ANTI-PARKINSON

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Pendahuluan


James C Parkinson

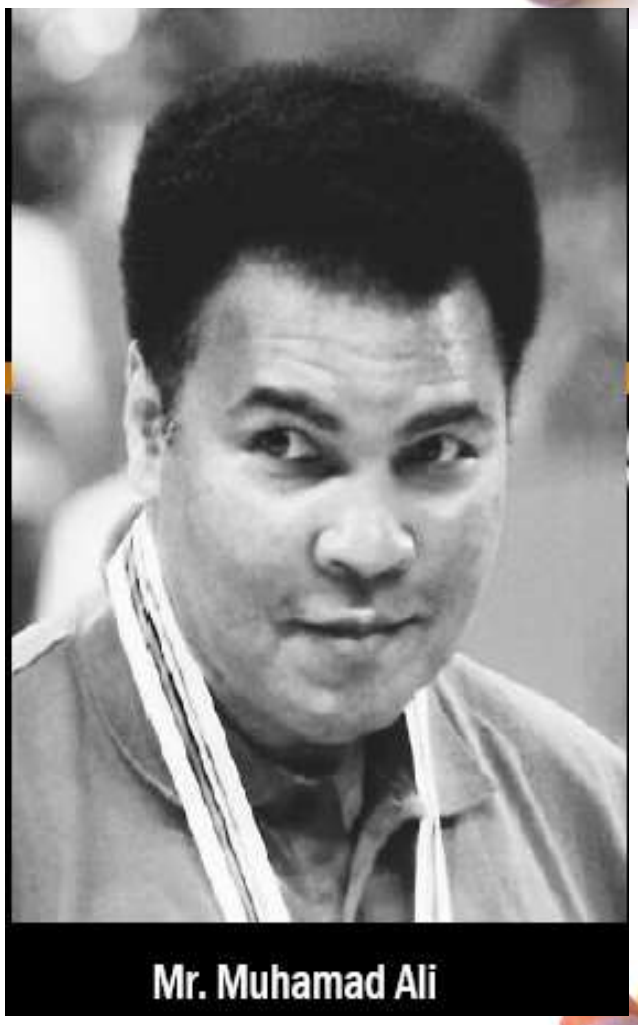
- Th 1817 → Dr. James Parkinson mempublikasikan kasus pasien yang mengalami "shaking palsy" (shake = gemetar, palsy = kelumpuhan) ➔ Sejak saat itu muncul istilah Parkinsonism ➔ menggambarkan gejala klinik yang ditandai dg : gemetar, kekakuan, bradikinesia, dan instabilitas postural.

Klasifikasi Parkinsonism

- Primer (idiopatik) : Penyakit Parkinson
- Sekunder (simptomatik)
  - Drug induced
  - Infeksi
  - Metabolik
  - Struktural (tumor otak, hidrosefalus, trauma)
  - Toksin (CO, CS2, CN, Mg, MPTP)
  - Vaskular (multiinfark)

Penyakit Parkinson (PD)

- Penyakit gangguan syaraf kronis dan progresif yang ditandai dengan gemetar, kekakuan (rigiditas), berkurangnya kecepatan (akinesia) gerakan, dan ekspresi wajah kosong seperti topeng dg salivasi berlebihan.
- Kejadian meningkat dengan meningkatnya usia (angka harapan hidup) → Onsetnya terjadi pada sekitar usia 60 th



Mr. Muhamad Ali

Gejala dan tanda

Tanda utama :

tremor → pada saat istirahat, tingkat keparahan relatif stabil

kekakuan → gerakan putar siku dan pergelangan tangan berkurang, ekspresi wajah kaku

melemahnya gerakan → akinesia atau bradikinesia → langkah pendek pendek, lambaian tangan berkurang

ketidakseimbangan tubuh → sering jatuh

Tanda non-motorik :

inkontinensia

dementia

depresi

dysphagia

gangguan tidur

konstipasi

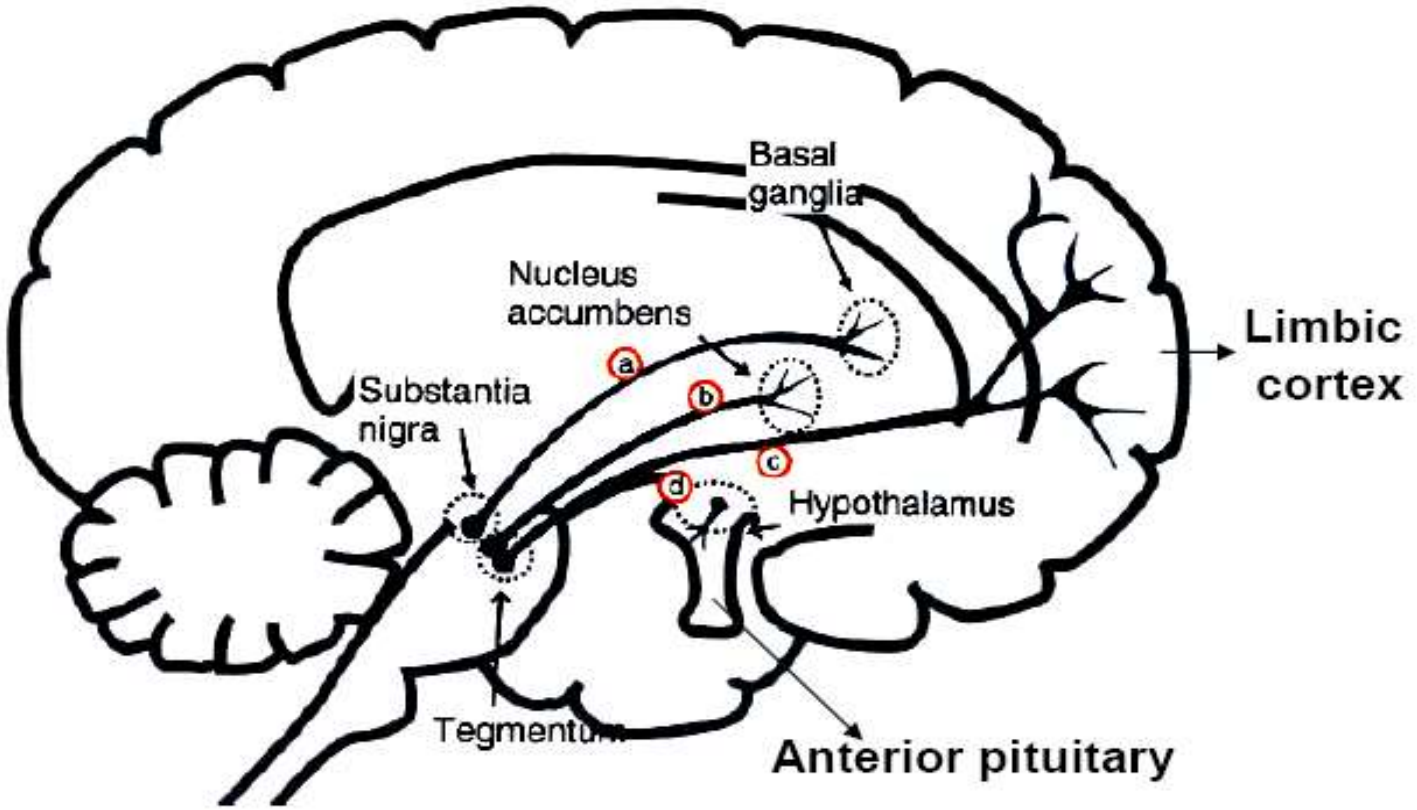
berkeringat,

dll.

Patofisiologi

- Abnormalitas patologis yang utama: degenerasi sel dengan hilangnya neuron dopaminergik yang terpigmentasi di pars compacta substansia nigra di otak dan ketidakseimbangan sirkuit motor ekstrapiramidal (pengatur gerakan di otak).
- Pd orang normal : berkurangnya dopamin 5% per dekade
- Pd penderita Parkinson ➔ 45% selama dekade pertama setelah diagnosis
- Biasanya gejala baru muncul ketika dopamin di striatal sudah berkurang sampai 80%

Dopamine Pathway



a = nigrostriatal pathway

b = mesolimbic pathway: ***Increase in dopamine causes positive symptoms of schizophrenia***

c = mesocortical pathway: ***Deficit in dopamine causes negative and cognitive symptoms of schizophrenia***

d = tuberoinfundibular pathway

Jalur Dopaminergic Di SSP

- ✓ **Mesolimbic : VTA (mid brain) →limbic system**
  Aktifitas DA meningkat → positive symptom Schizoprenia

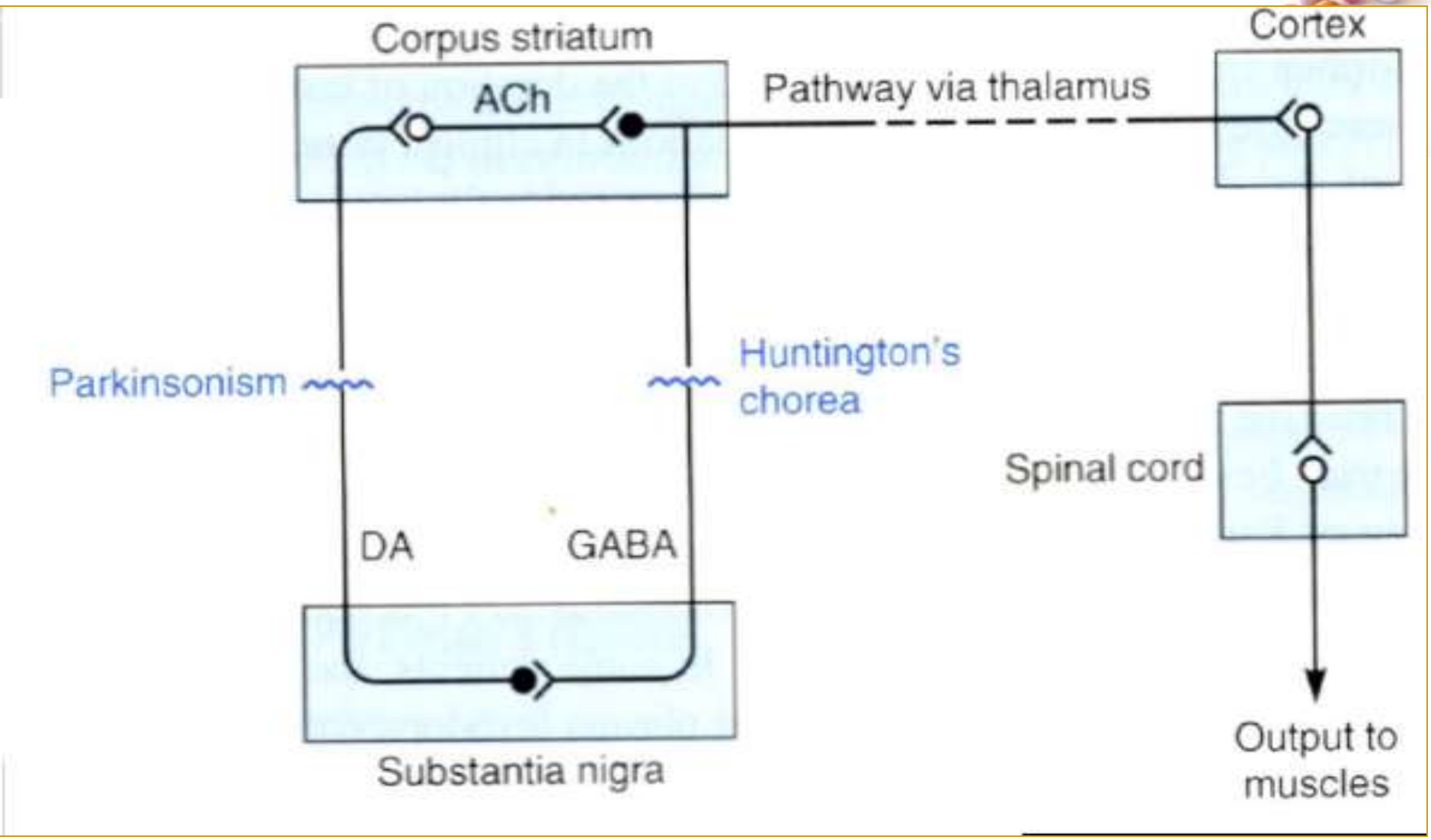
- ✓ **Mesocortical: VTA →prefrontal cortex :**
  Aktifitas DA turun → negative symptom Schizoprenia

- ✓ **Nigrostriatal : s.nigra (mid brain) → corpus striatum (extrapyramidal tract):pengendalian motorik.**
  Aktifitas DA turun → Extra Pyramidal Syndrome

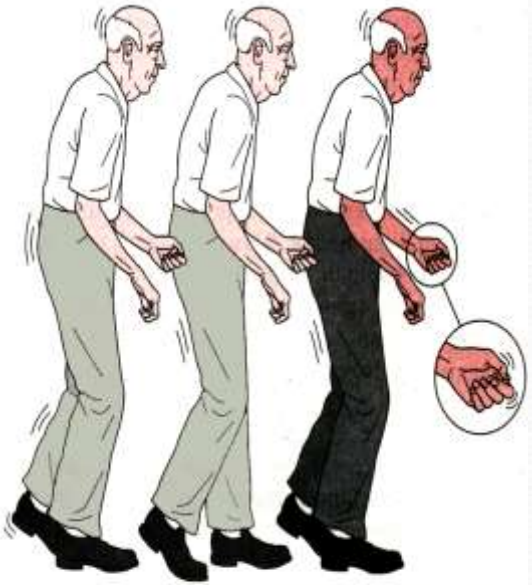
- ✓ **Tuberoinfundibular : Hypothalamus →Hypophyse**
  Aktifitas DA naik → menghambat sekresi Prolactin

- ✓ **Area prostrema : Chemotrigger Zone (CTZ)**
  Aktifitas DA naik → Emesis

- Hilangnya neuron dopaminergik di subt nigra menyebabkan turunnya dopamin di striatal ➔kontrol motorik terganggu ➔kekakuan & bradikinesia
- Degenerasi saraf dopamin pada nigrostriatal menyebabkan peningkatan aktivitas kolinergik striatal ➔ efek tremor

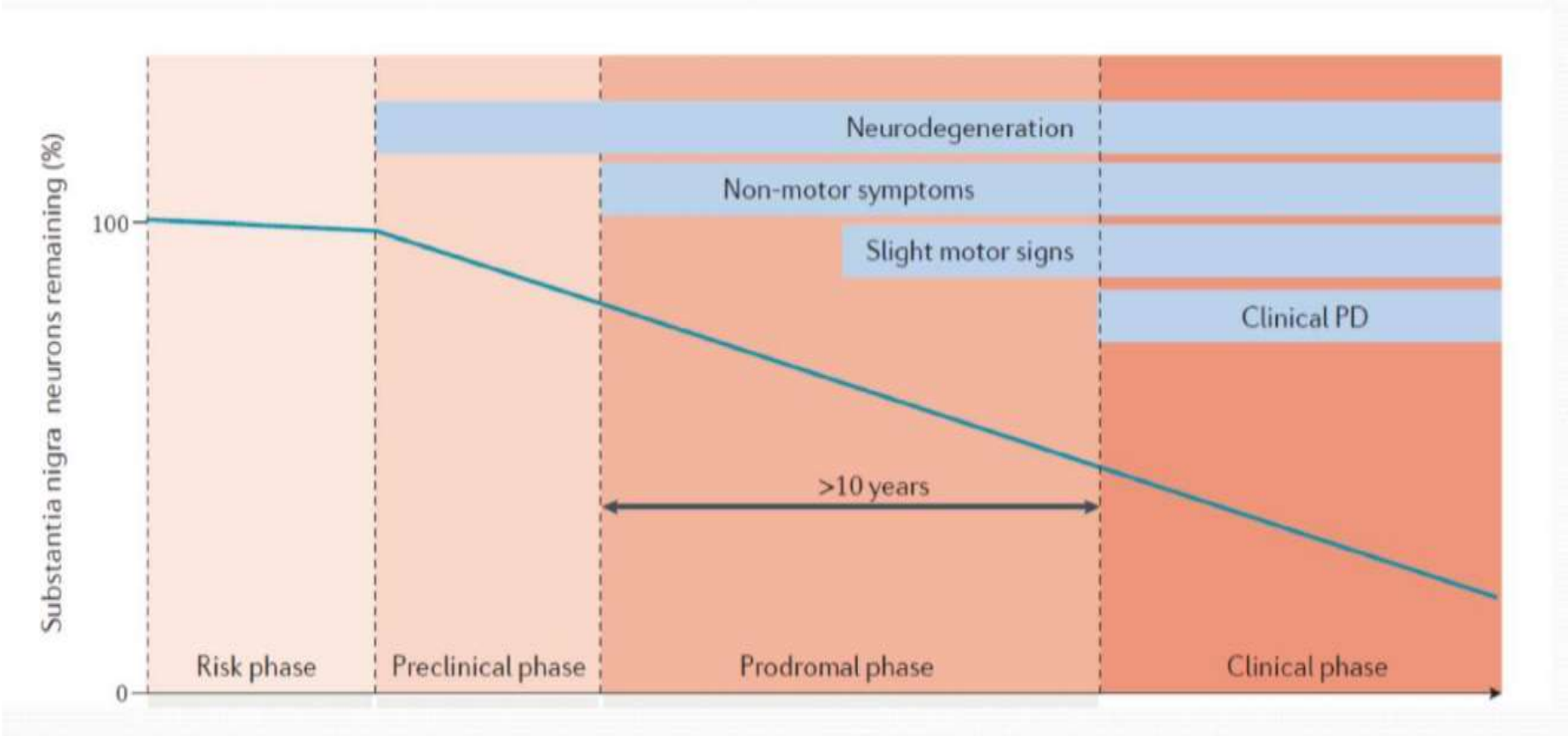


Dopamine from Substantia Nigra decreases release of acetylcholine from striatum ➔ **Dopamin di corpus striatum meregulasi aktivitas kolinergik**
Degenerasi dopamin di striatal ➔ aktivitas kolinergik meningkat

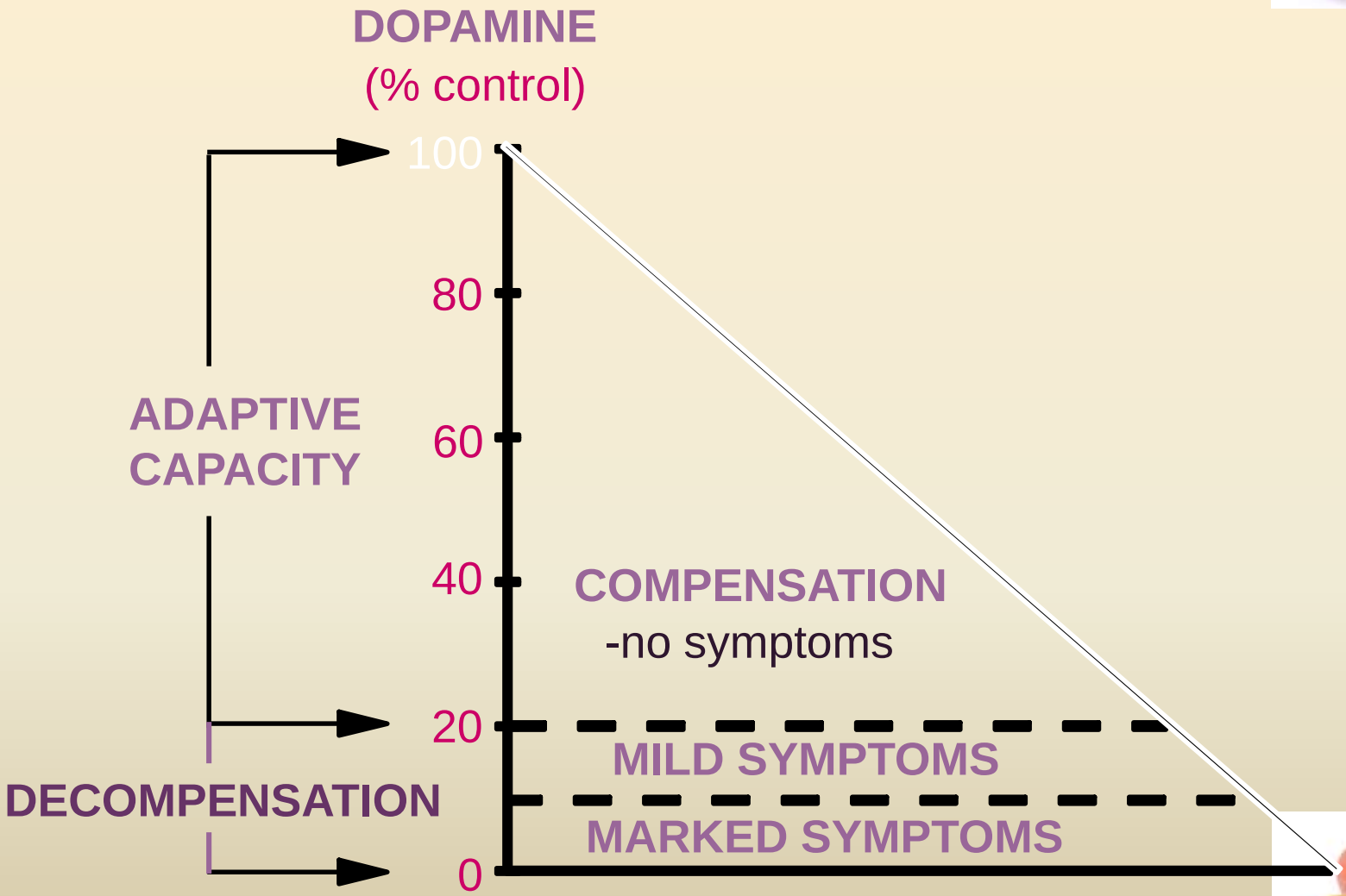


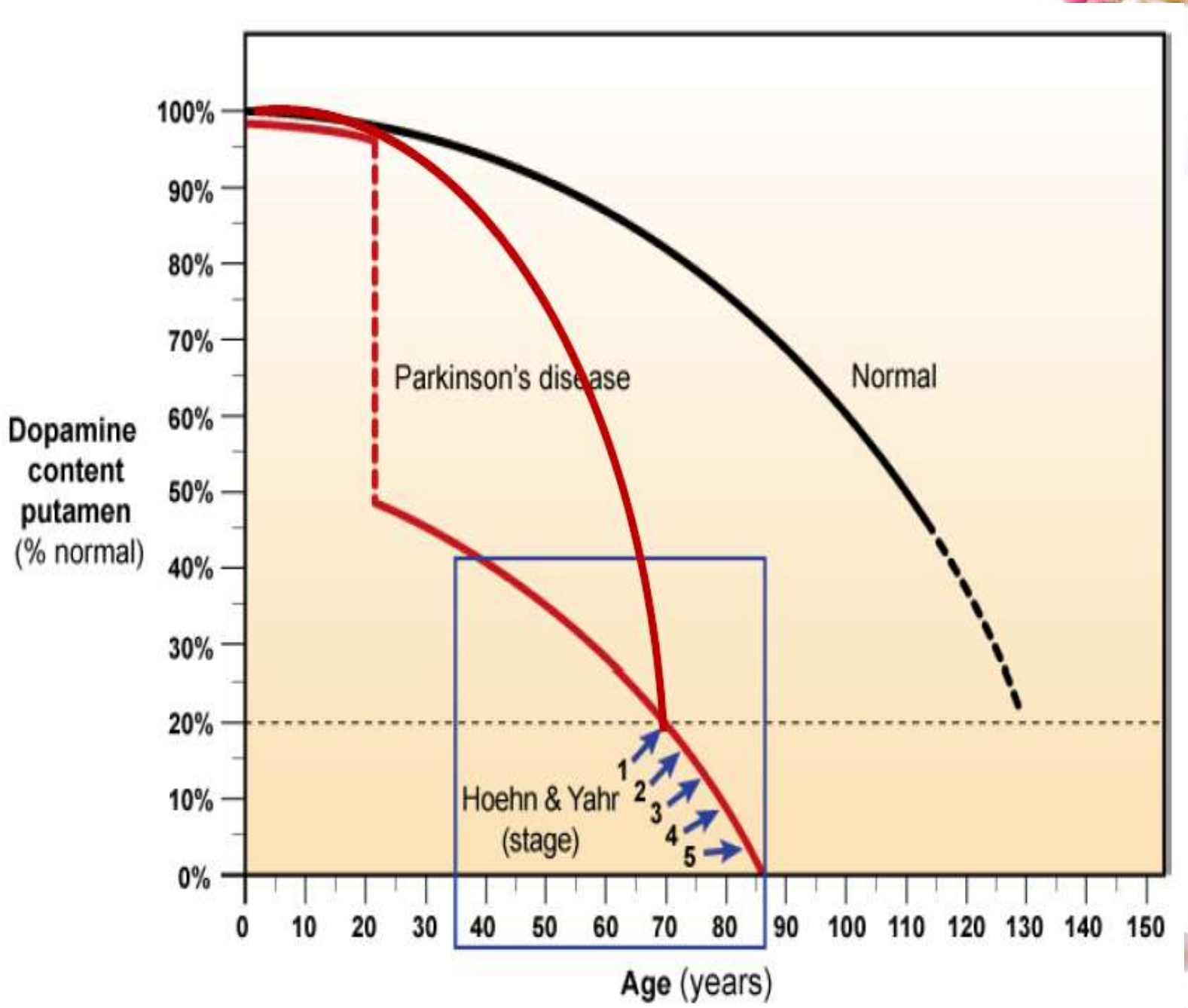
20.2 CLASSIC SYMPTOMS OF LATE-STAGE PARKINSON'S DISEASE, including a stooped and rigid posture, shuffling gait, tremor, a masklike facial appearance, and "pill rolling" (*inset*). (After Markey, 1986.)

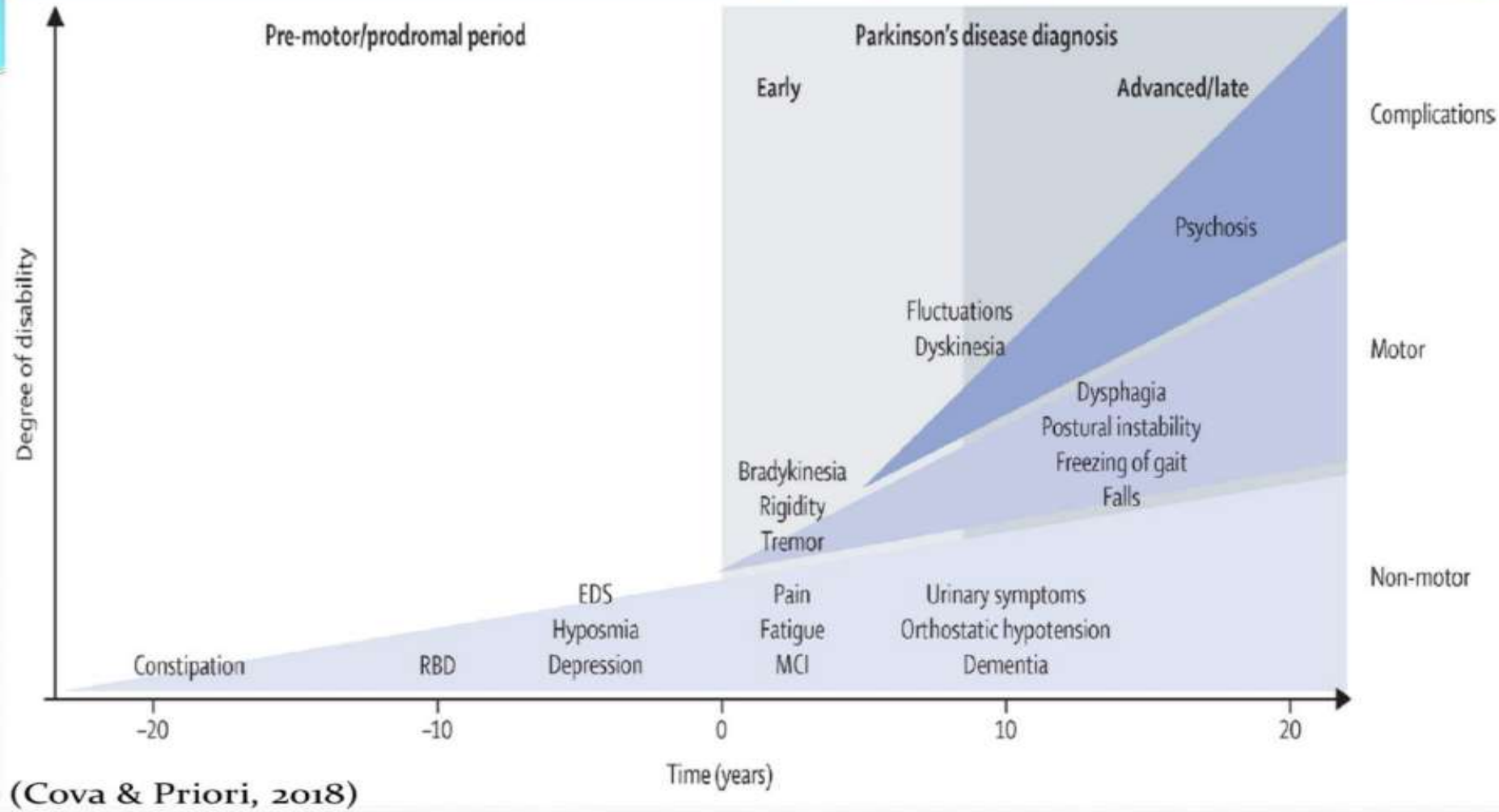
- PD awal dibagi menjadi tiga tahap:
  - PD praklinis : proses neurodegeneratif dimulai, tanpa gejala atau tanda-tanda penyakit yang jelas.
  - PD prodromal : gejala dan tanda-tanda penyakit ini hadir, tetapi tidak cukup untuk mendefinisikan gambaran klinis lengkap PD.
  - PD klinis : diagnosis PD tercapai, berdasarkan adanya tanda motorik klasik (kriteria MDS-PD).


Substantia nigra neurons remaining (%)
100
0
Neurodegeneration
Non-motor symptoms
Slight motor signs
Clinical PD
>10 years
Risk phase
Preclinical phase
Prodromal phase
Clinical phase

STAGES OF PARKINSON'S DISEASE




Dopamine content putamen (% normal)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Parkinson's disease
Normal
Hoehn & Yahr (stage)
1
2
3
4
5
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
Age (years)



(Cova & Priori, 2018)

DRUG INDUCED PARKINSONISM

- Iatrogenic- induced by antipsychotic drugs.

- Butyrophenone dan Phenothiazine → antagonist reseptor D2
- Reserpine dosis tinggi → deplesi Dopamine

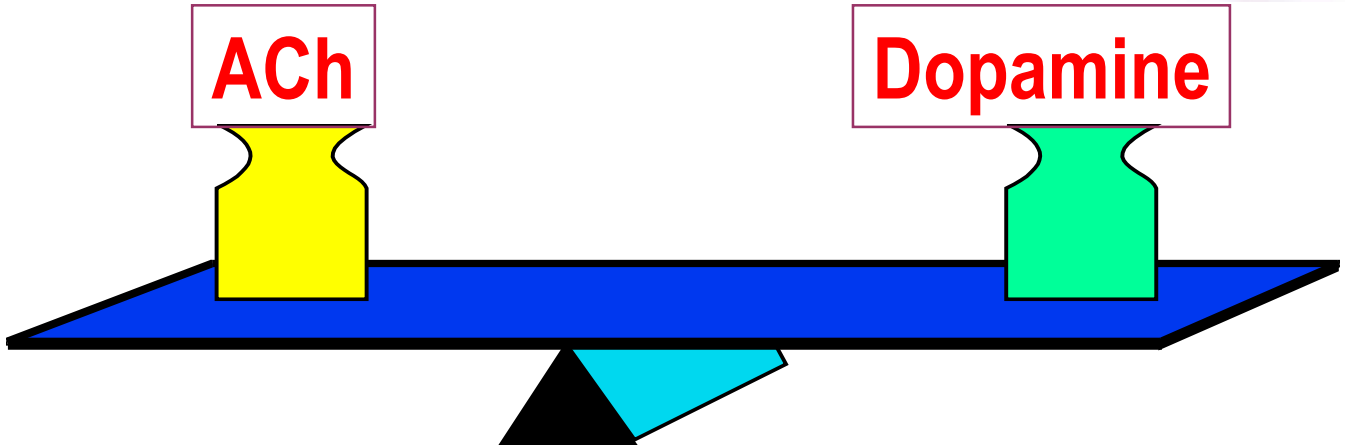
Tujuan terapi

- *Meminimalkan kecacatan (disability) dan efek samping, serta meningkatkan kualitas hidup semaksimal mungkin*

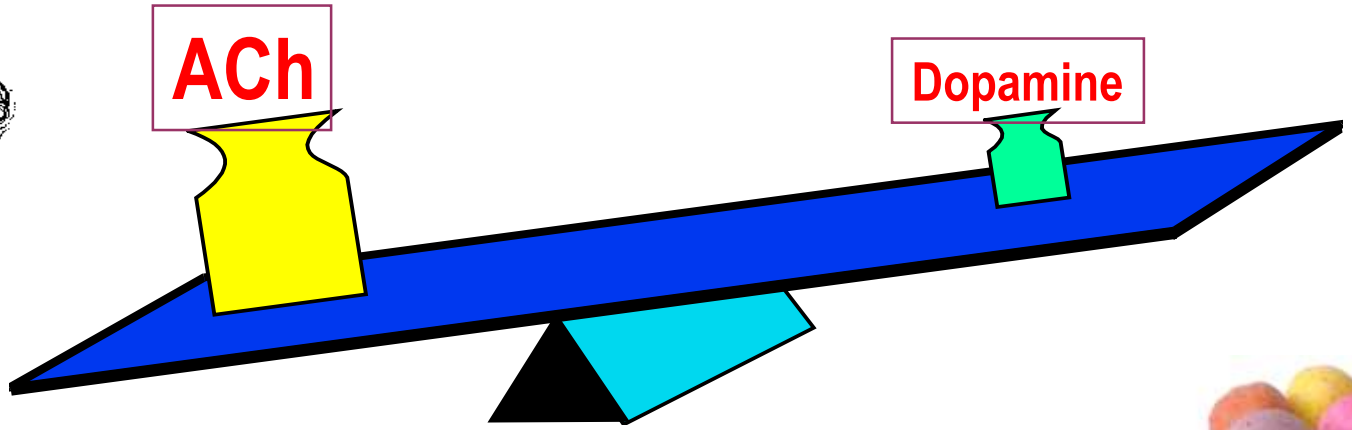
Strategi terapi

- **Non-farmakologi :**
  - Latihan
  - Edukasi
  - Nutrisi
  - Pembedahan
- **Farmakologi :**
  - Meningkatkan kadar dopamin endogen
  - Mengaktifkan reseptor dopamin dengan agonis dopamine
  - Menekan aktivitas kolinergik dgn obat antikolinergik
  - Melindungi neuron

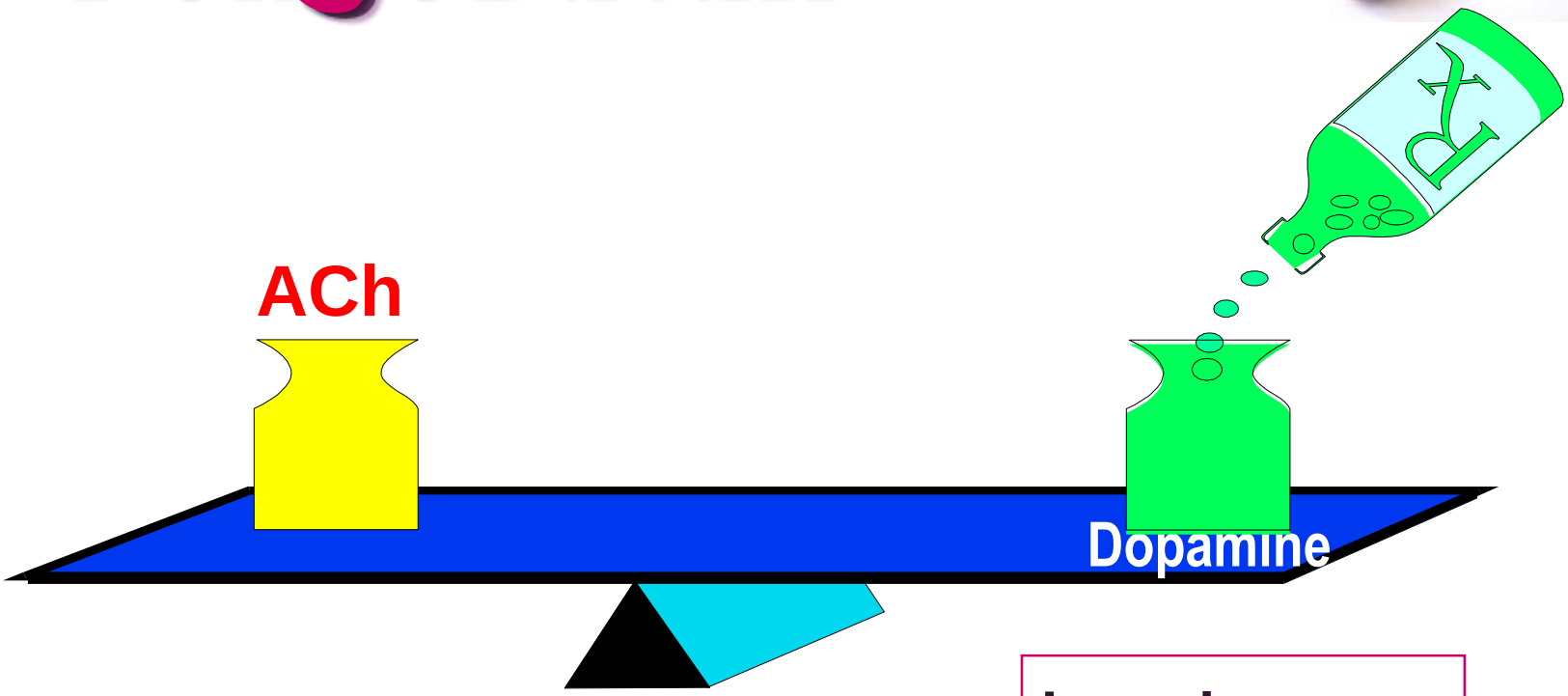
Normal subjects



Parkinson's disease

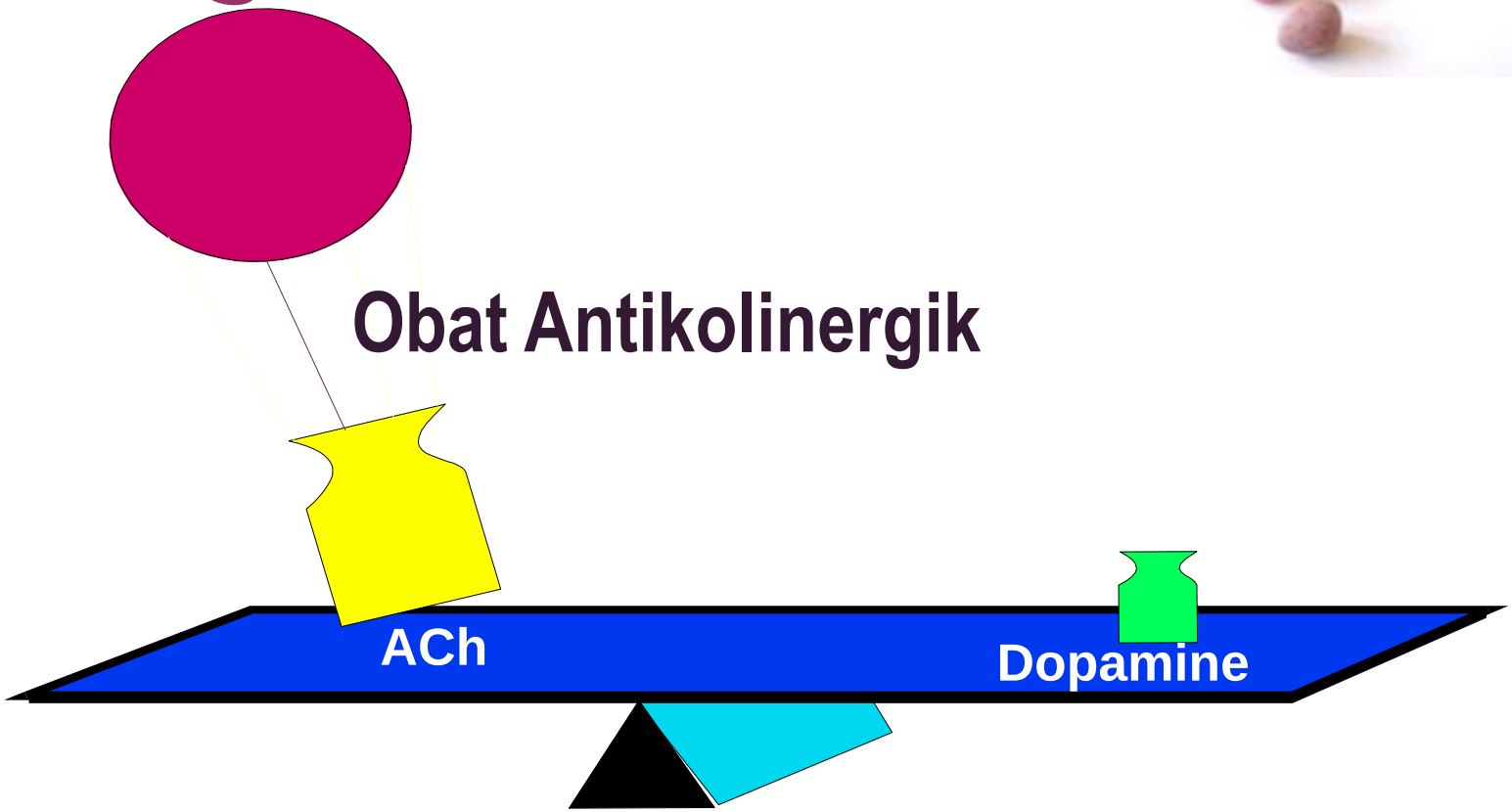


Pengobatan

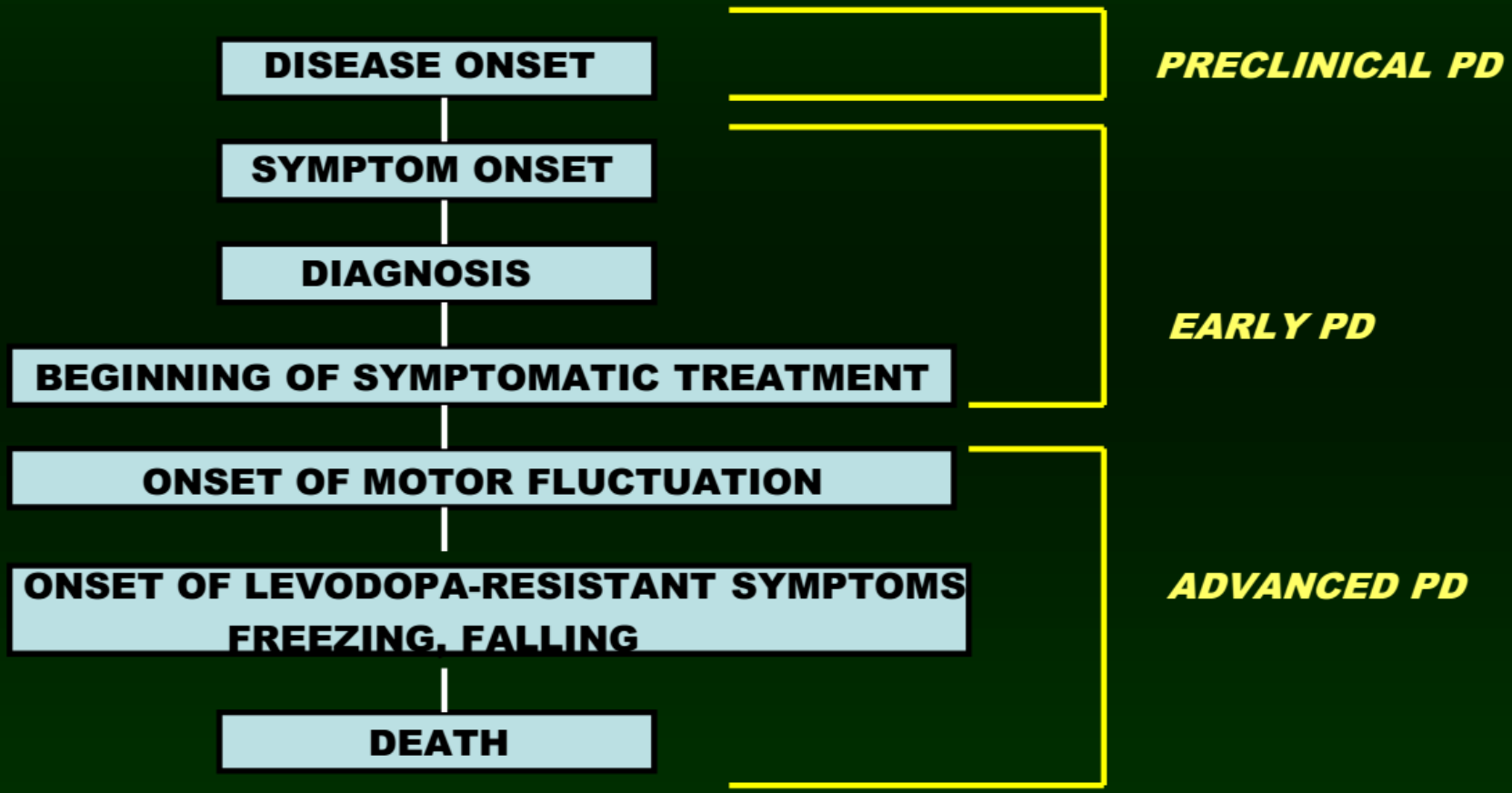


Levodopa
Amantidine
Bromocriptine
Deprenyl

Pengobatan



TERAPI BERKESINAMBUNGAN, DAPAT DI "BEDA" KAN:
→ PENGOBATAN PADA PENYAKIT DINI (*EARLY*)
→ PENGOBATAN PADA KEADAAN LANJUT (*ADVANCED*)

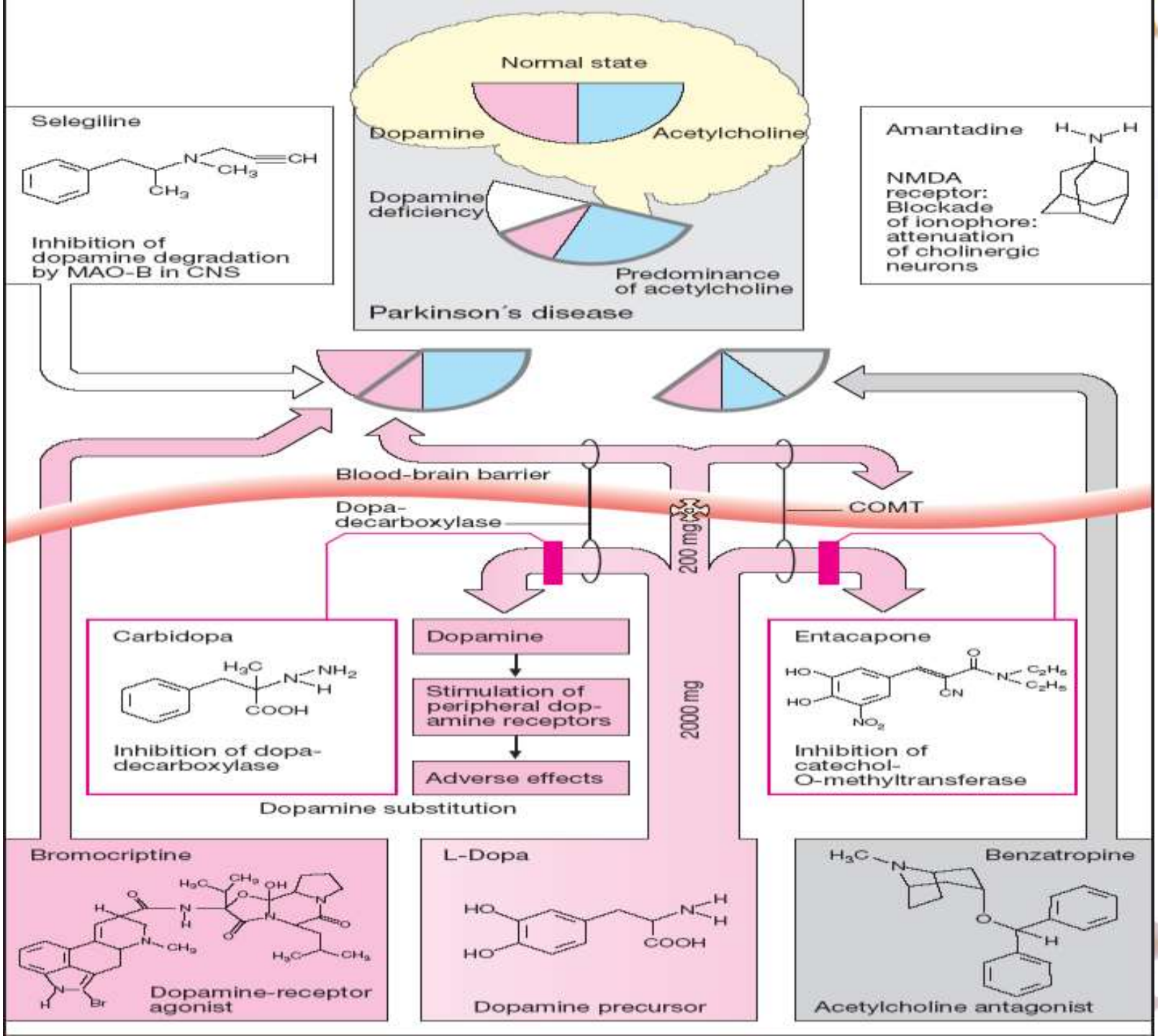


Drugs used to treat Parkinson's Disease

Class	Drug	Dose Range (mg/day po)
Anticholinergics		
Antihistamines	Diphenhydramine	25–200
	Orphenadrine	50–200
Antidepressants	Amitriptyline	10–150
	Doxepin	10–150
	Imipramine	10–150
	Nortriptyline	10–150
Miscellaneous	Benztropine	0.5–6
	Biperiden	2–6
	Ethopropazine	40–400
	Procyclidine	5–40
	Trihexyphenidyl	2–15
Dopaminergic		
Dopamine precursor (with decarboxylase inhibitor)	Carbidopa/levodopa	75/300–250/2500
Dopamine agonists	Bromocriptine	5–60
	Pergolide	0.1–7
MAO-B inhibitor	Selegiline	5–10
Mechanism of action unknown	Amantadine	100–300

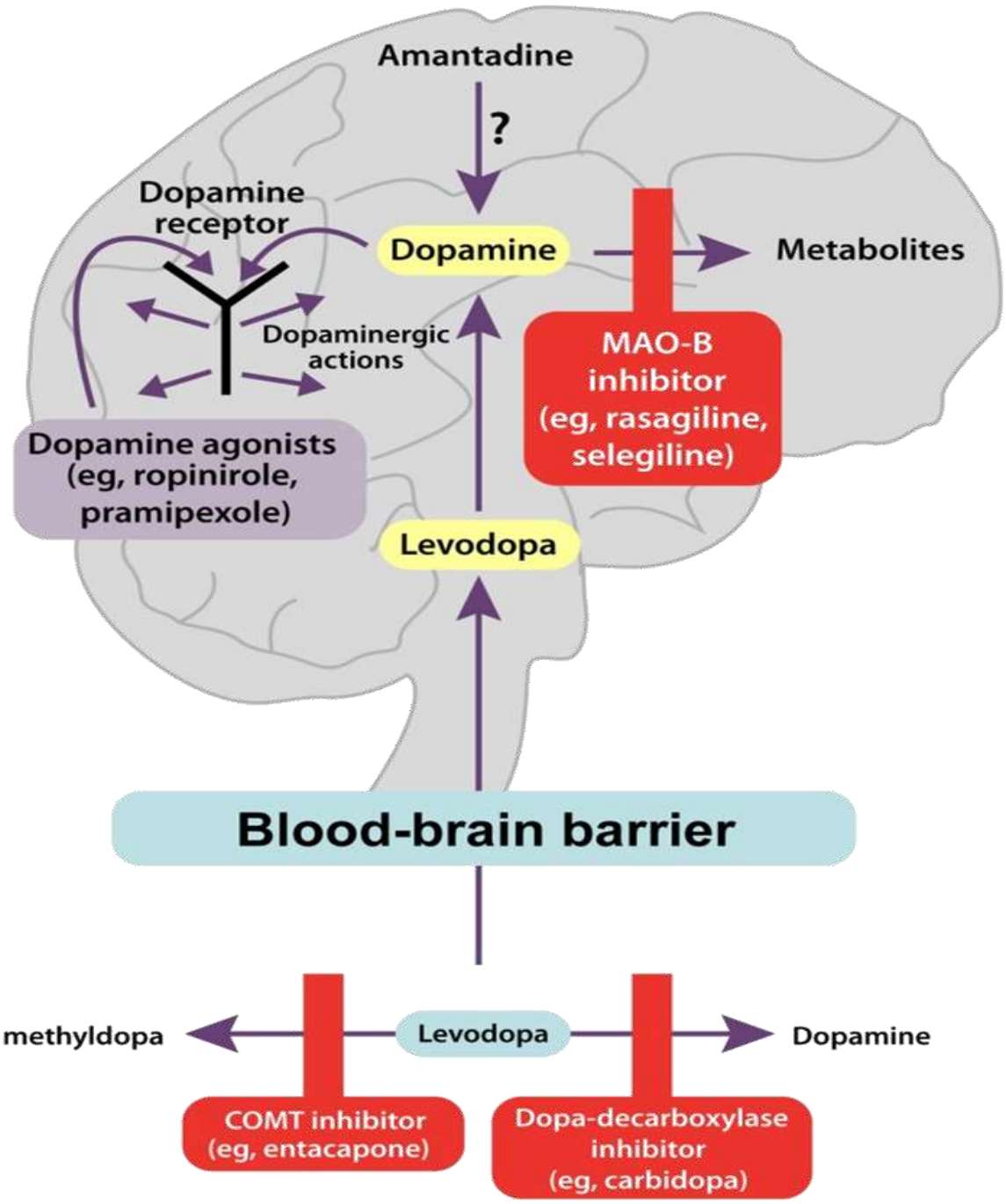
MAO-B = monoamine oxidase type B.

Based on McDowell FA, Cedarbaum JM: "The extrapyramidal system and disorders of movement," in *Clinical Neurology* [looseleaf publication], edited by RJ Joynt. Philadelphia, JB Lippincott Company.


Normal state
Dopamine
Acetylcholine
Dopamine deficiency
Predominance of acetylcholine
Parkinson's disease
Selegiline
Inhibition of dopamine degradation by MAO-B in CNS
Amantadine
NMDA receptor: Blockade of ionophore: attenuation of cholinergic neurons
Blood-brain barrier
Dopa-decarboxylase
COMT
200 mg
2000 mg
Carbidopa
Inhibition of dopa-decarboxylase
Dopamine
Stimulation of peripheral dopamine receptors
Adverse effects
Dopamine substitution
Entacapone
Inhibition of catechol-O-methyltransferase
Bromocriptine
Dopamine-receptor agonist
L-Dopa
Dopamine precursor
Benzatropine
Acetylcholine antagonist

FARMAKODINAMIK OBAT

- **Meningkatkan kadar dopamin endogen**
  - – L-Dopa (prekursor Dopa (DOC) ± Carbidopa, Benserazid (inhibitor metabolisme perifer oleh dopa dekarboksilase)
  - – Entacapon, tolcapon → hambat degradasi Dopamin oleh Cathecol O-metiltransferase (COMT)
  - – Selegilin, Rasagiline → menghambat degradasi Dopamin(tdk pd NE/5HT)oleh MAO B
  - – Amantadin → me↑ sintesis dan pelepasan dopamin, menghambat re-uptake dopamine, NMDA receptor antagonis
  - - Amfetamin → me↑ pelepasan dopamin
- **Mengaktifkan reseptor dopamin dengan agonis**
  - – Bromokriptin, lisurid → agonis D2
  - – Pramipeksol, ropinirol → agonis D2 dan D3
  - – Pergolid, apomorfin → agonis D1 dan D2
- **Menekan aktivitas kolinergik dgn obat antikolinergik**
  - – Benztropin, triheksifenidil


Amantadine
?
Dopamine receptor
Dopamine
Metabolites
Dopaminergic actions
MAO-B inhibitor (eg, rasagiline, selegiline)
Dopamine agonists (eg, ropinirole, pramipexole)
Levodopa
Blood-brain barrier
3-O methyldopa
Levodopa
Dopamine
COMT inhibitor (eg, entacapone)
Dopa-decarboxylase inhibitor (eg, carbidopa)

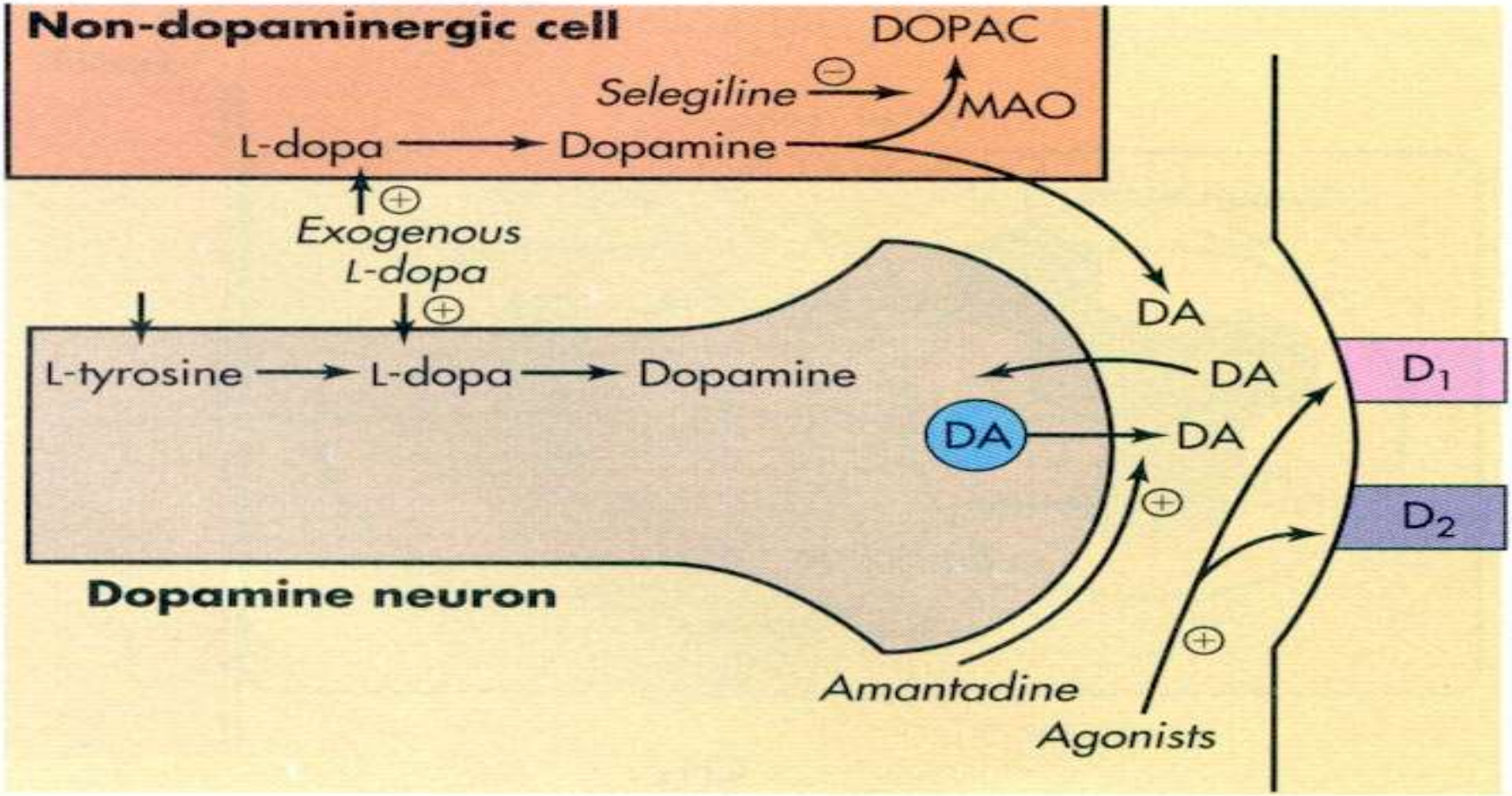
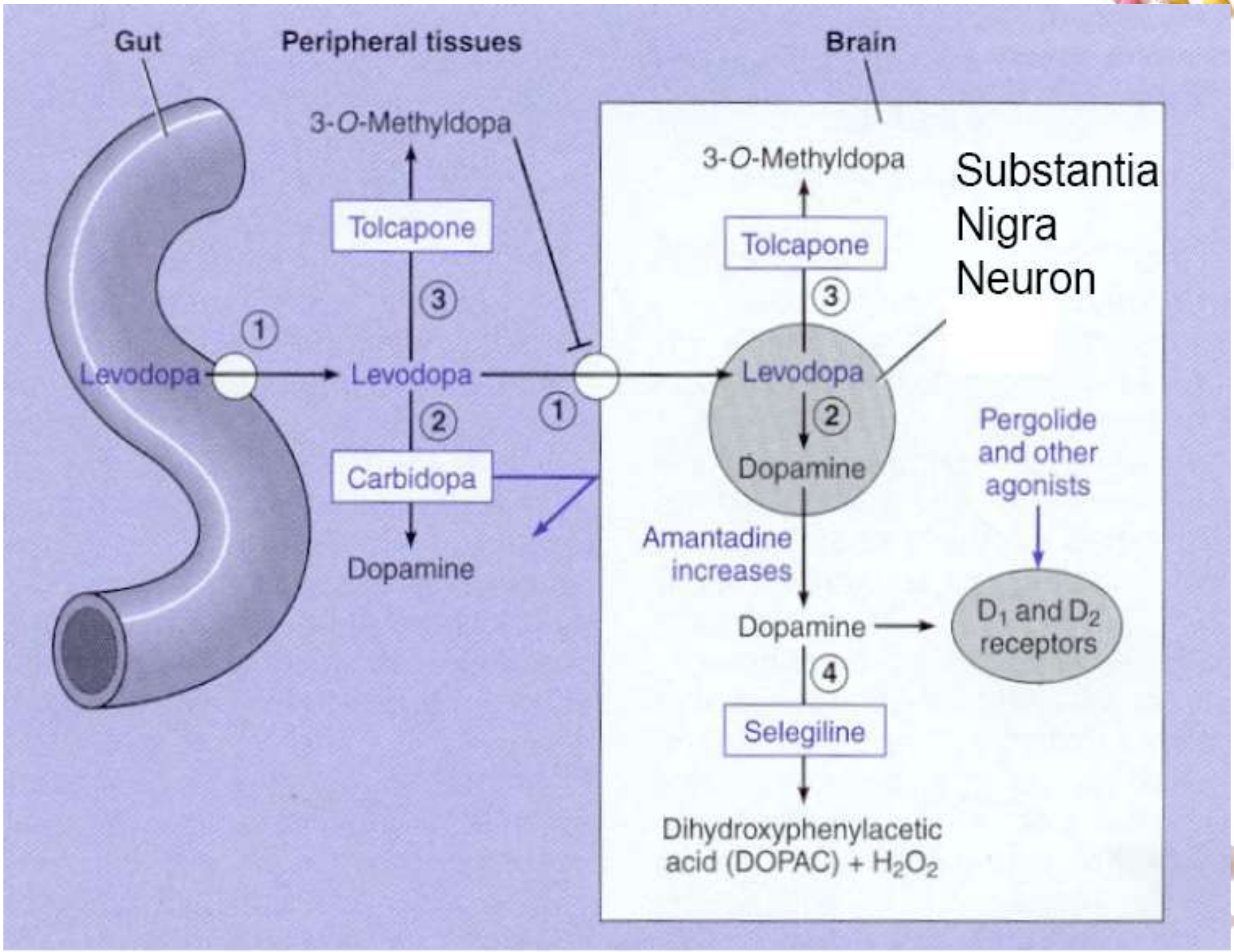
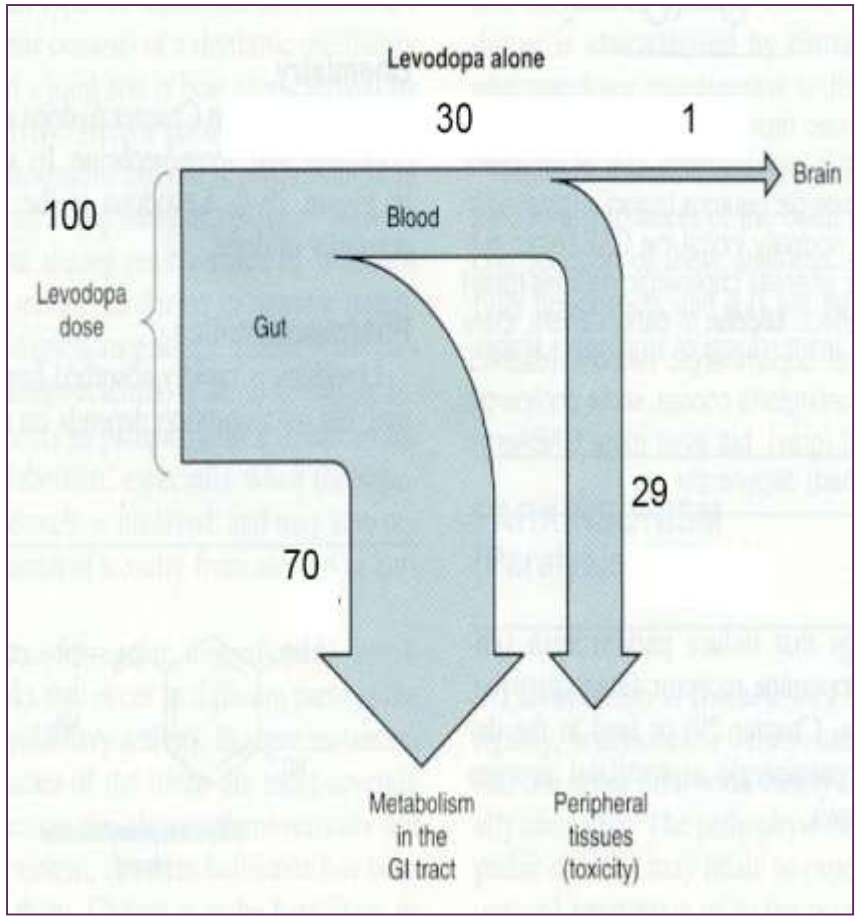


FIGURE 29-4 Sites of action of antiparkinsonian agents to facilitate dopaminergic function. L-Dopa enhances the synthesis and ultimately the release of dopamine (DA). Amantadine facilitates the release of dopamine. Dopamine agonists directly activate dopamine receptors (D_1 and D_2) on the postsynaptic cell. Selegiline inhibits the metabolism of dopamine in non-dopaminergic neurons or glia, or both.


Gut
Peripheral tissues
Brain
3-O-Methyldopa
Tolcapone
3
1
Levodopa
Levodopa
2
Carbidopa
Dopamine
1
3-O-Methyldopa
Tolcapone
3
Substantia Nigra Neuron
Levodopa
2
Dopamine
Pergolide and other agonists
Amantadine increases
Dopamine
D1 and D2 receptors
4
Selegiline
Dihydroxyphenylacetic acid (DOPAC) + H2O2

L-DOPA

- Dopamin & tirosin tdk dpt dipakai sbg anti Parkinson
- Dopamine tdk menembus BBB
- Sejml besar tyrosine me↓ aktivitas Tyrosine Hydroxylase dlm mengubah tirosin menj dopamin
- L-DOPA=Biosintetik prekursor dopamin
- L-DOPA dpt menembus BBB
- Mengalami ekstensif first pass effect di jar perifer oleh COMT dan MAO sblm mencapai SSP
- L-DOPA ditangkap neuron dopaminergik di subst nigra, diubah menj dopamin dg bantuan LAAD (L-Amino Acid Decarboxilase)



L Dopa- Pharmacokinetics

- L Dopa is readily absorbed from GI Tract
- Large amount of L Dopa has to be given due to *First Pass Effect,* metabolized by dopa decarboxylase in liver and periphery to dopamine ~1% actually cross Blood Brain Barrier enters CNS
- Secreted in urine unchanged or conjugated with glucoronyl sulfate
- Most of L Dopa converted in periphery to NE and EPI

Effects of L Dopa

- Bradykinesia ↓↓ and Rigidity ↓↓, Tremor ↓ (dg Tx lanjutan)
- Postural Instability & Shuffling (-)
- Mood ↑ & Sense of Well Being ↑
- Me↓ hrmon prolaktin
- Cardiac Stimulation ↑ (tachycardia, cardiac arrhythmias and hypertension) → (hati2 lansia) →beta blocker
- Stimulation CTZ → Nausea, Vomiting, and Anorexia → Low Doses and gradually increase dose
- activation of Peptic Ulcer → Give Drug with some food
- Toleransi dlm bbrp minggu
- Long term : induce Psychosis, Confusion, Hallucination, Anxiety, Delusion, on-off phenomen (wearing off), diskinesia

Wearing off

- Wearing off= rekurensi gejala motorik dan non motorik sebelum masa kerja Levodopa berakhir (paling sedikit 4 jam), hal ini berkaitan dengan berkurangnya kapasitas penyimpanan dopamine.
- Diatasi dg :
  - menyesuaikan dosis levodopa dengan pemberian (frekuensi) yang lebih sering, misalnya 4 – 6 kali/hari,
  - mengganti standar levodopa ke formula lepas lambat,
  - penambahan penghambat COMT atau MAO, agonis dopamin, serta
  - Prioritas pemberian amantadin atau antikolinergik untuk pasien usia muda

Diskinesia

- Diskinesia adalah gerakan involunter yang menggeliat-geliat dan meliuk-liuk (memilinmilin), atau bisa juga berupa distonia atau mioklonus.
- krn pemakaian dopamine jangka panjang dan perangsangan reseptor dopamin yang tidak fisiologis, oleh karena pemberian terapi dopamin yang pulsatil.
- Dengan bertambahnya denervasi, reseptor dopamin akan mengalami supersensitivitas.
- diskinesia timbul akibat tingginya kadar levodopa dalam plasma

Drug Interactions with L Dopa

- **co-administered with Carbidopa** →antagonistic to Peripheral L Dopa Decarboxylation → metabolism of L Dopa in GI Tract & Peripheral Tissues ↓ → L Dopa ↑ into CNS → L Dopa dose ↓
- Carbidopa Doesn't Cross BBB → not influence converted L dopa to dopamin in CNS
- **Antipsychotic Drugs** - Block Dopamine Receptor
- **Reserpine** - Depletes Dopamine Storage
- **Anticholinergics** - Used Synergistically with L Dopa as an Antiparkinson Agent, but Anticholinergics Act to decrease L Dopa absorption since Anticholinergics have an effect on gastric emptying time which delays absorbtion L Dopa in GIT

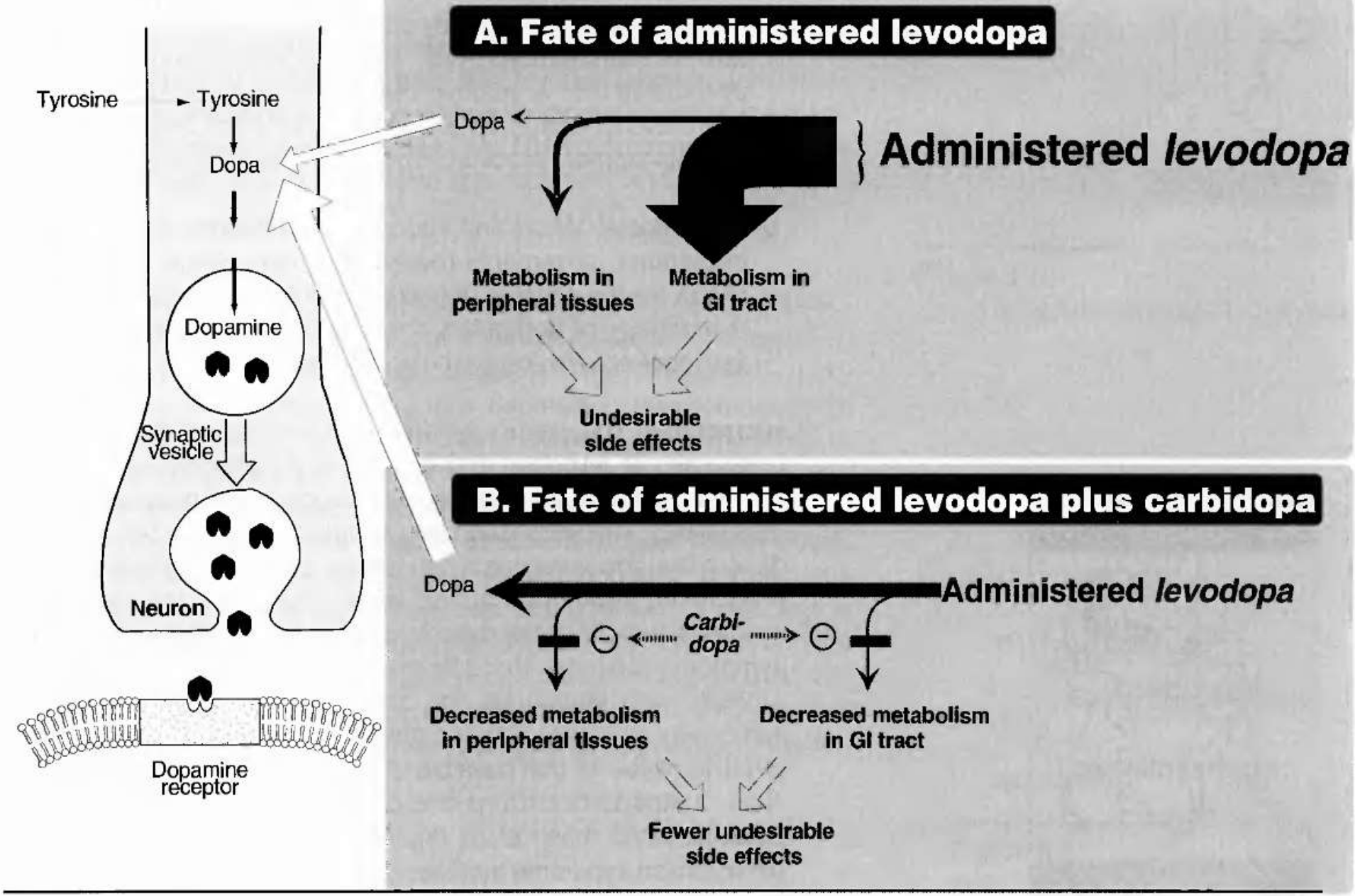


Figure 8.5
Synthesis of dopamine in the absence and presence of *carbidopa*, an inhibitor of dopamine decarboxylase in the peripheral tissues.

Drug Interactions with L Dopa

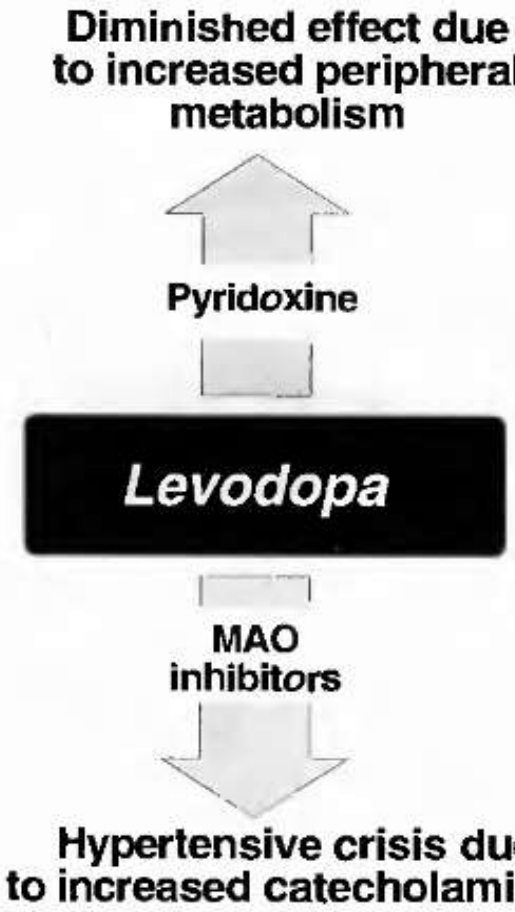


Figure 8.6
Some drug interactions observed with *levodopa*.

- **Vitamin B6 –** (Vitamin B6 = Cofactor for Decarboxylation of L Dopa) → Conversion of L Dopa to Dopamine in Periphery ↑
- **Nonspecific MAO Inhibitors** - Interfere with L Dopa Breakdown →Precipitate Hypertensive Crisis
- **tyramine-cheese effect** (Tyramine Is Found in Cheese, Coffee, Beer, Pickles, Chocolate, and Herring), →Precipitate Hypertensive Crisis (when given to a person taking a MAO Inhibitor)

AGONIS DOPAMIN

- Merangsang rec dopamine
- Menurunkan reseptor dopamine (down-regulation)-gejala PD ↑
- Indikasi = tx awal / txtambahan PD
- Ada 2 gol :
  - Gol ergot : bromokkriptin, pergolide, cabergoline, lisuride infus subkutan
  - Gol non-ergot : rotigotine transdermal. apomorfin., pramipeksol, ropinirole

- Indikasi =
- Pasien yg mengalami serangan berfluktuasi dan dyskinesia e.c levodopa dosis tinggi
- ES= halusinasi, psikosis, edema kaki, mual-muntah, eritromeralgia, serangan tidur mendadak

MAO-B inhibitor

- Memperlambat progressifitas Parkinson
- Menangguhkan penggunaan levodopa
- Menghaluskan pergerakan pd PD

- Ada efek antidepressant ringan
- ES = insomnia, aritmia, dyskinesia, halusinasi

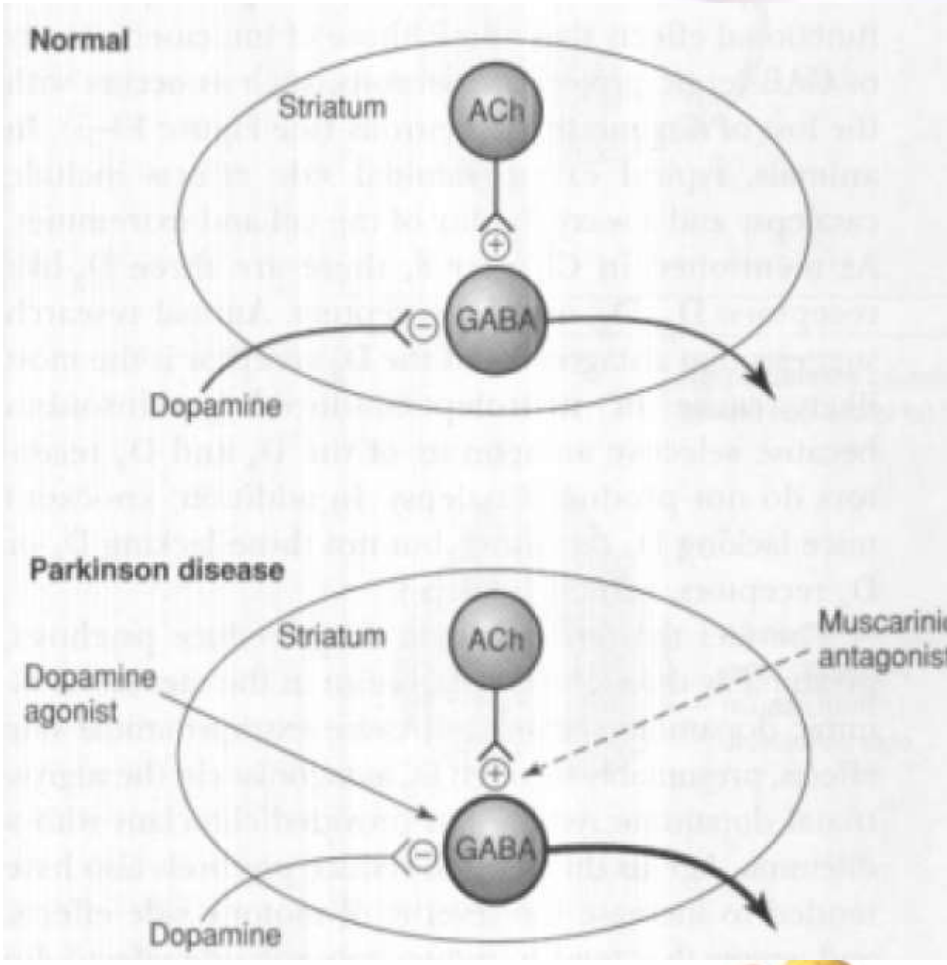
COMT inhibitor

- Kombinasi dg levodopa
- mengurangi resiko wearing off, mengurangi dosis levodopa

- ES = hepatotoksik (tolcapone), diare, diskinesia

ANTIMUSCARINIC AGENTS

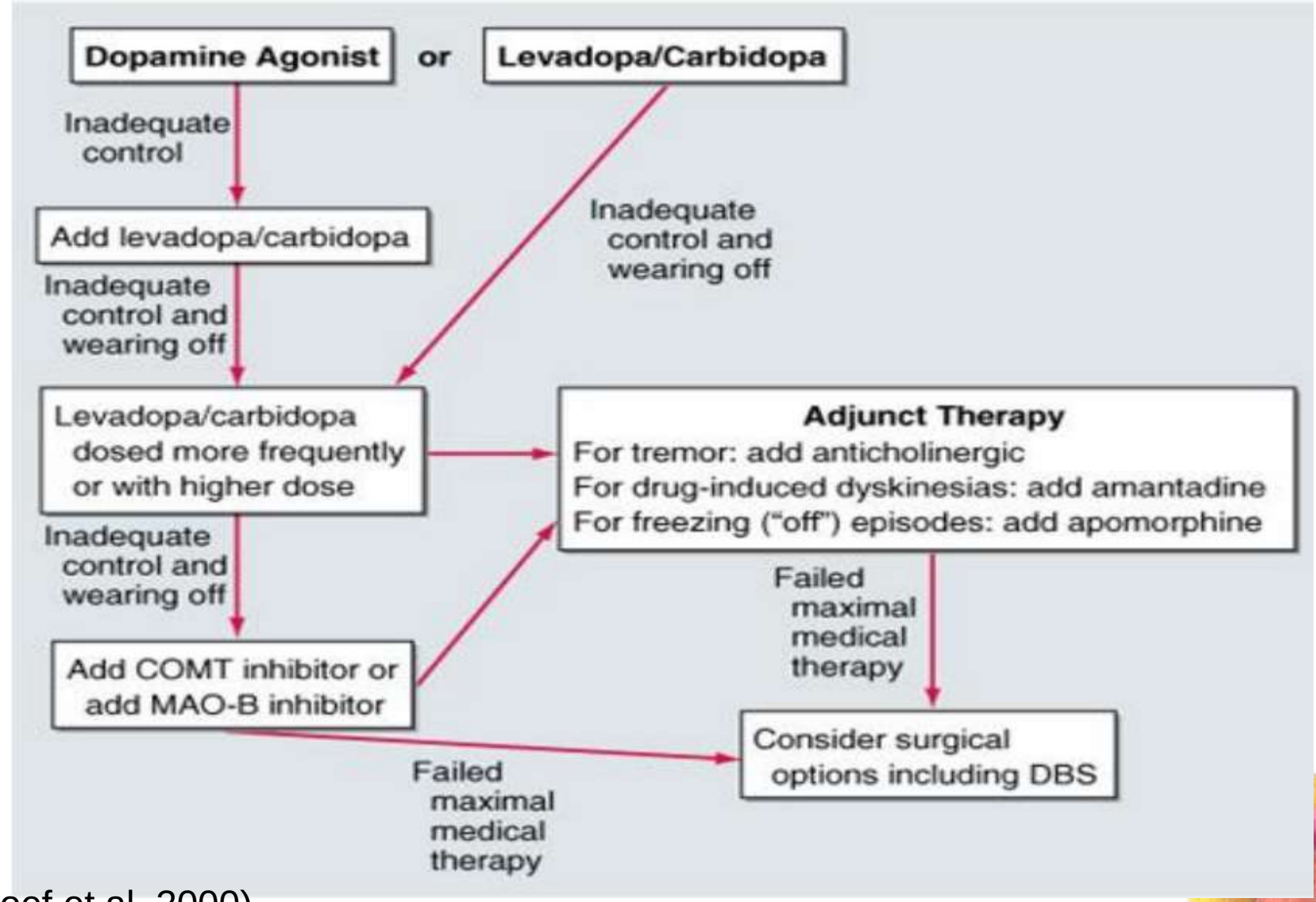
- Antimuscarinic Agents effikasi lebih rendah dp Levodopa → berperan sbg adjuvan Tx antiparkinson
- Mis : Atropine, Scopolamine, Benztropine, Trihexyphenidyl, & Biperidon, orphenadrine, procyclidine
- Berguna dalam mengobati tremor
- ES=Drowsiness, inattention, confusion, delusions delusions, hallucinations, Peripheral adverse effects (atropine-like drugs such as dry mouth, mydriasis, urinary retention and cardiac arrythmias).
- KI = lansia>70 (penurunan daya ingat)



NEUROPROTEKTOR AGENT

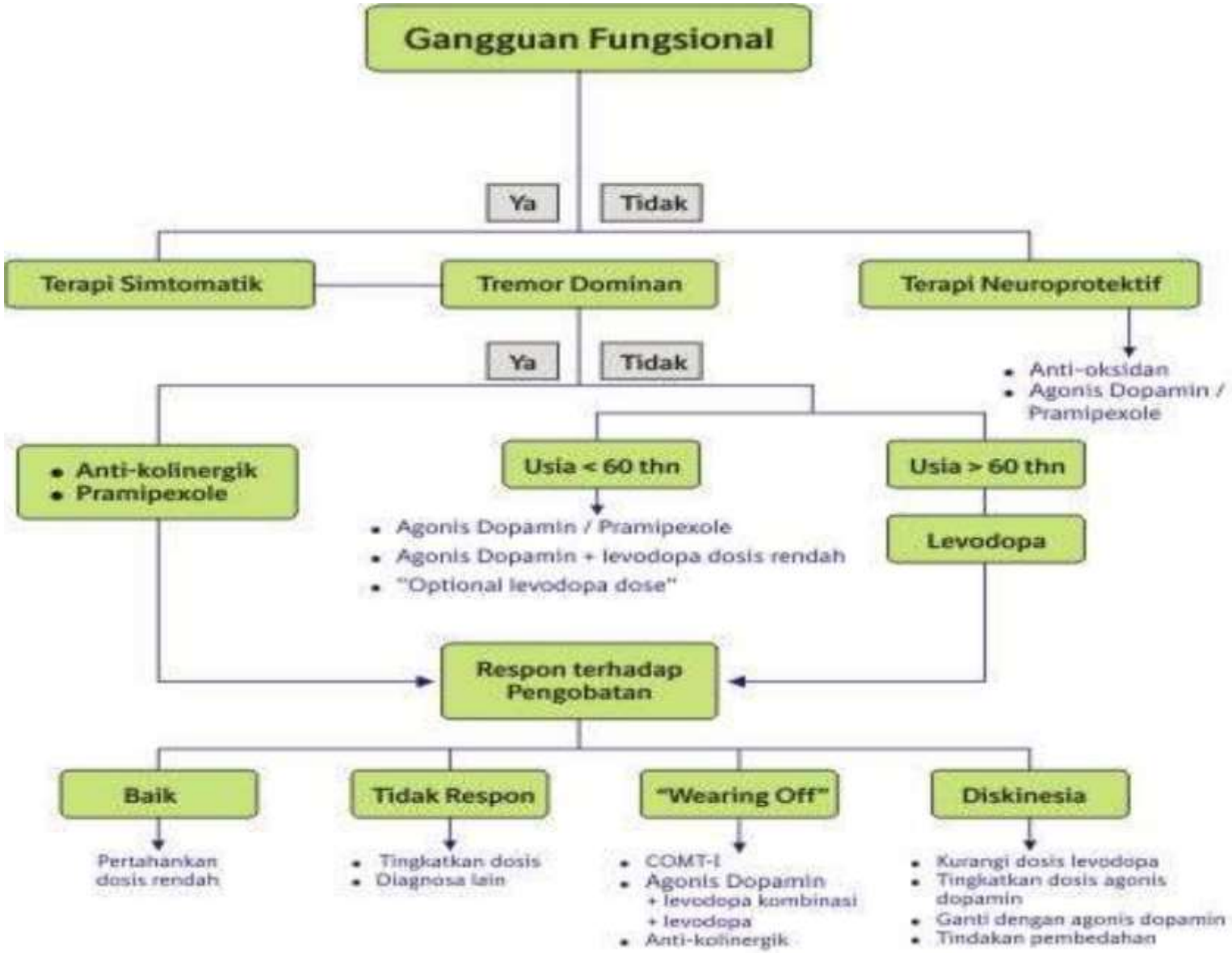
- a.neurotrpik faktor : BDNF, GDNT
- b. anti-eksitotoksin (antagonis R/NMDA,riluzole)
- c. antioksidan (selegiline, 7-nitroindazole)
- d. suplemen bioenergetics – memperbaiki metab energy di mitokondria (coenzim Q10) nikotinamide)
- Rotigotine transdermal

Algoritma Terapi Penyakit Parkinson

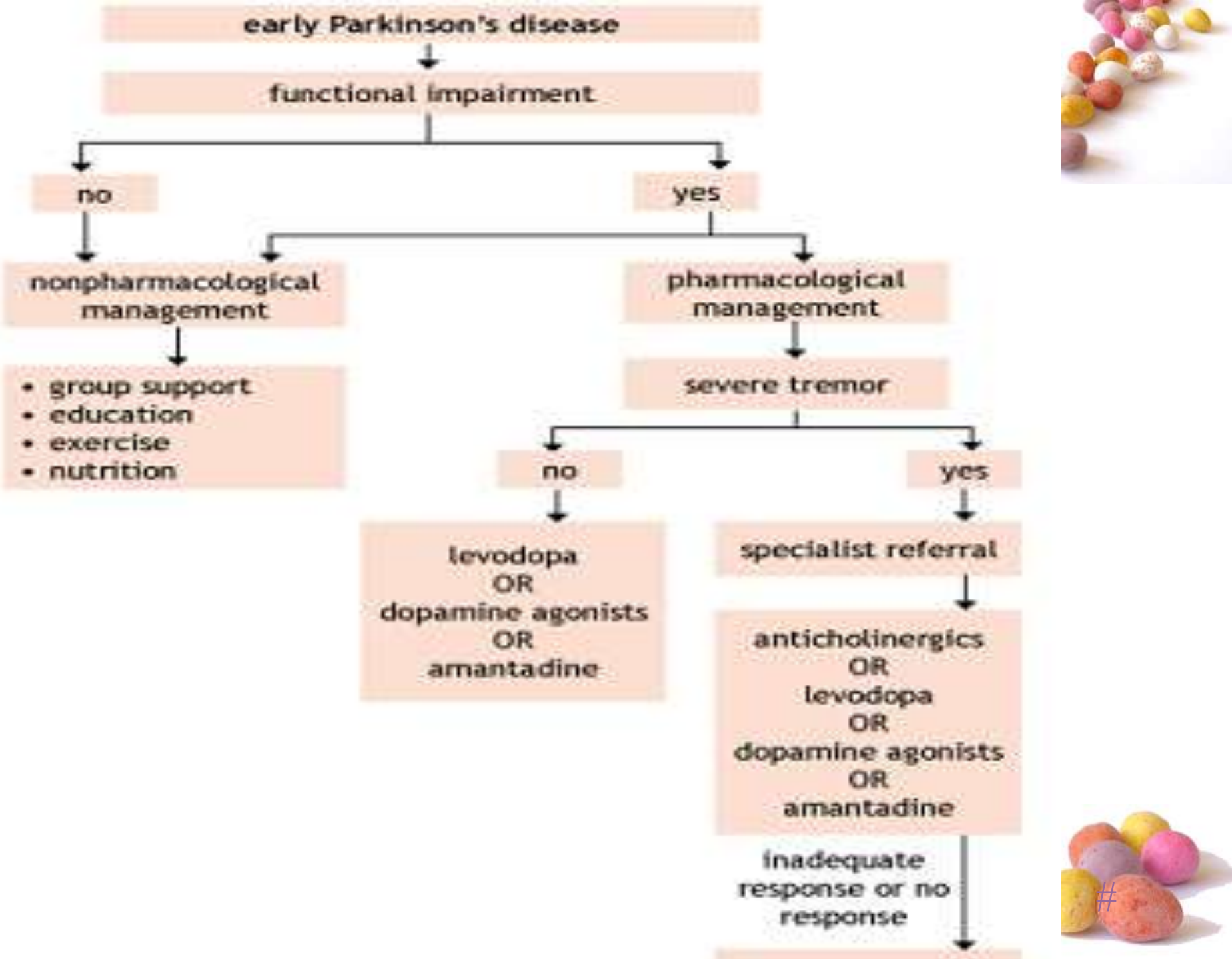


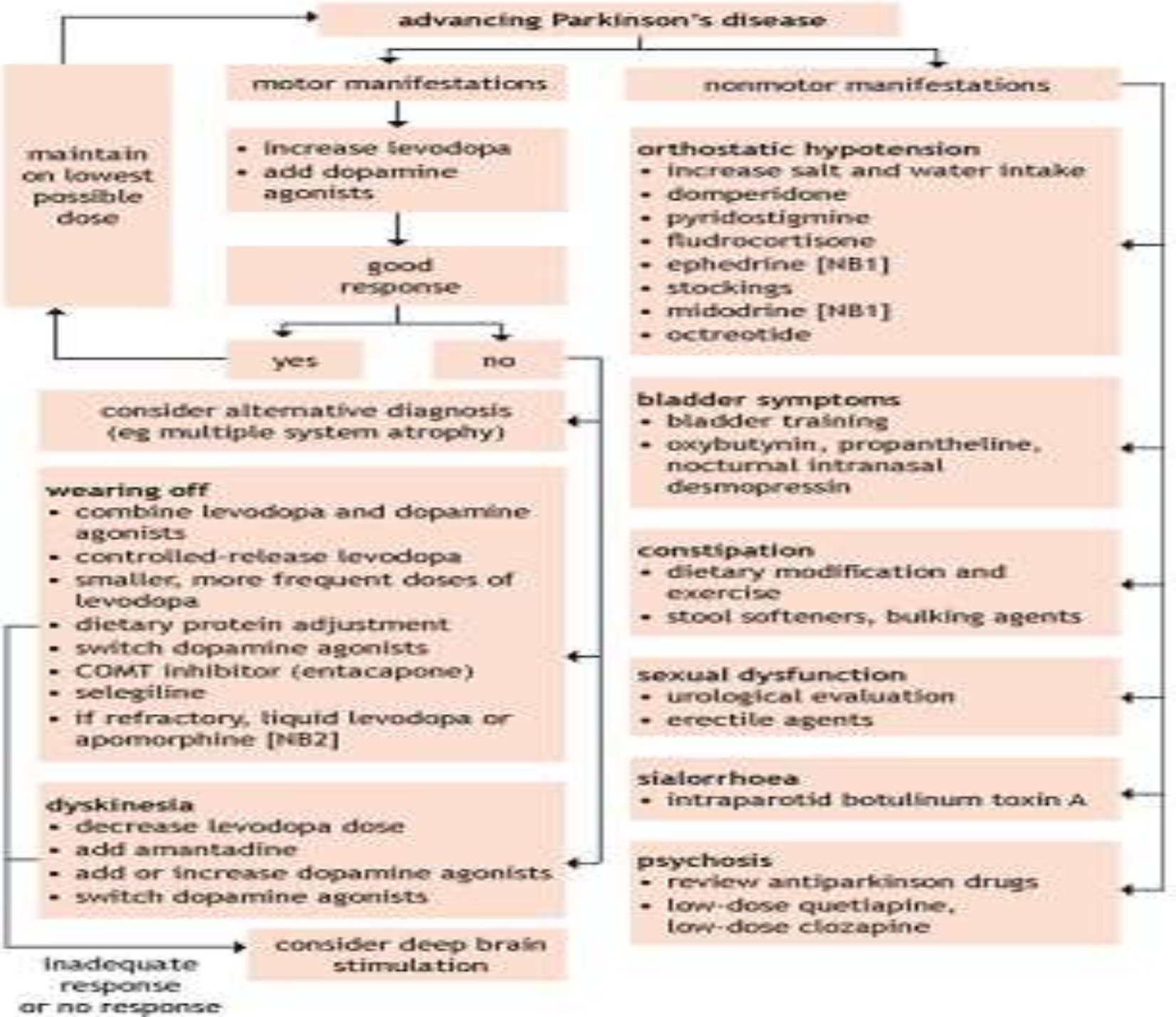
(Joesoef et al, 2000)

Algoritma Terapi Penyakit Parkinson



Konsensus POKDI Gangguan Gerak PERDOSSI 2003


early Parkinson's disease
functional impairment
no
yes
nonpharmacological management
pharmacological management
• group support
• education
• exercise
• nutrition
severe tremor
no
yes
levodopa OR dopamine agonists OR amantadine
specialist referral
anticholinergics OR levodopa OR dopamine agonists OR amantadine
inadequate response or no response


advancing Parkinson's disease
motor manifestations
nonmotor manifestations
maintain on lowest possible dose
• increase levodopa
• add dopamine agonists
good response
yes
no
consider alternative diagnosis (eg multiple system atrophy)
wearing off
• combine levodopa and dopamine agonists
• controlled-release levodopa
• smaller, more frequent doses of levodopa
• dietary protein adjustment
• switch dopamine agonists
• COMT inhibitor (entacapone)
• selegiline
• if refractory, liquid levodopa or apomorphine [NB2]
dyskinesia
• decrease levodopa dose
• add amantadine
• add or increase dopamine agonists
• switch dopamine agonists
Inadequate response or no response
consider deep brain stimulation
orthostatic hypotension
• increase salt and water intake
• domperidone
• pyridostigmine
• fludrocortisone
• ephedrine [NB1]
• stockings
• midodrine [NB1]
• octreotide
bladder symptoms
• bladder training
• oxybutynin, propantheline, nocturnal intranasal desmopressin
constipation
• dietary modification and exercise
• stool softeners, bulking agents
sexual dysfunction
• urological evaluation
• erectile agents
sialorrhoea
• intraparotid botulinum toxin A
psychosis
• review antiparkinson drugs
• low-dose quetiapine, low-dose clozapine

POTENTIAL PARKINSON'S TREATMENTS

- Neurotropik →melindungi sel-sel saraf dari kematian dini yang mendorong Parkinson. Hamb= protein yg mampu menembus BBB ???.
- Neuroprotektif agent- Para peneliti sedang meneliti enzim alami yang tampaknya dpt menonaktifkan "radikal bebas," bahan kimia yang mungkin terkait dengan kerusakan sel-sel saraf pd Parkinson dan gangguan neurologis lainnya.
- Transplantasi jaringan saraf - menanamkan jaringan saraf dari janin babi ke dalam otak untuk memperbaiki area degeratif. Dalam uji coba klinis yang dilakukan di Boston University School of Medicine, tiga pasien dari 12 →penurunan yang signifikan dalam gejala.
- Rekayasa genetika - Para ilmuwan memodifikasi kode genetik dari sel individu untuk menciptakan sel yg memproduksi dopamin dari sel-sel lain, seperti dari kulit.
- ????????

The end