Drug Discovery for Parkinson's Disease

New targets and drug discovery

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What Strategy Is Most Straight Forward In PD Drug Discovery ?

Problems:

Animal models in PD have limited predictable value; genetic links between target and disease population may not have general applicability, and it is difficult to confirm disease modifying activity in clinical trials.

Potential solutions:

(1) focus on symptoms where reliable animal models are available and

(2) incremental enhancement of efficacy/tolerability of drugs with established mechanisms and effects in patients.

Disease Modification

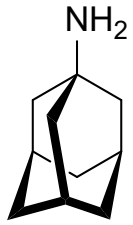
- Anti-Lewy body related efforts: focus on changing the alpha-synuclein dynamics (distribution, break down, generation of Lewy bodies)
- Targets derived from genetic linkage studies
- Neurotrophic factors
- Tau
- Targets reducing oxidative stress
- Targets reducing inflammation

Symptomatic focus: Motor symptoms

- Dyskinesias
- On-off symptoms
- Restless leg syndrome

Symptomatic focus: motor symptoms

- COMT inhibition: Develop brain-selective (membrane bound) COMT inhibitors to enhance tolerability
- Enhance receptor profile of amantadine

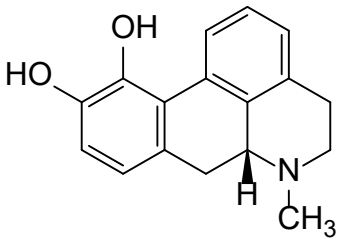


Amantadine

Parkinson's disease: causes & cures

Symptomatic focus: On-Off

- Dual acting drug candidates: Adenosine A2A antagonist + NMDA antagonist
- Apomorphine-like pharmacodynamics with improved kinetics



Apomorphine

Symptomatic focus: Dyskinesias

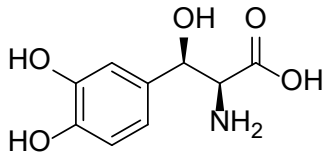
- mGlu5: negative allosteric inhibitors
- mGlu4: positive allosteric inhibitors
- 5-HT1A receptor agonism

Symptomatic Focus: Non-Motor Symptoms

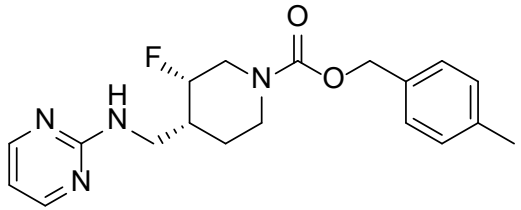
- Constipation
- nOH
- Dementia/cognitive decline
- Psychosis
- Sleep disturbances
- Depression

Symptomatic Focus: nOH

- Northera (droxidopa): prodrug of NE
- NMDA antagonism: CERC-301 (rislenemdaz), a NR2B antagonist



Droxidopa

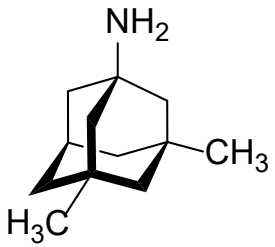


Rislenemdaz

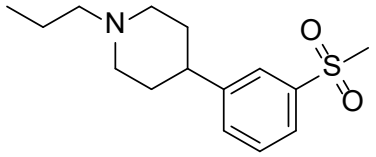
Parkinson's disease: causes & cures

Symptomatic Focus:Dementia/Disease Modification

- Muscarinic m1 or m4 agonist
- Memantine: NMDA antagonist and sigma-1 partial agonist
- Huntexil: D2 modulator, sigma-1 agonist.



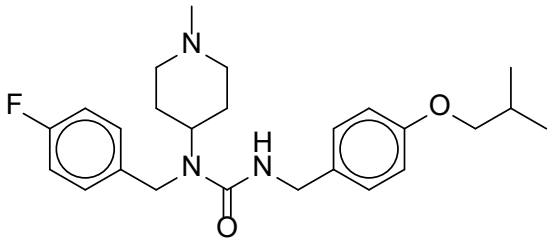
Memantine



Huntexil

Symptomatic Focus: Psychosis/sleep

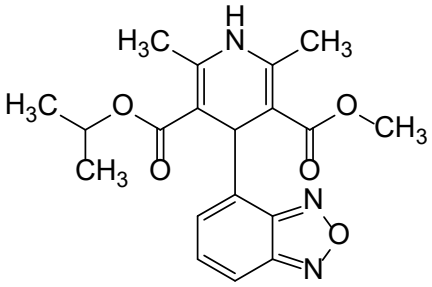
Pimavanserin: 5-HT2A receptor antagonist, sleep modulator



Pimavanserin

Antagonizing oxidative stress

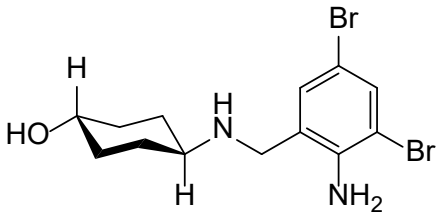
- Calcium channel antagonism, in particular Cav1.3 antagonism may protect dopaminergic neurons
- Isradipine is a non-selective Cav1.2/Cav1.3 antagonist. Has produced promising data in patients but edema a problem.



Isradipine

Target Identified by Genetic Link

- GBA1 mutations major risk factor for PD
- GBA1 encodes glucocerebrosidase (GCase). Mutations affect improper folding of Gcase. Decreased GCase levels lead to increased alpha synuclein accumulation and cognitive and motor deficits
- Ambroxol acts as a chaperone on mutated Gcase but is also an enzyme inhibitor.



Ambroxol

Conclusions

- Many targets have potential to slow down or stop progression of disease but difficult to prove efficacy in pivotal studies.
- PD patients suffer from many symptoms that are sub-optimally treated. By developing symptomatic treatments that address known targets, or by generating new medicines with improved target profiles, one may achieve great benefits to patients.