patient who have shown no therapeutic response to Levodopa (as dopaminergic neurons are already been lost).

Note : Guidelines until now still recommend usage of Levodopa and carbidopa at early stages (but it's controversial in clinical practice).

Ropinirole and Pramipexole : They alleviate the deficit in both patients who have never treated with Levodopa and in patients with advanced Parkinson disease taking Levodopa.
They may delay the need to employ Levodopa in advanced Parkinson and may decrease the dose of Levodopa in advanced Parkinson.

Side effects : mainly hallucination (uncommon and occur more here than in Levodopa/carbidopa), hypotension and Involuntary sleep (uncommon and not seen in Levodopa/carbidopa).

V. Amantadine NOT important

An antiviral drug that may increase the release of dopamine from its neurons that was found by chance. Amantadine is less officious than Levodopa and tolerance develops more readily, However, it has lower side effects.

VI. Antimuscarinic agents (Benztropine and Biperidine)

Blocking of the cholinergic transmission produces effects similar to augmentation (rise) of dopaminergic transmission (Rarely used to treat Parkinson).

These agents may cause mood change and produce dryness of the mouth and visual problems. Interfere with the gastrointestinal peristalsis (constipation). Contraindicated in glaucoma.

Alzheimer Disease

Alzheimer characterized by loss of cholinergic neurons (but we really don't understand the full mechanism).

Pharmacological intervention for Alzheimer disease is only palliative (calming) and provides modest short-term benefit.
None of the current therapeutic agents alter the underlying neurodegenerative process (similar to Parkinson's disease).

Current therapeutics are aimed at either :-

1. Improving cholinergic transmission within the CNS.
2. Preventing the excitotoxicity actions of NMDA glutamate receptors in selected brain areas.

Many studies have linked the progressive loss of cholinergic neuron and presumably cholinergic transmission within the cortex, to the memory loss that hallmark symptoms of Alzheimer disease. Inhibition of Acetylcholinesterase within CNS will improve cholinergic transmission. The most common drug is **Donepezil**. At best these agents provide a modest reduction in the rate of loss of cognitive functioning in Alzheimer disease.

Common adverse effect include : anorexia, muscles gramps, and diarrhea.

Also we have NMDA receptor antagonist : Memantine.

Memantine has shown to prevent or slow the rate of memory loss in Alzheimer dementia, even in patient with moderate to severe cognitive losses.
Memantine is well tolerated, with few dose related adverse effects, which include confusion and restlessness.