



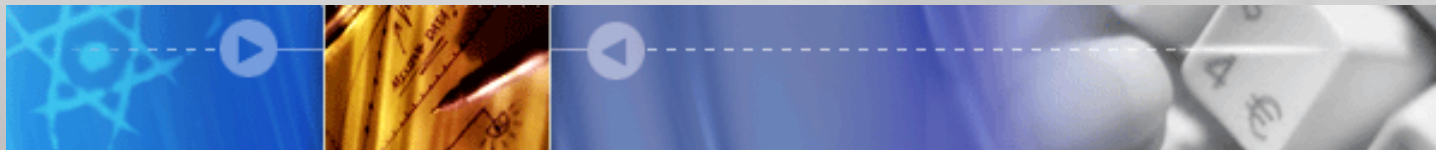
精神與神經科用藥評估

Psychiatry and Neurology

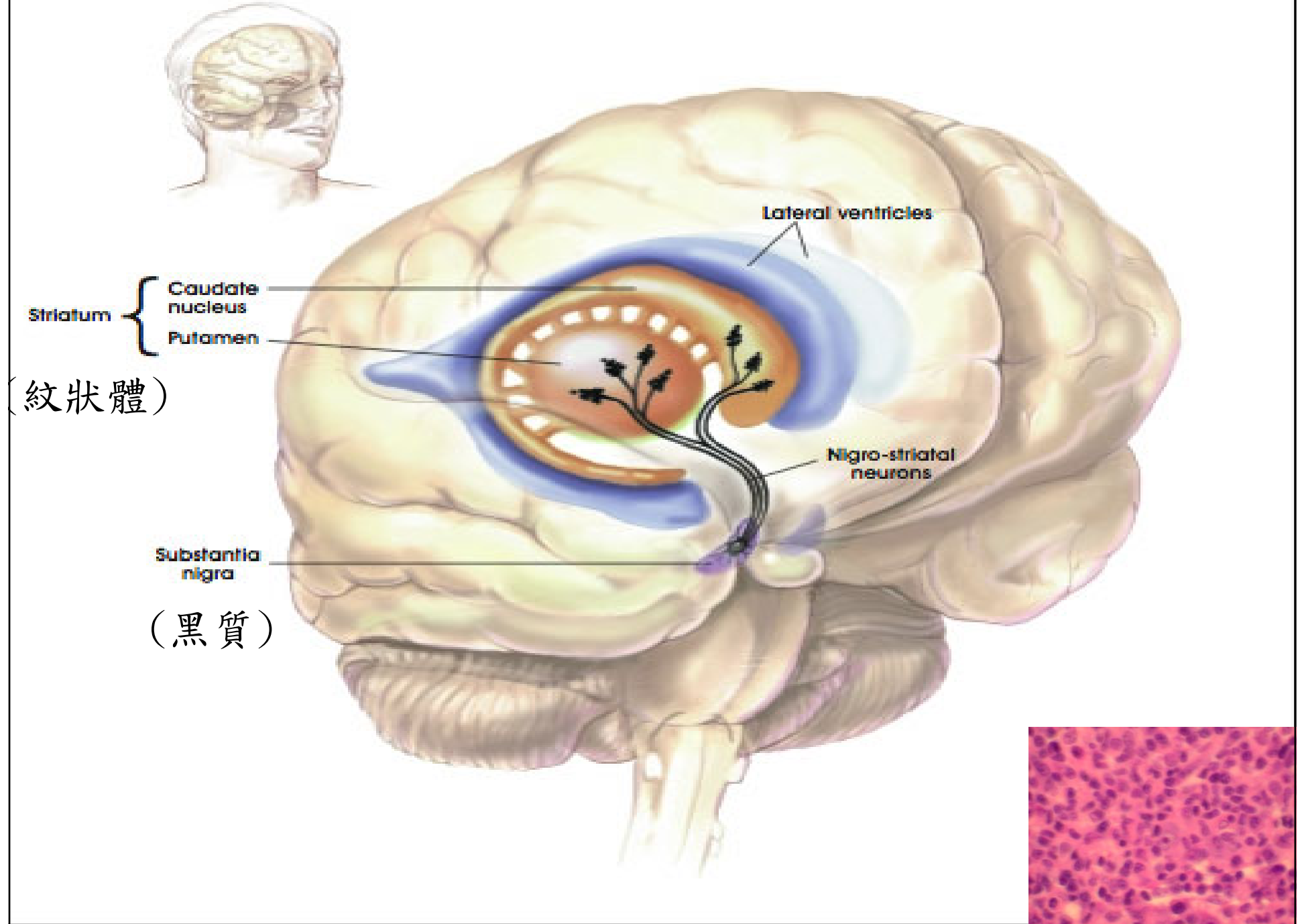
Depression & Parkinson's disease

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Parkinson's disease





Parkinson's disease

- ▶ 症狀:TRAP
- ▶ Tremor靜止性震顫
- ▶ Rigidity肌僵直
- ▶ Akinesia運動不能, 運動徐緩
- ▶ Postural imbalance姿勢不平衡



可能引發或惡化的藥物

▶ 精神病用藥

- ▶ Phenothiazine:
Chlorpromazine(Morefi
ne[®])

- ▶ Thioxanthene:
Chlorprothixene(Tarni
n[®])

- ▶ Butyrophenone:
Haloperidol(Apo-
Haloperidol[®])

- ▶ Prochlorperazine

- ▶ Lithium

▶ 抗憂鬱劑

- ▶ Amoxapine

- ▶ Lithium

- ▶ SSRI

- ▶ Metoclopramide(Pri
mperan[®])

▶ 抗癲癇劑

- ▶ Valproic acid

- ▶ Phenytoin



可能引發或惡化的藥物

▶ 鈣離子通道阻斷劑

- ▶ Amlodipine
- ▶ Diltiazem
- ▶ Verapamil

▶ Amiodarone

▶ Metoclopramide

▶ Droperidol

▶ Disulfiram

▶ 中樞作用抗高血壓劑

- ▶ α -Methyldopa
- ▶ Reserpine

▶ Cholinesterase抑制劑

- ▶ Donepezil
- ▶ Tacrine



Parkinson's d的治療問題

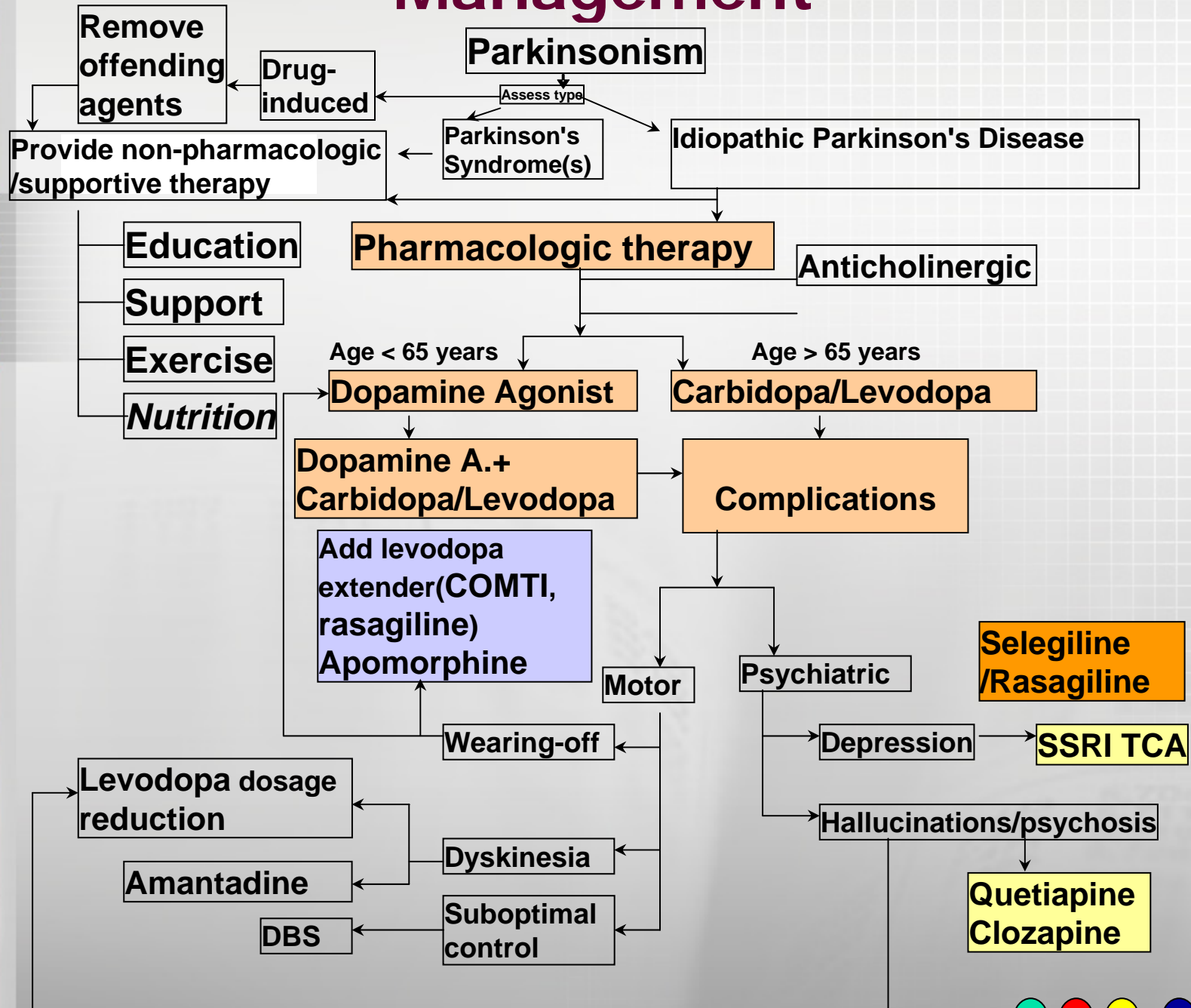
- ▶ 未有標準治療準則
- ▶ 藥品的選擇與病患主觀條件有密切關係
- ▶ 藥品副作用常會改變治療重點
- ▶ 非藥物療法應更被重視



藥物治療

- ▶ Start Low , Go slow
 - ▶ Wait until patient is functionally impaired
 - ▶ ↓ adverse effects
 - ▶ ↓ cost
 - ▶ Use lowest dose possible

Management

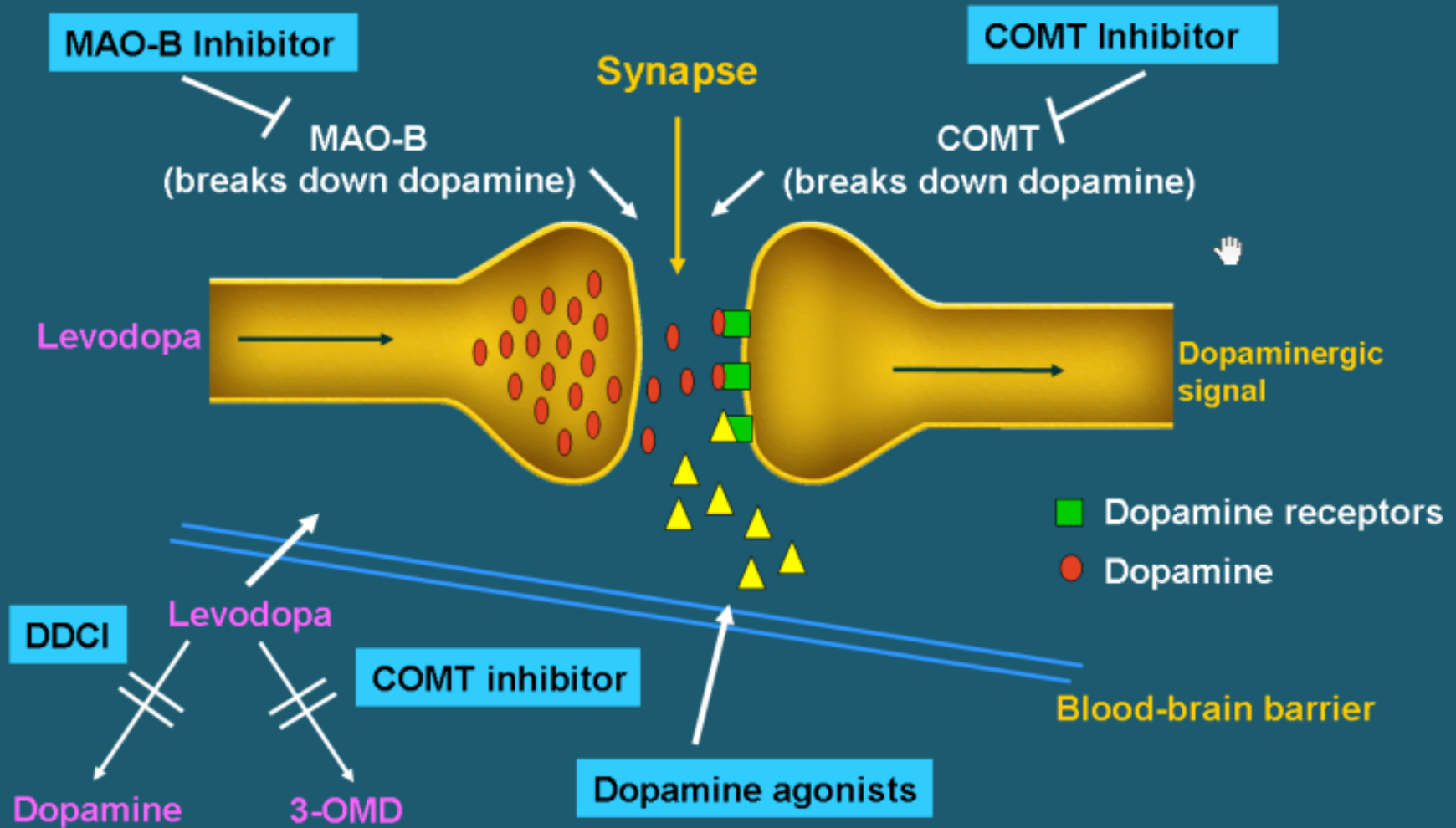




Treatment

- ▶ Pharmacologic therapy
 - ▶ Neuroprotective therapy
 - ▶ Symptomatic therapy
- ▶ Nonpharmacologic therapy
- ▶ Surgical therapy

Sites of Action of Parkinson's Disease Drugs



DDCI = dopa decarboxylase inhibitor; 3-OMD = 3-O-methyldopa.

Deleu D et al. *Clin Pharmacokinet.* 2002;41:261-309.



Symptomatic therapy

- ▶ Anticholinergic
- ▶ Dopamine precursor
- ▶ Dopamine receptor agonist
- ▶ Catechol-O-methyltransferase (COMT) inhibitors
- ▶ N-Methyl-D-aspartate antagonist
- ▶ Selective monoamine oxidase B (MAO-B) inhibitor
- ▶ Adjunctive



Anticholinergic Drugs

- Block central muscarinic receptors and restore the balance between cholinergic and dopaminergic activity
- May be used alone or in conjunction with levodopa.
- May be given for tremor that responds poorly to levodopa.



Anticholinergic Drugs

- ▶ Biperiden (Akineton[®] 2mg)
 - ▶ Parkinsonism: 2 mg ORALLY 3 to 4 times daily, titrate upward to MAX 16 mg/day
 - ▶ Parkinsonism due to drug : 2 mg ORALLY 1 to 3 times daily
- ▶ Trihexyphenidyl (Artane[®] 2mg)
 - ▶ Parkinson's disease: maintenance, 5 to 15 mg ORALLY DAILY (divided 3 to 4 times daily)
 - ▶ Parkinsonism due to drug: 5 to 15 mg ORALLY DAILY (divided 3 to 4 times daily)



Adverse effects

- Blurred vision
- Dry mouth
- Anticholinergic delirium/psychosis
- Difficulty urinating
- Constipation
- Withdrawal effects
 - Immediate worsening of Parkinsonian sym.
 - Taper over 7-10 days
 - 老年患者以Propranolol 取代



Dopamine 直接作用劑

- ▶ 直接刺激Dopamine receptor
- ▶ 適用於早期單一治療
- ▶ 與Levo-dopa併用可改善dyskinesia, dystonia, motor fluctuation





Levodopa v.s DA

Levodopa	Dopamine agonists
最有效的症狀治療	比Levodopa弱
可能提高致死率	尚無研究
運動併發症比神經心理病發症明顯	神經心理病發症比運動併發症明顯
半衰期短紋狀體波動大	半衰期長紋狀體波動小
受飲食影響	不受飲食影響



Dopamine agonists

- ▶ **Bromocriptin** (Parlodel[®])
- ▶ **Pramipexole** (Mirapex[®])
- ▶ **Ropinirole** (Requip[®])
- ▶ **Rotigotine** (Neupro[®] transdermal patch)
- ▶ **Apomorphine** (Apo-Go[®] pen inj.)
 - ▶ 限用於rescue therapy





Adverse effect

- ✓ Gradual dosage titration over several months may limit adverse effect
- ▶ Nausea and vomiting
- ▶ Dopaminergic dysregulationsyndrome
- ▶ Hallucinations
- ▶ Impulse control disorder
- ▶ Postural hypotension
- ▶ Dizziness , Sleep attack



Interaction

▶ PRAMIPEXOLE

- ▶ increased risk of pramipexole adverse effects : **Cimetidine**

▶ Ropinirole

- ▶ an increase in INR: Warfarin
- ▶ increased **ropinirole** exposure : Ciprofloxacin, Norfloxacin
- ▶ increased risk of **ropinirole** adverse effects: Ethinyl Estradiol
- ▶ diminished effectiveness of **ropinirole**: Metoclopramide, Risperidone
- ▶ Tobacco : decreased ropinirole plasma concentrations and efficacy
- ▶ **Kava**
- ▶ **Lithospermum**
- ▶ **Vitex**



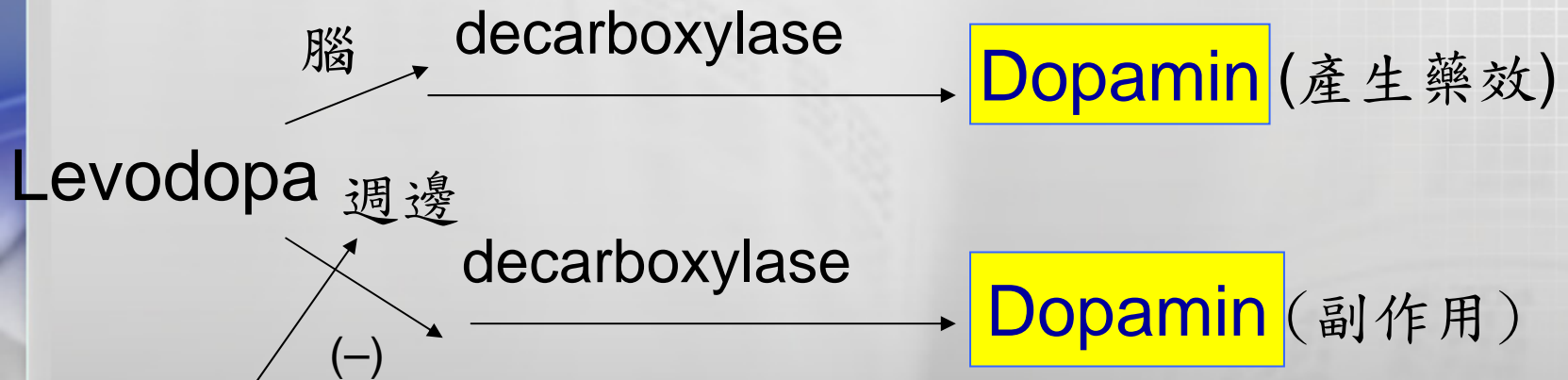
Levodopa

- ▶ Most effective for akinetic symptoms
- ▶ Tremor and Rigidity can also respond to levodopa therapy
- ▶ Postural instability
- ▶ Neurotoxic or Neuroprotective ?



Levodopa

- ▶ Dopamin 無法通過BBB，但是Levodopa可以
 - ▶ Levodopa $\xrightarrow{\text{decarboxylase}}$ Dopamin
- ▶ 進入中樞神經系統的Levodopa因DDCI可由1%增至10%



Carbidopa: Peripheral dopa decarboxylase inhibitor



Dopa Decarboxylase Inhibitor

- ▶ Carbidopa、Benserazide
- ▶ 單獨使用沒有療效，無法通過BBB，只能留在週邊，因此能有效的抑制levodopa在週邊被代謝，降低levodopa在週邊的副作用
- ▶ 當Levodopa和其並用時劑量可減少達75%。
- ▶ Madopar® Levodopa + benserazide
- ▶ Sinemet® Levodopa + carbidopa

Adverse effects

▶ peripheral dopamine generation:

▶ 胃腸道反應: nausea; vomiting

▶ 給予Ondansetron或Domperidone

▶ 心血管反應: postural hypotension; 心搏過速，甚至心律不整

▶ 評估已併用藥品並建議避免

▶ Midodrine或長統襪

▶ CNS dopamine generation

▶ Agitation, confusion, hallucinosis, psychosis

▶ Clozapine or Quetiapine用於藥物減量之惡化症狀



Levodopa Related Motor Complications-1

- ▶ 3-5years after
- ▶ Wearing-Off phenomenon
 - ▶ The duration of symptomatic benefit after each dose reduced < 4 hours
 - ▶ dystonia (involuntary, sustained cramping), worsening parkinsonism
 - ▶ shortness of breath; fatigue; tachycardia; facial flushing
- ▶ 降低給藥間隔
- ▶ 補充長效劑型
- ▶ 併用COMTI或MAOBI



Levodopa Related Motor Complications-2

▶ On-Off phenomenon(開-關現象)

- ▶ 即患者突然多動不安(開)而後又出現肌僵直運動障礙(關),兩種現象可交替出現.
- ▶ Clonazepam可改善夜間小腿肌疼痛



Levodopa Interaction

- ▶ ↓ Levodopa effect
 - ▶ Central dopamine depletion: Reserpine, Chlorpromazine, Olanzapin
 - ▶ decreased levodopa absorption: Iron
 - ▶ ↑ peripheral decarboxylation of levodopa: Pyridoxine(VitB6)
 - ▶ Phenytoin



Levodopa Interaction

- ▶ ↑ risk of adverse effects
 - ▶ Bupropion
- ▶ Hypertensive crisis
 - ▶ Linezolid
 - ▶ MAOAs, MAOBI?
 - ▶ ↑ peripheral dopamine and norepinephrine
- ▶ increased levodopa bioavailability and an increased incidence of extrapyramidal symptoms : Metoclopramide



Levodopa的食物交互作用

- ▶ Levodopa宜在空腹時服用，因為攝取含神經胺基酸的食物，會與Levodopa競爭
- ▶ Levodopa飯後吃可降低胃腸道反應

COMT inhibitors

▶ Mechanism

- ▶ COMT is responsible for catalyzing levodopa
- ▶ Inhibition of COMT in conjunction with Levodopa-Carbidopa leads to higher plasma level of levodopa

▶ COMT – Inhibit需跟Levodopa併用才有療效，單獨使用沒有療效

▶ 併用Levodopa時L需降低劑量

▶ Tolcapone、Entacapone





COMT inhibitors

- ▶ Entacapone則無法通過BBB
 - ▶ Dosage: 200 mg ORALLY with each dose of levodopa/carbidopa, MAX 1600 mg/day
- ▶ Tolcapone可通過BBB
- ▶ Adverse effects
 - ▶ Dyskinesias, hallucinations
 - ▶ Nausea, vomiting, abdominal pain, diarrhoea



MAO-B inhibitor

- ▶ Dopamin $\xrightarrow{\text{MAO-B}}$ Metabolites
- ▶ Monotherapy dose not produce functionally benefit
- ▶ Selegiline 5mg bid with **breakfast** and **lunch**
 - ▶ Lose MAO-B selectivity at doses > 20mg/d
- ▶ Side effects: Nausea, Headache, Insomnia



Interaction

- ▶ Hyperpyretic crisis, convulsant: TCA
- ▶ Serotonin syndrome: SSRI, Dextromethorphan
- ▶ Hypertension crisis: Dopamin

NMDA antagonist

- ▶ Amantadine(PK-Merz®)
- ▶ ↑ DA release and ↓ DA reuptake
- ▶ 拮抗cholinergic或glutamatergic receptor
- ▶ Dosage:100mg qd; increased by 100mg 1-2 wk; usual daily dose:100-300mg
- ▶ 對於僵直及運動遲緩方面，效果比anticholinergic agents佳，對於顫抖的治療則效果較差
- ▶ 本品Onset快，但20%的病人在治療6~8週之後，就會產生Tolerance
- ▶ ↓ dose in patients with renal insufficiency
CCI<50ml/nin





Adverse effect

- ▶ Nervousness, insomnia or hallucinations with high doses
- ▶ Livedo reticularis(網狀青斑)併有 Ankle edema(踝部水腫)
- ▶ Nausea
- ▶ Postural hypotension



Neuroprotective therapy

- ▶ Levodopa
- ▶ MAO-B inhibitor
- ▶ Dopamine receptor agonist
- ▶ Others
 - ▶ Coenzyme Q10
 - ▶ Vit E x
 - ▶ Vit C ?
 - ▶ Riluzole ?
 - ▶ Uric acid
 - ▶ Glutathione
 - ▶ Creatine




Nonpharmacologic therapy

- ▶ Education
- ▶ Support
- ▶ Exercise and Physical
- ▶ Speech
- ▶ Nutrition



Depression的治療問題

- ▶ 未達目標或過度
- ▶ 藥物與患者身心環境的交互反應
- ▶ 藥物的使用有正面的治療作用



輕度憂鬱的解決方式

- ▶ 運動
- ▶ 睡眠
- ▶ 監測1-2週
 - ▶ 自我解決問題能力
 - ▶ 行爲認知改變



Pharmacotherapy

- ▶ TCAs
- ▶ SSRIs
 - ▶ Fluoxetine
 - ▶ Citalopram
 - ▶ Sertraline
- ▶ SSRIs offer advantages over TCAs
- ▶ Alternative
 - ▶ Moclobemide



- ▶ Initial choice of drug must be avoidance

- ▶ Dothiepin

- ▶ Venlafaxine

- ▶ ADR

- ▶ Hyponatremia

- ▶ Seizure

- ▶ Stop treatment

- ▶ 6M



轉介專業

- ▶ 不正常舉動 過度進食或睡眠
- ▶ 服用兩種抗憂鬱劑仍無法達到療效
- ▶ 精神病傾向
- ▶ 自殺傾向
- ▶ 躁鬱症傾向

Thank you for your attention

