Pharmacologic Treatment of Parkinsonism & other movement disorders

Parkinson's disease

- Parkinson's disease results from the degeneration of dopaminergic neurons in the substantia nigra
- These neurons project to other structures in the basal ganglia
- The basal ganglia includes the striatum, substantia nigra, globus pallidus and subthalmus

Parkinson's Disease

- 'classic triad':
  - Resting tremor
  - Muscle rigidity
  - Bradykinesia.

Aetiology

- Remain largely unknown
- Heredity have a limited role
- Defective gene responsible for a rare condition called autosomal recessive juvenile parkinsonism (teens and 20s)
- **Oxidative stress theory (environmental origin)**

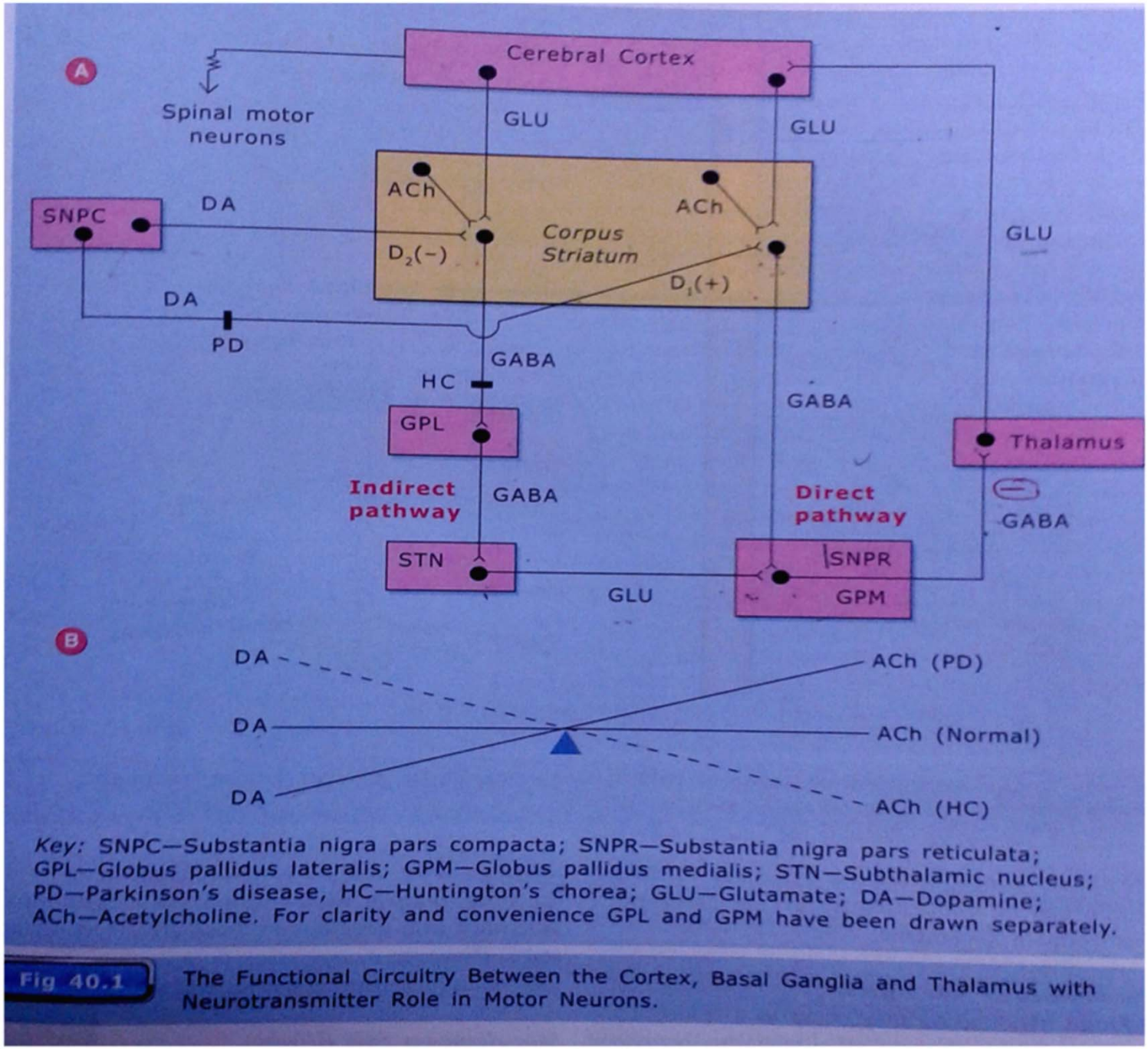
Oxidative stress and Parkinson's Disease

- Dopamine metabolism results in reactive oxygen species (oxidative deamination of dopamine by MAO -> H2O2).
- Glutathione (primary CNS antioxidant) levels are depressed in Parkinson's disease.
  - Renders neurons more susceptible to ROS toxicity.
  - Observed in workers exposed to insecticides/pesticides.

MPTP and Dopaminergic Neurons

- MPTP – induces oxidative damage to dopaminergic neurons.
  - Effect identified in 1976 due to incorrect synthesis of MPPP, an analogue of pethidine (Demerol – opioid analgesic).
  - Symptoms of Parkinson's disease observed within 3 days.

- Effect on dopaminergic neurons is indirect.
  - MPTP itself is not a neurotoxin.
  - Enzymatically converted (via MAO-B) in the CNS to MPP+, which selectively targets dopaminergic neurons in the substantia nigra.
  - MPP+ - high-affinity substrate for dopamine reuptake transporters localized to the pre-synaptic membrane of neurons in the substantia nigra.

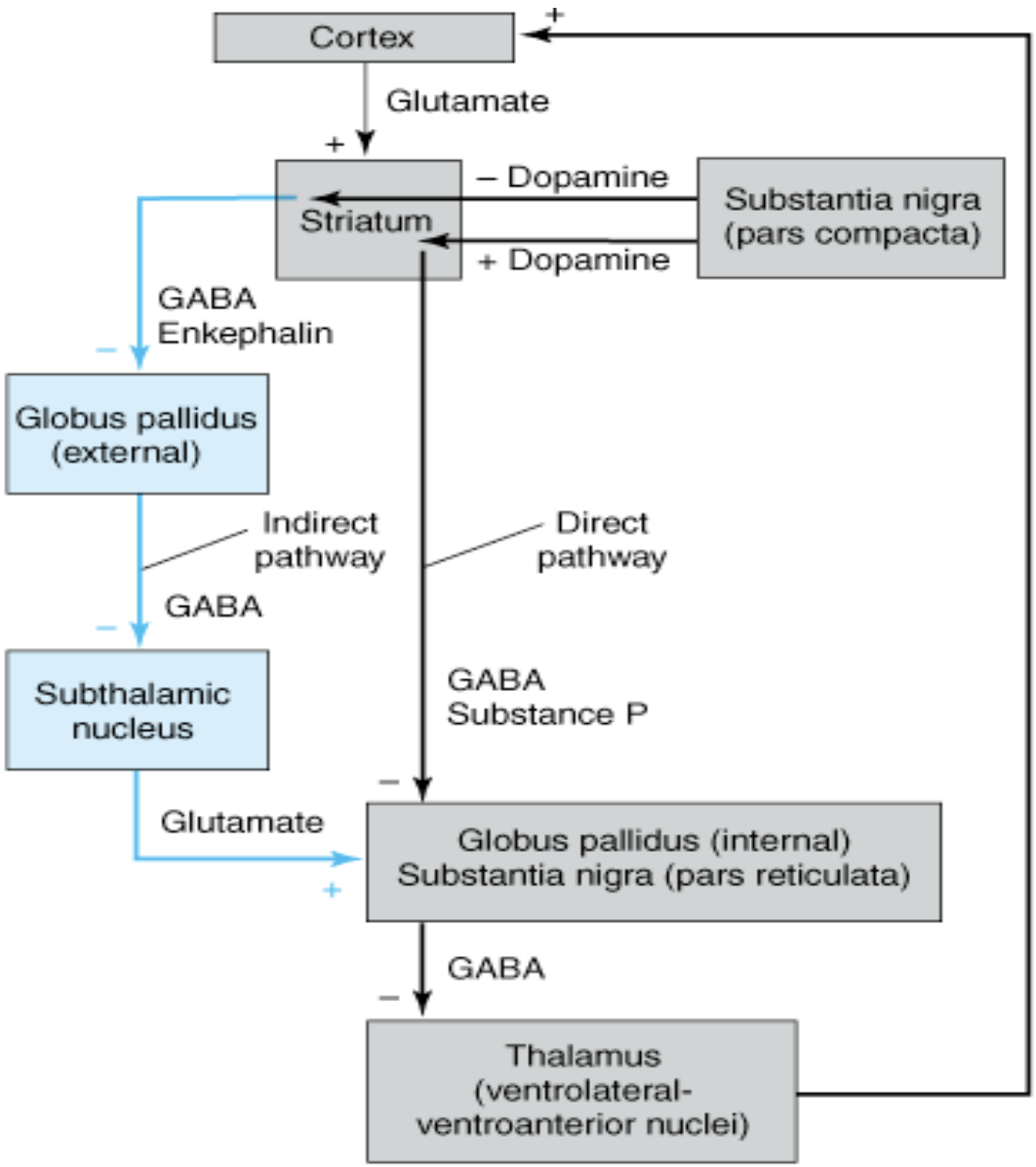


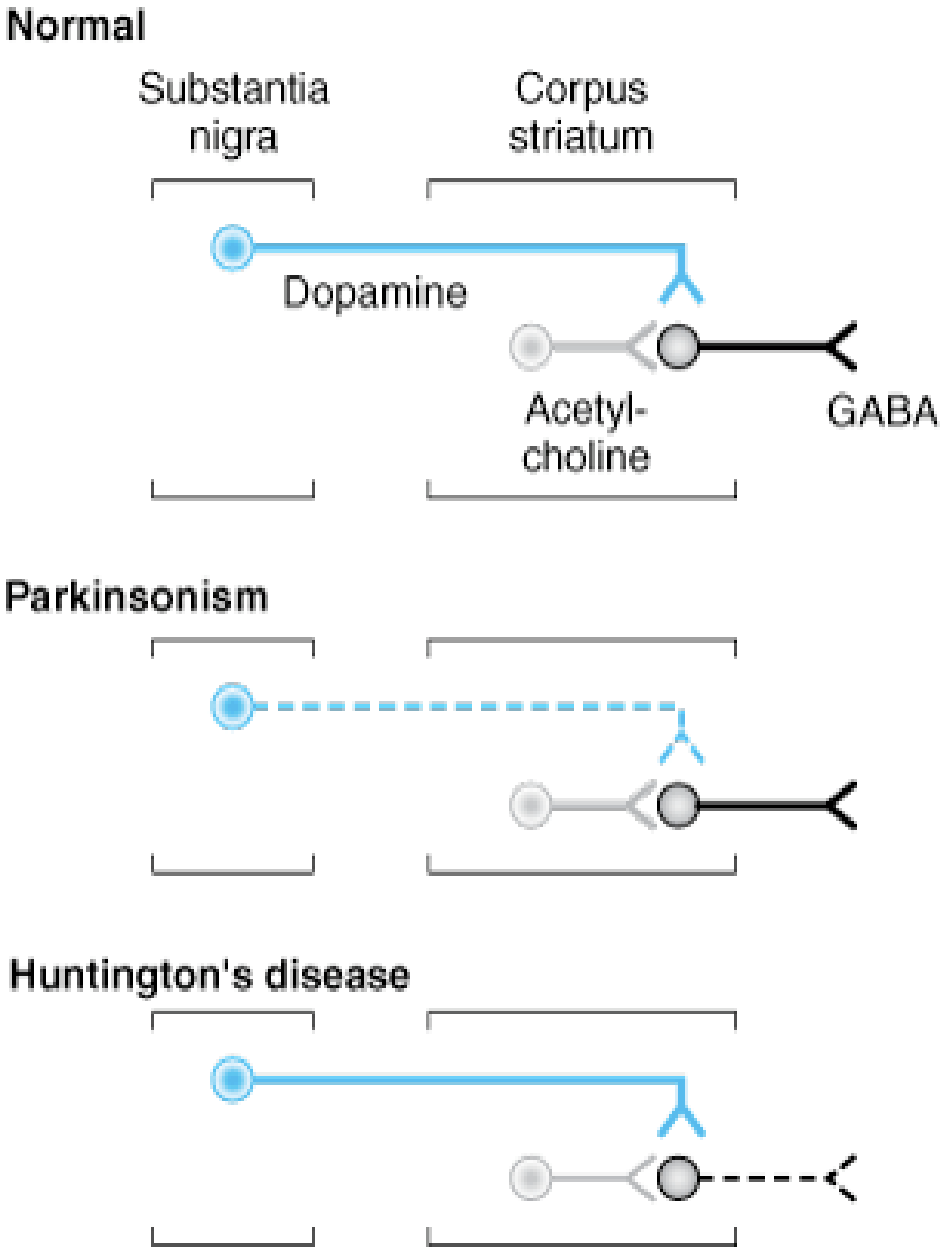
Key: SNPC—Substantia nigra pars compacta; SNPR—Substantia nigra pars reticulata; GPL—Globus pallidus lateralis; GPM—Globus pallidus medialis; STN—Subthalamic nucleus; PD—Parkinson's disease, HC—Huntington's chorea; GLU—Glutamate; DA—Dopamine; ACh—Acetylcholine. For clarity and convenience GPL and GPM have been drawn separately.

Fig 40.1 The Functional Circuitry Between the Cortex, Basal Ganglia and Thalamus with Neurotransmitter Role in Motor Neurons.

Pathogenesis

- Dopaminergic neuron degeneration: decreased activity in the direct pathway and increased activity in the indirect pathway
- As a result thalamic input to the motor area of the cortex is reduced …..Patient exhibits rigidity and bradykinesia
- α-synuclein – abnormally deposited in the CNS in Parkinson's Disease, leading to the formation of Lewy bodies (the pathological hallmark of PD).


Cortex
+
Glutamate
+
Striatum
– Dopamine
+ Dopamine
Substantia nigra
(pars compacta)
GABA
Enkephalin
–
Globus pallidus
(external)
Indirect
pathway
Direct
pathway
GABA
–
Subthalamic
nucleus
GABA
Substance P
–
Glutamate
Globus pallidus (internal)
Substantia nigra (pars reticulata)
+
GABA
–
Thalamus
(ventrolateral-
ventroanterior nuclei)



Parkinson's disease

(bradykinesia, akinesia, rigidity, tremor, postural disturbances)

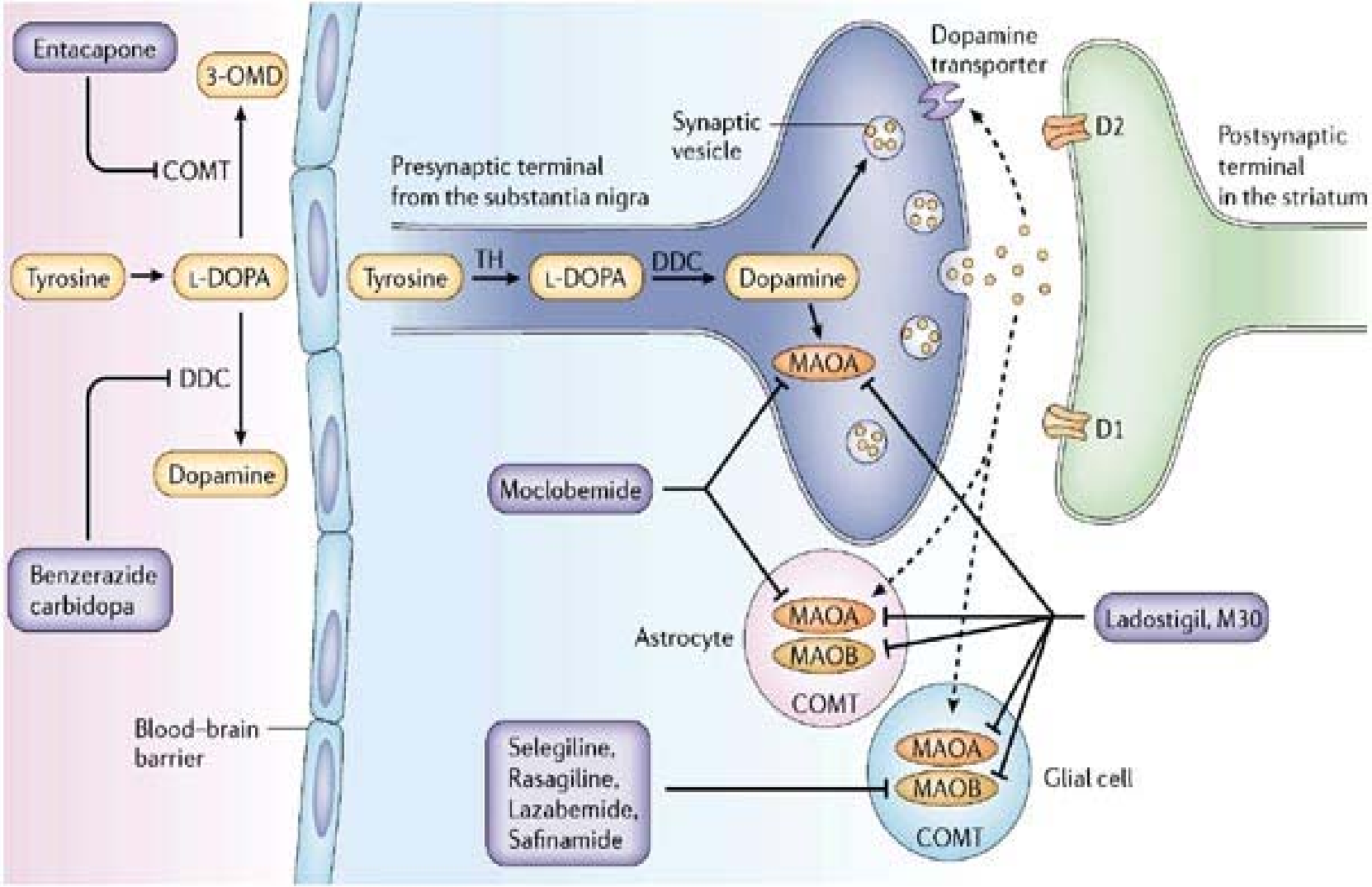
Huntington's disease

(hyperkinesia)

Pharmacological Treatment of Parkinson's Disease

- Goals:
  - Primary = restore dopamine receptor function.
  - Secondary = inhibition of muscarinic cholinergic receptors.
- Drugs used :
  - Levodopa
  - Dopamine Receptor Agonists
  - Monoamine Oxidase Inhibitors (MAOIs).
  - Catechol-*O*-Methyltransferase (COMT) inhibitors.
  - Muscarinic Cholinergic Receptor Antagonists.
  - Amantidine.

Pharmacological Treatment of Parkinson's Disease



From: Youdim et al. 2006. *Nature Rev Neurosci.* **7**: 295-309

1. Levodopa

- Prodrug – immediate metabolic precursor of dopamine.
  - Levodopa can cross the blood-brain barrier while dopamine cannot.
  - CNS – enzymatically converted to dopamine by L-aromatic amino acid decarboxylase.
- 1-3% of Levodopa actually enters the brain.
  - Primarily due to extracerebral metabolism.
  - Extracerebral metabolism can be reduced by administering a non-BBB permeating peripheral L-aromatic amino acid decarboxylase inhibitor.

1. Levodopa…. Mechanism of Action:

- Restoration of synaptic concentrations of dopamine.
  - Activation of post-synaptic D2 receptors = inhibit adenylyl cyclase = promote voluntary movement via indirect pathway.
  - Additional benefit obtained via activation of post-synaptic D1 receptors = stimulate adenylyl cyclase = facilitate voluntary movement via direct pathway.

Therapeutic Use

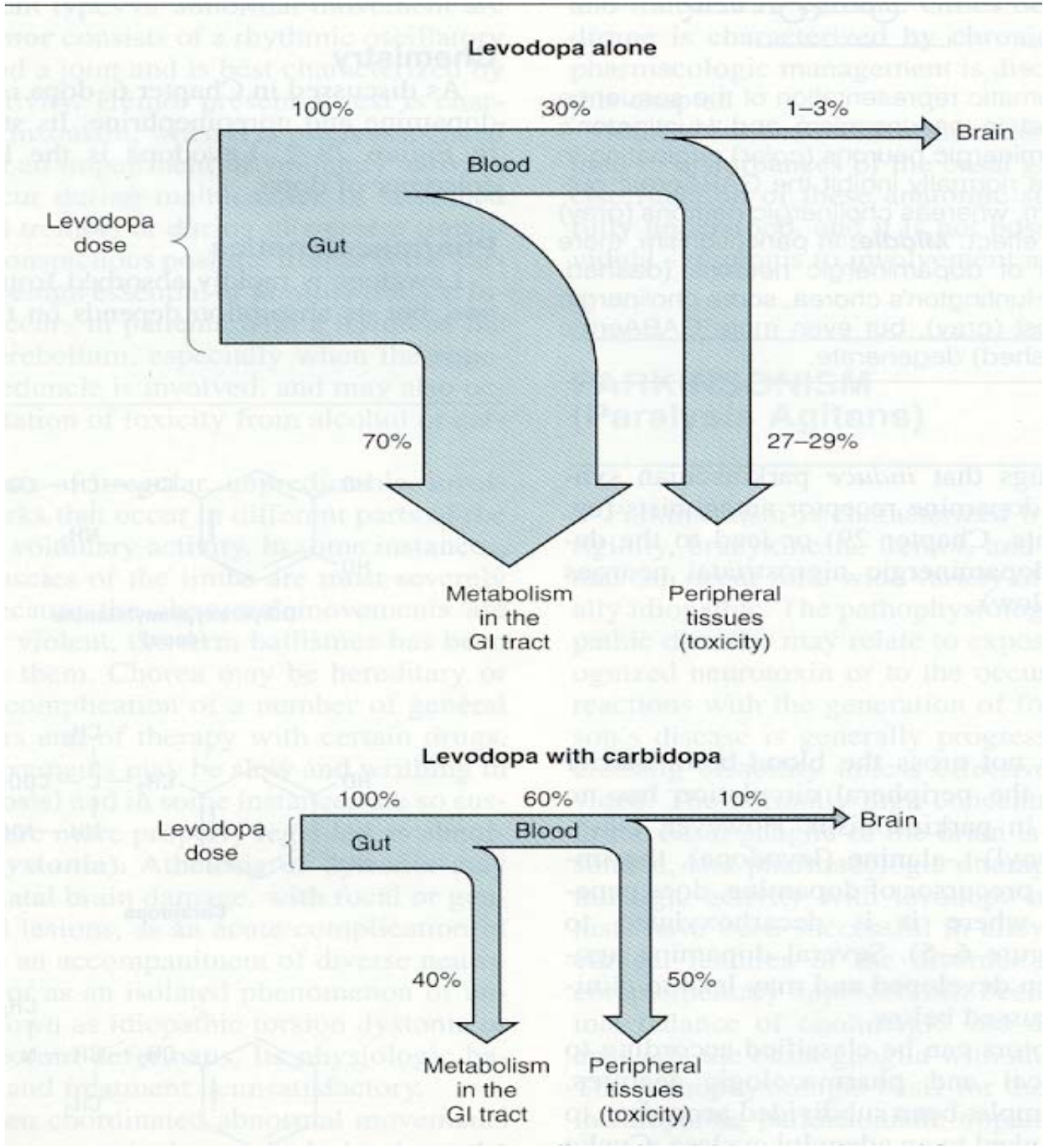
- **Best results obtained in first few years of treatment.**
- 80% of patients show marked initial improvement (primarily in terms of resolution of muscle rigidity and bradykinesia).
- 20% show virtually normal motor function.
- Over time, levodopa therapy becomes less effective
  - Progressive loss of dopaminergic neurons.
  - Downregulation of D1/D2 receptors on post-synaptic terminals.
  - Some patients require reduced doses of levodopa to prevent side effects.

Carbidopa

- Is a structural analogue of L-dopa
- Inhibits the conversion of L-dopa to dopamine in peripheral tissue
- Carbidopa is highly ionized at physiological pH and does not cross the blood-brain barrier, so it does not inhibit the formation of dopamine in CNS
- It reduces GI and cardiovascular side effects of L-dopa and enables about 75% reduction in dosage of L-dopa

Levodopa-carbidopa

- L-dopa-carbidopa sustained release combination designed to reduce “wearing off” effect or end 0f dose akinesia
- Sinemet®, Co-carbidopa® =
- carbidopa+ levodopa 1:4 ,1:10
- 25:100mg ; 25:250 mg


Levodopa alone
100%
30%
1–3%
Brain
Blood
Levodopa dose
Gut
70%
27–29%
Metabolism in the GI tract
Peripheral tissues (toxicity)
Levodopa with carbidopa
100%
60%
10%
Brain
Levodopa dose
Gut
Blood
40%
50%
Metabolism in the GI tract
Peripheral tissues (toxicity)

1. Levodopa – Adverse Drug Effects.

- Acute side effects – related to increased peripheral concentrations of dopamine.
  - Nausea
  - Anorexia – treated with peripherally-acting dopamine antagonist (i.e., Domperidone).
  - Hypotension – particularly in patients on anti-hypertensives.
- Other common side effects:
  - Confusion.
  - Insomnia
  - Nightmares.
  - Schizophrenic-like syndrome – delusions and hallucinations due to enhanced CNS concentrations of dopamine.

1. Levodopa – Adverse Drug Effects….

Dyskinesias – occur in 80% of patients on long-term levodopa therapy.

- Choreiform movements
- Dose-related – higher doses = increased risk.
- Occur more frequently in younger Parkinson's patients

"Wearing off " effect

ADRs…..

"On-off" Effect – fluctuations in clinical response to levodopa.

- "Off" = marked akinesia.
- "On" = improved mobility but marked dyskinesia.
- Thought to be related to fluctuations in levodopa plasma concentrations.
- Fluctuations can be "smoothed out" by incorporating a dopamine receptor agonist into pharmacotherapy.
  - Pramipexole./Ropinirole./Apomorphine

Levodopa: DI & CI

- Pyridoxine: not to be given with levodopa alone
- MAO –A inhib: hypertensive crisis
- CI: Psychotic patients, Angle –closure glaucoma. Cardiac disease-only with carbidopa, Active peptic ulcer: gi bleeding

- DRUG HOLIDAY :d/c for 3-21 days: not recommended

2. Dopamine Receptor Agonists.

- Ergot derivatives:

1. Bromocriptine – selective D2 receptor agonist. Now rarely used ,better new DA agonists . Dose built up slowly over 2-3mths from 1.25mg BID to upto 7.5-30 mg
2. Pergolide : directly stimulates both D1 and D2 receptors.

- Loses efficacy over time.
  - Associated with valvular heart disease (33%).,hence d/c in many countries

Dopamine Receptor Agonists…

Ropinirole – D2 receptor agonist.

- Effective as monotherapy in patients with mild disease.
- Started -0.25 mg TDS---upto 2-8mg TDS.
- Metab by CYP3A2 : DI

Pramipexole

- preferential affinity for D3 receptor (also D2/D4).
- Used primarily in patients with advanced Parkinson's disease.
- Possibly neuroprotective – scavenge H_2O_2
- Started at 0.125 mg TDS---upto 0.5-1.5 mg TDS. Dose adjustment in renal ds

Rotigotine: TTS patch , efficacy similar ,local rxn

Dopamine Receptor Agonists…Adverse Effects

1. GIT : anorexia, N, V : minimized by taking with meals. Constipation, Dyspepsia, bleeding peptic ulcers
2. CVS: postural hypo esp on initiation, painless digital vasospasm (ergots).Arrythmias
3. Dyskinesias: like that by levodopa

Misc.: headache, nasal congestion,pulm. Infiltrates,pleural & retroperitoneal fibrosis,erythromelalgia

ADRs: Dopamine agonists…contd..

4. Mental disturbances: confusion, hallucinations, delusions : more common with these than with levodopa.

Disorders of impulse control – compulsive gambling, shopping ,betting,

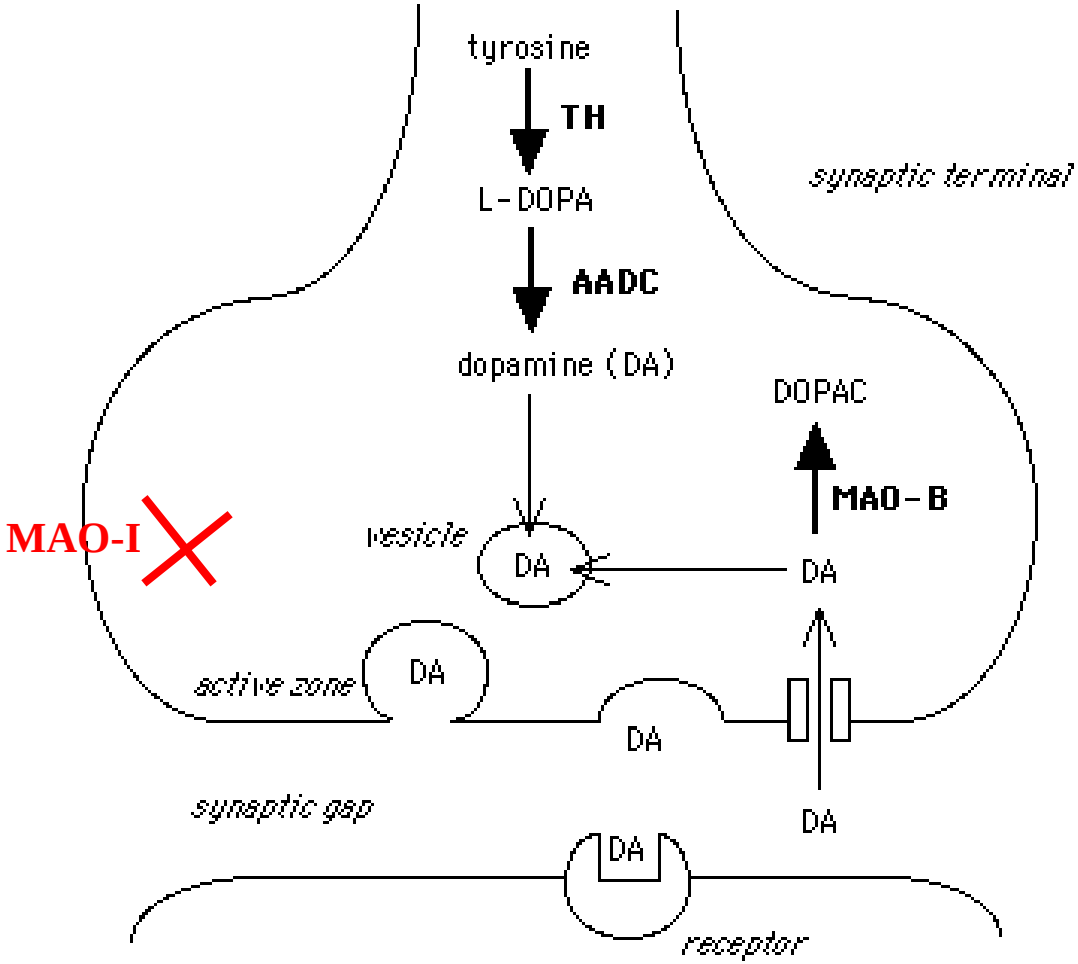
daytime sleep attacks: ropinirole, pramipexole

CI: h/o psychotic illness or recent MI ,active peptic ulcer. Ergot deriv CI in peripheral vascular disease.

3. Monoamine Oxidase Inhibitors (MAOIs)

- Two types of MAO have been characterized.
  - MAO-A – primarily metabolizes NE and 5-HT.
  - **MAO-B – primarily metabolizes dopamine.**
- Selegiline and Rasagiline.
  - Selective, irreversible inhibitors of MAO-B.

MAO-B Inhibitors



3. Selegiline – MAO-B Inhibitor

- Effective in early Parkinson's disease (as monotherapy or in combination with levodopa).
- Enables reduction in levodopa dose or may smooth the "on-off" fluctuations associated with levodopa.
- Metabolite = Desmethylselegiline – neuroprotective.

- Adverse Effects
  - Selectivity for brain MAO-B makes selegiline less likely to produce ADRs involving peripheral tyramine (i.e. cheese rxn).

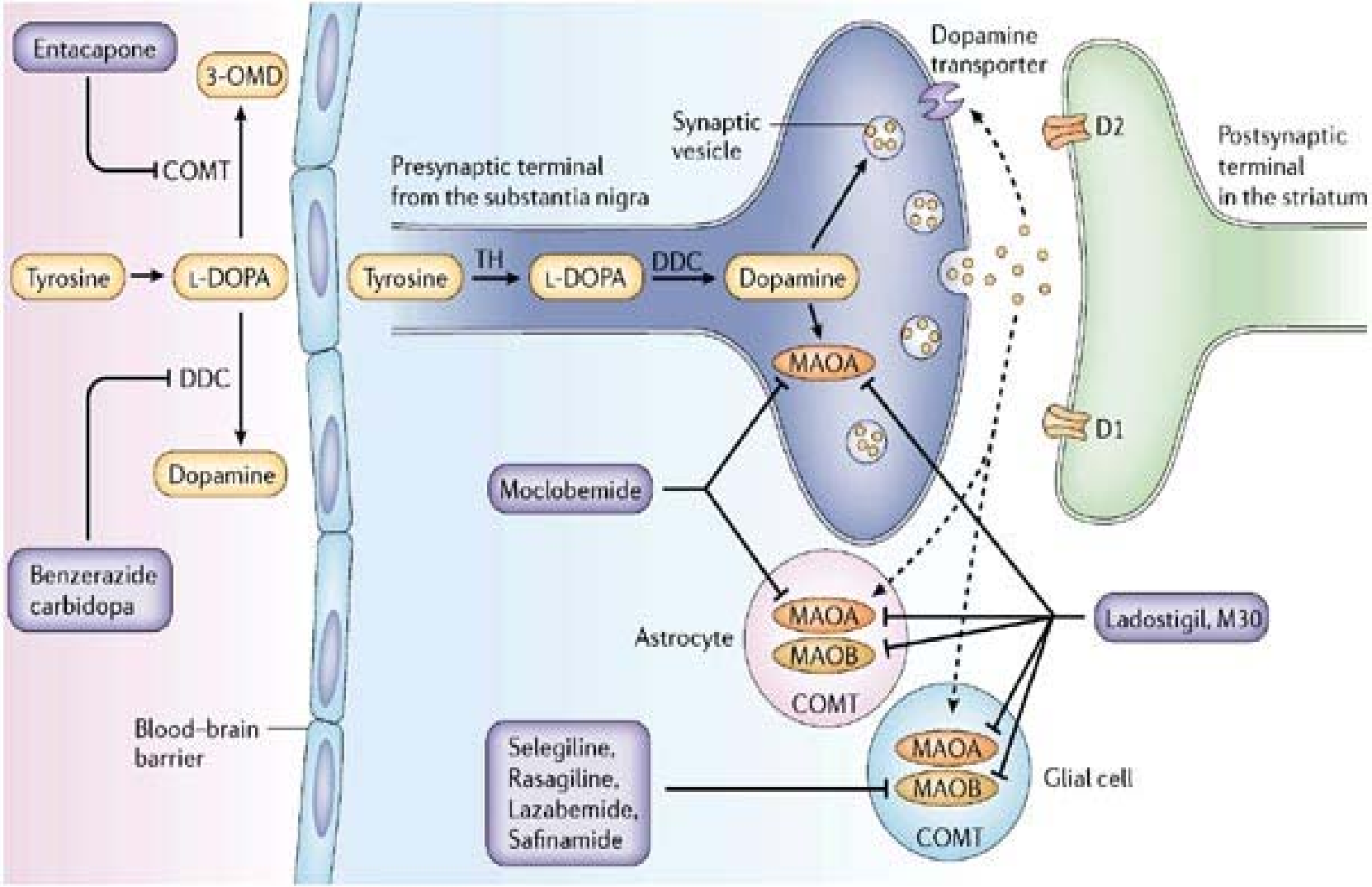
Selegiline – MAO-B Inhibitor…

- Blocks MAO-A at high doses.
  - Hypertensive crisis due to peripheral accumulation of NE.
- Fatal hyperthermia – may occur when administered in conjunction with meperidine, cocaine, or fluoxetine

4. Catechol-*O*-Methyltransferase (COMT) Inhibitors.

- Inhibition of L-aromatic amino acid decarboxylase is associated with compensatory activation of COMT.
  - Increased plasma levels of 3-OMD = poor response to levodopa (competition for active transporter in the gut and at the BBB?).
- Adjunctive therapy in patients treated with levodopa.

Pharmacological Treatment of Parkinson's Disease



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4. Catechol-*O*-Methyltransferase (COMT) Inhibitors.

- Tolcapone and Entacapone
  - Selective COMT inhibitors – diminish peripheral metabolism of levodopa.
  - May also reduce “on-off” fluctuations.
  - Adverse Effects: Related to increased plasma concentrations of levodopa.
    - Include dyskinesias, nausea, and confusion.
    - Other side effects: diarrhea, abdominal pain, orthostatic hypotension, sleep disorders, orange urine discoloration.
    - Tolcapone – potentially hepatotoxic.

5. Muscarinic Cholinergic Receptor Antagonists.

- Muscarinic Receptors – localized to striatal neurons.
  - Mediate cholinergic tremor
  - May cause presynaptic inhibition of dopamine release.
- Trihexyphenidyl and Benztropine –
    - Useful in patients administered neuroleptics as anti-dopaminergic properties of these drugs antagonize effects of levodopa.
    - Improve muscle rigidity and tremor but have little effect on bradykinesia.

Antimuscarinics….

– Adverse Effects –

- Characterized as “atropine-like” = dry mouth, inability to sweat, impaired vision, urinary retention, constipation, drowsiness, confusion.

6. Amantidine

- Antiviral drug with anti-Parkinsonian properties.
- Mechanism of action is unclear
  - Potentiates dopaminergic function by modifying synthesis, release, or reuptake of dopamine.
  - Therapeutic Effectiveness –
    - Less effective than levodopa or bromocriptine
    - Therapeutic benefits are short-lived.
  - .

Amantidine..

– Adverse Effects –

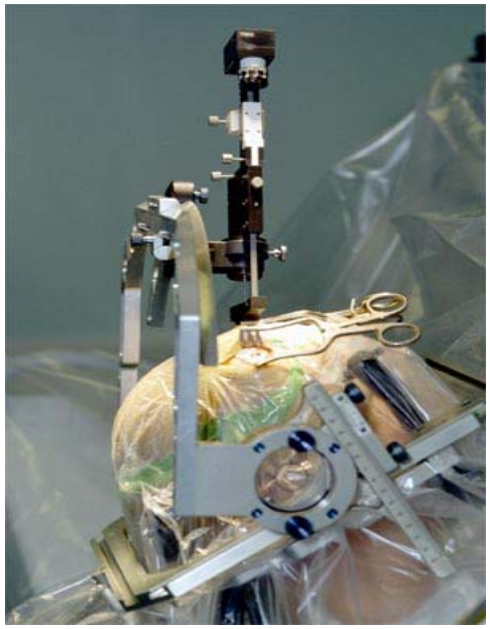
- Primarily CNS = restlessness, depression, irritability, insomnia, agitation, excitement, hallucinations, confusion.
- Overdoses = acute toxic psychosis.
- Others = headache, edema, postural hypotension, heart failure, GI disturbances

Apomorphine

- Apomorphine – potent D1/D2 agonist.
  - Given via subcutaneous injection to provide temporary relief of “off” periods of akinesia.
  - Short period of effectiveness (~ 2 h).
  - Associated with several side effects (i.e., dyskinesias, drowsness, sweating, hypotension

Surgery -

- **Deep Brain Stimulation**
  - Brain pacemaker, sends electrical impulses to brain to stimulate the subthalamic nucleus.
  - Improves motor functions and reduce motor complications.
  - Complications include: brain hemorrhage, seizures, death.



Huntington's disease

- Characterized by loss of GABAergic medium spiny projection neurons in the striatum
- Caused by glutamate-induced neurotoxicity (?)
- Loss of GABAergic neurons that project from GP leads to disinhibition of thalamic nuclei and increase output to motor area of the cortex
- Symptoms consistent with excess dopaminergic activity

Huntington's disease: Treatment

- D2 receptor antagonist such as haloperidol and chlorpromazine have some effect at controlling the excess movement and some aspects of the psychiatric dysfunction
- Diazepam potentiates GABA and may reduce excess movement but only in the early stages of the disease
- Depression and impulsive behaviours may respond to antidepressant or propranolol (β-adrenergic antagonist)