Parkinson's disease and tremor

고 성 범
고려의대

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Today's Talk

- Drugs for PD
  - Levodopa
  - Dopamine agonist
  - MAO-B inhibitor
  - Anticholinergics
  - Amantadine
  - COMT inhibitor
- Therapeutic strategies & practice

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Pharmacologic management of PD

MEDICATIONS FOR PD

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Option # 1 Levodopa

- Pros
  - ✓Best efficacy
  - ✓Can be used in most situations
- Cons
  - ✓More motor complications

- Other issues
  - Controlled-release vs. Immediate-release
    - F/Up 5 year study : no difference btw IR & CR (Neurology 1999;53:1012-9)
    - The CR first study group : no difference (Eur Neurol 1997;37:23-27)
  - Combined with COMT-inhibitor
    - STRIDE PD : failed, onset of dyskinesia occurred earlier in stalevo group (Ann Neurol 2010;68:18-27)
    - FIRST step

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Adverse effect

- peripheral acting : **nausea/ vomiting**
- peripheral/ central : **orthostatic hypotension**
- central : **motor fluctuation, dyskinesia**, **mental change (sedation)**

- Cautions/ contraindication: angle closure glaucoma, history of malignant melanoma or skin cancer
- Controversial issues: malignant melanoma (related to PD itself)

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Sinemet-CR/ Madopar HBS

- Aim
  - Smooth out fluctuations
  - Useful as a 1st line drug in older patients (70 years old <): lower peak level→ ***less*** peak dose drowsiness or confusion
- Limitation
  - Some of medication reached in large intestine ***before*** all of it was **absorbed** in small intestine
  - **Difficulty** in **predicting 'on' time** (sometimes delayed response→ night time med: sustained severe dyskinesia during night)

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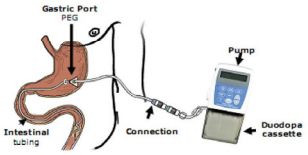
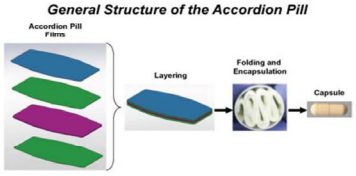
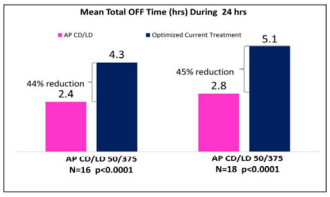
New formulation of L-dopa

- Continuous intra-duo/jejunal infusion (Duodopa)

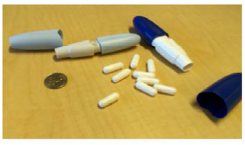


- IPX066: extended release form(Rytary®)
- Accordion pill





- Inhaled formulation (CVT-301)



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Option # 2 Dopamine agonists

• Pros	• Cons
✓moderate efficacy ✓Less motor complications ✓Delays use of L-dopa	✓Moderate efficacy ✓Slow titration ✓More psychosis, ICDs ✓Daytime somnolence

- Issues
  - Immediate-release vs Slow-release
  - dosage

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Dopamine agonists

Name	D1	D2	D3	5HT	α-adrenergic	T ½(Hr)	metabolism	Recommended daily dose (mg)
Bromocriptine	-	++	++	1A,1B	α1, α2	6	? (bile)	10-60
Pramipexole	0	+++	++++	1A	α2	8-12	**renal**	1.5-4.5
Ropinirole	0	+++	++++	1A	α2	6	**hepatic**	6-24
Pramipexole-ER	0	+++	++++	1A	α2		renal	
Ropinirole-PD	0	+++	++++	1A	α2		hepatic	
Rotigotine patch	+	++	+++	1A	α2	5-7	**hepatic (avoid first-pass hepatic metabolism)**	8-16

+:agonist; -:antagonist;0:no activity;D:dopamine;5HT:5-hydroxytriptamine

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Receptor affinity

- **Reversal of parkinsonian symptoms**
  - Synergic activation of both D1 & D2 receptors
    - Both D1 & D2 receptors (ideal)
      - apomorphine, pergolide
    - Mainly interact with D2 receptors
      - other DAs (ropinirole, pramipexole, rotigotine)
- **D3 receptor**
  - Localized in *forebrain limbic areas*, low in striatum
  - High affinity on D3 receptor : ropinirole, pramipexole, rotigotine
  - Potential benefit for **depression**, but risk of **psychosis** & **ICDs**

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Pharmacokinetics

- **Bioavailability after oral administration**

Very high	Intermediate	Low
pramipexol	rotigotine / ropinirole	bromocriptine

  - Equivalent dose
    - Pramipexole: Rotigotine: Ropinirole: Bromocriptine = 1:4:4-5:10
- **Hepatic clearance**
  - Ropinirole, bromocriptine
  - With CYP450 inhibitor (ciprofloxacine) : dose reduction required
- **Renal clearance**
  - Pramipexole : excreted unchanged by renal tubular secretion
  - Competition with H2 blocker(cimetidine), diuretics, verapamil

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ICRBD

- **Impulse control and repetitive behavior disorders**
  - **Impulse control disorders**
  - **Repetitive behavior disorders**
    - **Punding**
    - Walkaout
    - **Dopamine dysregulation syndrome**

❖Risk factors : dopamine agonist, younger age-onset

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증례

- 3년 전부터 파킨슨병 투약 중인 42세 남자 환자가 최근 공금까지 사용하며 도박을 하고 있다. .....치료는?

Dopamine agonist (ropinirole, pramipexole) 중지 혹은 소량으로 유지
Amantadine, zonisamide, etc 투약 고려 (evidence는 없음)

↓

문제점
1. motor symptoms의 악화
2. DAWS 발생

→

해결 방안
LD 용량 증량 혹은 COMT inhibitor 추가 (MAO-B inhibitor 추가시에는 주의 요망!)

1.Parkinsonism Relat Disord 2013;19:483-484
2. Mov disord 2015; 30:150-159

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- **Adults** with **PD taking dopaminergic therapy** are given information about the **risk** of developing **impulse control disorders**, when ***starting*** treatment and at least ***annually***. (NICE 2018 Guideline, UK)

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DAWS: Definition

- **A cluster of physical & psychological symptoms that**
  (usually consists of **non-motor symptoms**: psychological, autonomic, sensory, GI symptoms)
  - Correlate with DA withdrawal
  - Cause distress or social/occupational dysfunction
  - Do ***not*** respond to **levodopa** or **other medications**
  - Are not explained by other clinical factors

Rapidly improve with DA repletion

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Option # 3 MAO-B inhibitors

• Pros	• Cons
✓Well tolerated ✓Easy to use (good compliance) ✓Possible disease modifying	✓Mild to moderate efficacy

- Which drug to use
  - Rasagiline
  - Selegiline

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Selegiline

- Indications
  - disease modifying effects in early PD
  - Wearing off in advanced PD (?)
- Dosage: 5mg (morning)→ 5-5mg (morning-noon)
- Side effects
  - Most common side effects
    - nausea, **dizziness (orthostatic BP drop)**, **insomnia**, agitation, **confusion**
  - Infrequent side effects
    - **Dyskinesia** (involuntary movements), headaches
  - Rare side effects
    - **drug interactions (with SSRI: serotonergic syndrome)**, depression, hallucinations

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Rasagiline (Azilect®)

- **Moderate symptomatic effect**
  - TEMPO (TVP-1012 in Early Monotherapy for Parkinson's disease)[1] : monotherapy in early PD
  - LARGO (Lasting effect in Adjunct therapy with Rasagiline Given Once daily) [2]: levodopa sparing effects
  - PRESTO (Parkinson's Rasagiline: Efficacy and Safety in the treatment of "Off") [3]: on time prolongation
  - ANDANTE (Add on to Dopamine Agonists in the Treatment of Parkinson's disease) [4]: significant improvement, tolerable (dizziness, somnolence, headache)
- **Potentially disease modifying action**
  - TEMPO: -4.2 units in t-UPDRS in rasagiline 1mg (vs placebo)
  - ADAGIO (Attenuation of Disease progression with Azilect Given Once daily) [5]: significant better outcomes in1mg, but not in 2 mg (Floor effect ?)
  - ADAGIO post hoc (for upper quartile UPDRS) [6]: significance in both 1mg and 2 mg
- **Dosage**: 1mg once a day
- **Adverse effects**
  - Drug interaction: Serotonergic syndrome with SSRI, TCA, meperidine

1. Arch Neurol 2002;59:1937-43
2. Lancet 2005;365:947-54
3. Arch Neurol 2005;62:241-8
4. Mov Disord 2014;29:1028-31
5. N Eng J Med 2009;361:1268-78
6. Lancet Neurol 2011;10:415-23

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Safinamide (Xadago™)

- DA: highly selective & reversible inhibition of monoamine oxidase B → similar to selegiline, rasagiline
- Non-DA: selective sodium channel blockade & calcium channel modulation, with consequent inhibition of excessive glutamate release → effective in motor complications including dyskinesia (?), cognition
- 50-100mg, once daily
- Effective in PD, RLS & epilepsy(?)

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JAMA Neurology | Original Investigation | CLINICAL TRIAL

Assessment of Safety and Efficacy of Safinamide as a Levodopa Adjunct in Patients With Parkinson Disease and Motor Fluctuations

A Randomized Clinical Trial

Table 2. Efficacy Findings in the Intention-to-Treat Population (Last Observation Carried Forward)

	Safinamide Group, Mean (SD) (n = 274)			Placebo Group, Mean (SD) (n = 275)			LS Mean Difference in Change (95% CI)[a]	*P* Value[a]
Outcome	Baseline	Week 24	Change	Baseline	Week 24	Change		
Primary Outcome								
"On" time without troublesome dyskinesia,[b] h/d	9.30 (2.41)	10.73 (2.75)	+1.42 (2.80)	9.06 (2.50)	9.63 (2.77)	+0.57 (2.47)	+0.96 (+0.56 to +1.37)	<.001
Key Secondary Outcomes								
"Off" time,[b] h/d	5.34 (1.97)	3.77 (2.56)	-1.56 (2.35)	5.38 (2.01)	4.84 (2.59)	-0.54 (2.21)	-1.03 (-1.40 to -0.67)	<.001
UPDRS Part III score[c]	22.26 (11.66)	18.83 (10.87)	-3.43 (7.72)	23.05 (12.65)	21.22 (11.78)	-1.83 (8.23)	-1.82 (-3.01 to -0.62)	.003
UPDRS Part II score[c]	9.97 (5.53)	8.90 (5.44)	-1.07 (3.63)	10.43 (6.29)	9.68 (5.94)	-0.75 (3.95)	-0.43 (-1.02 to +0.16)	.15
Patients with improvement on CGI-C, %[d]	NA	57.7	NA	NA	41.8	NA	1.92 (1.36 to 2.70)[e]	<.001[e,f]
PDQ-39 score	27.47 (14.61)	24.31 (13.73)	-3.17 (10.86)	26.94 (14.83)	26.26 (14.92)	-0.68 (10.51)	-2.33 (-3.98 to -0.68)	.006[e]

The most frequently reported adverse event was dyskinesia (in 40 [14.6%] vs 15 [5.5%] and as a severe event in 5 [1.8%] vs 1 [0.4%])

JAMA Neurol 2017;74(2):216-224

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Option # 4 Anticholinergics

- Clinical use
  - Less effective than dopaminergic drugs
  - Helpful in reducing all symptoms of PD
  - Special favor in reducing the severity of **tremor**
- Commercial drugs
  - Cogentin (Benztropine) Tab 0.5, 1, 2 mg
    - Usual dose: 1- 2 mg/day
  - Trihexin (Trihexyphenidyl) Tab 2 mg
    - Usual dose: 3-6mg/day
  - Proimer (Procyclindine) Tab 5mg
    - Usual dose: 7.5-15mg/day

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Adverse effect

- Peripheral adverse effects
  - dry mouth, urinary retention, impairment of ocular accomodation, decrease of sweating, constipation
- Central side effect (especially in old age)
  - memory disturbance, confusion, psychosis with hallucination

* attention ; not recommended to old age (esp, >70)

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Option # 5 Amantadine

- Mode of action
  - dopaminergic transmission
    - Release of dopamine from nerve terminal
    - Block dopamine uptake into nerve terminals
  - mild anticholinergic properties
  - NMDA receptor antagonism
- Clinical use
  - To reduce PD symptoms in about two-thirds of patients.
  - Amantadine monotherapy can be effective in early PD. (tolerance)
  - Dosage: 100-300 mg/day
  - For L-dopa induced dyskinesia: high dosage (400mg)
  - Oral 300mg/day for 30 days (MSA-P)
  - Amantadine ER: effective in reducing dyskinesia & off time

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Amantadine - side effect

- Usually transient, mild & reversible
  - ankle edema, livedo reticularis, dry mouth, visual hallucination/ confusion
  - Corneal edema (usually reversible)
- mainly kidney excretion
  - Warning to patients with renal dysfunction
  - Dosage > 200 mg/day : usually not recommended for old age

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Intravenous amantadine

- Short-term effect of amantadine sulphate on motor performane and reaction time in patients with idiopathic Parkinson's disease (Pinter et al 1999)
  - After 14d of iv amantadine, a significant improvement on UPDRS part III (45.3 to 39.4) and motor performance task
- Levodopa "Drug Holiday" with amantadine infusions as a Treatment of Complications in Parkinson's Disease (Koziorowski 2007)
- Intravenous amantadine is safe and effective for the **perioperative** management of patients with Parkinson's disease (Kim YE et al 2011)

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Amantadine extended release (GOCOVRI®)

- With a dosage of 274 mg (equivalent dosage of amantadine 340mg) once daily at bedtime,
  - For motor complications
    - increasing ON time without troublesome dyskinesia
    - reducing OFF time and ON time with troublesome dyskinesia from the morning and throughout the daycompared with placebo. (Mov Disords 2017)
  - AE: hallucinations, dizziness, dry mouth and peripheral edema (Mov Disords 2017)
  - Improvement of ADL (PDRD 2018)

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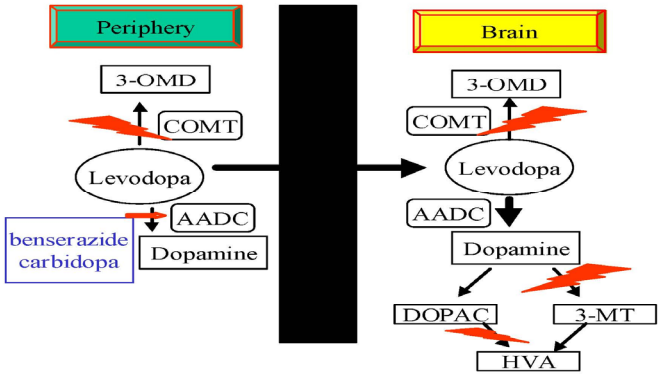
Option # 6. COMT inhibitor

- central acting ; tolcapone
- peripheral acting ; entcapone, nitecapone, tolcapone
- tolcapone - risk of fatal hepatic failure, diarrhea



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Entacapone

- Indication: wearing off
  - Increase elimination half of levodopa: 1.3→ 2.4 hr
  - Increase amount of "on" time a day
  - In PD patients, maximal effect occurs with 200 mg of entacapone
- Clinical use
  - Initial maintain dosage, fixed dosage on each dose (200mg)
  - Should be administered concomitantly with each dose of levodopa and carbidopa (average 4-6 times per day)
  - Adverse effects
    - urine discoloration (brownish orange); constipation; diarrhea; dizziness; drowsiness; dry mouth; nausea; stomach pain; tiredness; vomiting

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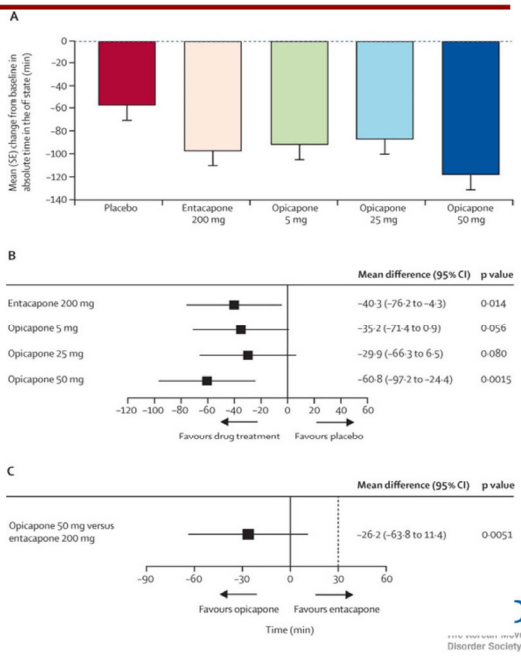
Opicapone

- long-acting, peripheral COMT inhibitor
- 50 mg once daily
- no serious cases of hepatotoxicity reported in clinical trials



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JAMA Neurology | Original Investigation | CLINICAL TRIAL

Opicapone as Adjunct to Levodopa Therapy in Patients With Parkinson Disease and Motor Fluctuations
A Randomized Clinical Trial

DESIGN This phase 3 international, multicenter outpatient study evaluated a 25- and a 50-mg/d dosage of opicapone in a randomized, double-blind, 14- to 15-week, placebo-controlled clinical trial, followed by a 1-year open-label phase during which all patients received active treatment with opicapone. Patients with PD who experienced signs of end-of-dose deterioration and had a mean total awake off-time (state of akinesia or decreased mobility) of at least 1.5 hours, not including morning akinesia, were enrolled. Data were collected from March 18, 2011, through June 25, 2013. Data from the evaluable population were analyzed from July 31, 2013, to July 31, 2014.

MAIN OUTCOMES AND MEASURES The primary efficacy outcome of the double-blind phase was the change from baseline in absolute off-time vs placebo based on patient diaries. The open-label phase focused on maintenance of treatment effect in off-time.

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Variable	Treatment Group		
		Opicapone Dosage	
	Placebo (n = 135)	25 mg/d (n = 125)	50 mg/d (n = 147)
Key Secondary End Points in Hierarchical Order			
Responder rate of off-time reduction of ≥1 h at end of double-blind phase			
No. (%)	68 (50.4)	78 (62.4)	97 (66.0)
OR (95% CI)	NA	1.7 (1.0 to 2.8)	1.9 (1.2 to 3.1)
P value vs placebo	NA	.04	.009
Change from baseline to end of double-blind phase in absolute total on-time, min[a]			
LS, mean (SE)	58.7 (14.2)	104.1 (14.7)	111.3 (13.7)
Treatment effect vs placebo (95% CI)	NA	45.4 (7.1 to 83.8)	52.6 (15.8 to 89.3)
P value	NA	.02	.005
Change from baseline to end of double-blind phase in off-time, %[b]			
LS, mean (SD)	−6.7 (1.4)	−11.0 (1.5)	−12.1 (1.4)
Treatment effect vs placebo (95% CI)	NA	−4.3 (−8.2 to −0.4)	−5.5 (−9.2 to −1.7)
P value	NA	.03	.004

JAMA Neurol 2017;74(2):197-206

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THERAPEUTIC STRATEGIES AND PRACTICES

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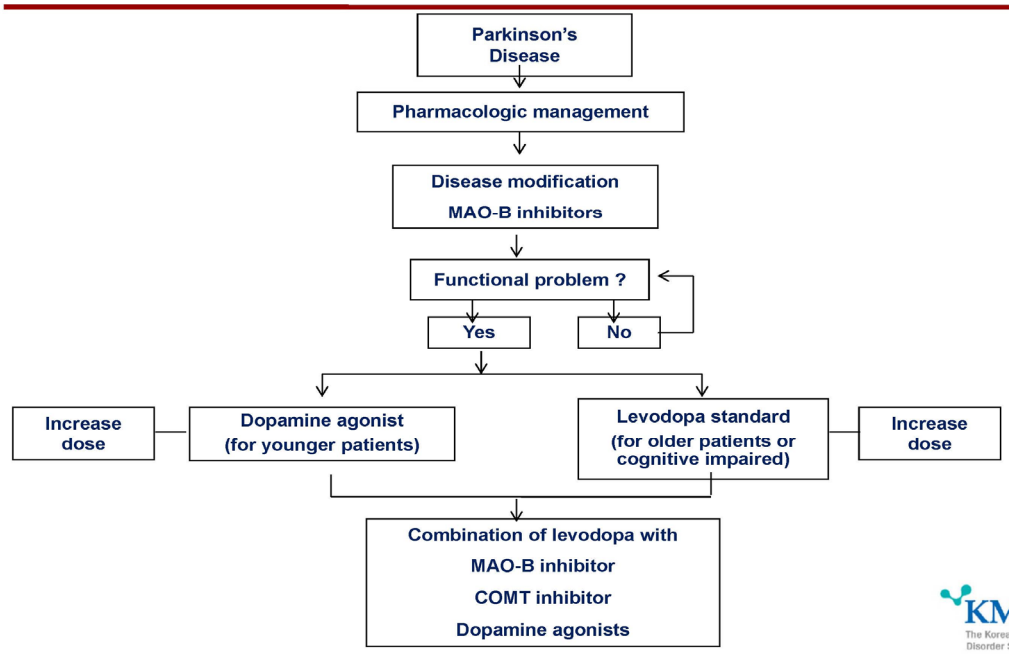
1. Suggested Algorithm for Early PD



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With these algorithm

- If possible, early diagnosis & early treatment is considered.
- In **early PD** patients,
  - For young patients, consider ***MAO-B inhibitors*** and/or ***dopamine agonists***.
  - For older patients, consider ***L-dopa***.

❖Early L-dopa vs L-dopa phobia

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MDS TFT 2018 review

early or stable PD

- **monotherapy** of early PD
  - nonergot dopamine agonists, oral levodopa preparations, selegiline, rasagiline, anticholinergics: clinically useful
  - Amantadine: possibly useful
- **adjunct therapy** [to L-dopa] in early/stable PD
  - nonergot dopamine agonists, rasagiline, and zonisamide : clinically **useful**
  - Amantadine: possibly useful
  - selegiline, bilateral STN DBS : investigational
  - entacapone, safinamide : ***not*** clinically useful

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MDS TFT 2018 review

adjuvant for specific symptoms

- **gait and balance**
  - Rivastigmine: clinically useful
  - Donepezil, methylphenidate, memantine: investigational
- **tremor**
  - Unilateral thalamotomy, thalamic DBS : clinically possible **useful**

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L-dopa phobia

- **Factors influencing motor complications in PD**
  - Age onset of PD: YOPD
  - Disease duration and severity of PD

  ✓ Earlier initiation and longer duration of levodopa exposure ?
  ✓ Dosage of levodopa

  ➢ Pharmacogenomics (Precision medicine)

  ❖ Motor fluctuations were influenced more likely with greater **disease duration** and **levodopa dose**.

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Factors predictive of development of MC

Time to wearing off

	Factor	χ^2 Statistic	*P* value	Effect on wearing-off (higher risk)
B. Time to Wearing Off				
1	Age at onset of PD	63.04	<0.001	Lower age
2	UPDRS Part II score	21.72	<0.001	Higher score
3	Region (North America/Europe)	33.81	0.001	North America
4	Nominal L-dopa dose	25.04	<0.001	Higher dose
5	Gender	8.84	0.003	Females
6	UPDRS Part III score	3.98	0.05	Higher score

PD, Parkinson's disease; LCE, L-dopa/carbidopa/entacapone; LC, L-dopa/carbidopa; UPDRS, Unified Parkinson's Disease Rating Scale.
[a]In total, 723 of 745 patients had no missing data on any of the potential factors and were included in the multivariate analysis.
[b]The steps are listed in the order in which the factors were selected for the model.

- Caution against increasing the L-dopa dose by large increments (avoiding greater than 400 mg/day, especially for dyskinesia)

Mov Disord 2013;28:1064-1071

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Disease duration, L-dopa duration & L-dopa dosage

	Model prediction (AUC)[a]	
Set of variables[b,c]	Motor fluctuations	Dyskinesias
A + B + C	0.77[d]	0.79[e]
B + C + D	0.71	0.75
Model for motor fluctuations[d]	**OR (95% CI)**	***P*-value**
Levodopa dose (mg/kg)	1.33 (1.05–1.68)	**0.019**
Duration of levodopa at occurrence (years)	1.09 (0.80–1.48)	0.606
Disease duration at onset of motor fluctuations (years)	1.36 (1.01–1.83)	**0.040**
Model for dyskinesias[e]		
Levodopa dose (mg/kg)	1.19 (1.00–1.42)	**0.045**
Duration of levodopa at occurrence (years)	0.93 (0.73–1.18)	0.550
Disease duration at onset of motor fluctuations (years)	1.42 (1.07–1.87)	**0.014**

Motor fluctuation and dyskinesia are ***not*** associated with the **duration of levodopa therapy**, but ***rather with*** longer ***disease duration*** and ***higher levodopa daily dose.***

Brain 2014;137:2731-2742

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Treatment of PD

MOTOR FLUCTUATIONS

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Motor fluctuations

- **Stable response**
  - a levodopa-induced improvement of motor function in the absence of motor fluctuations in a patient taking 4 or less doses of levodopa a day. (Factor SA. Parkinson's disease. 2nd ed. 576)
- Types
  1. Slow "wearing off"
  2. Sudden off
  3. Random off (might ***not*** be so **random**)
  4. Super off (worsening of off): induced by negative or inhibitory
  5. Delayed on
  6. Dose failure
  7. Weak response at the end of day
  8. Variable response in relationship with meal

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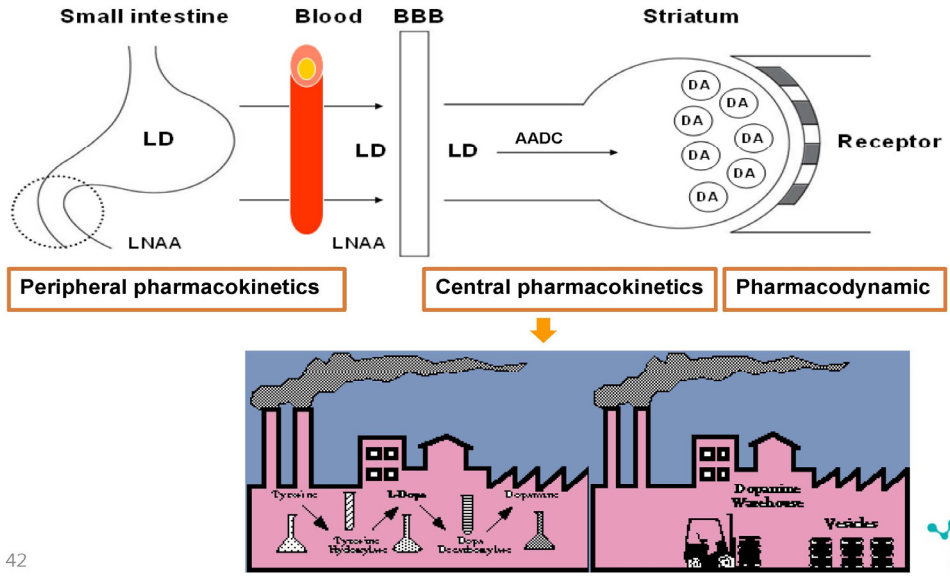
L-dopa : Pharmacologic considerations



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L-dopa : Motor Effects with different Temporal Patterns

- **L-dopa Responses:**
  1. Short-duration improvement (minutes to hours)
  2. Long-duration improvement (days to months)
  3. Inhibitory response

- **Superimposed on:**
  - Endogenous dopamine effects
  - Diurnal patterns (sleep benefits)

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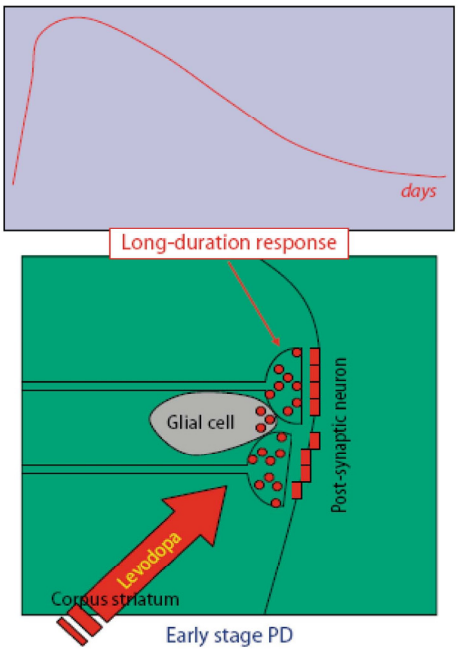
Long-duration Responses

- **Prolonged benefit after a single dose of levodopa**
- **Presynaptic buffering Function**



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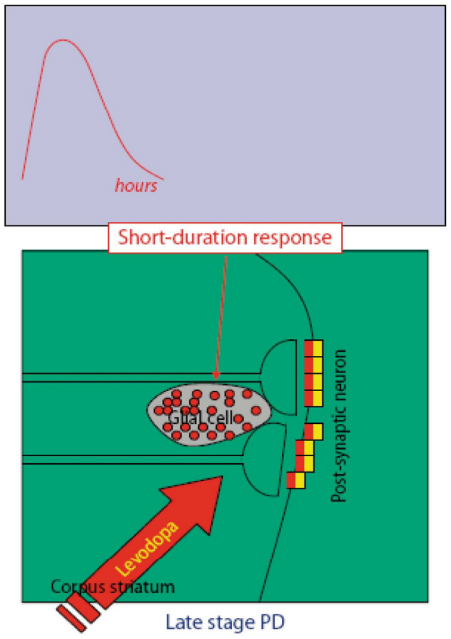
Short-duration Responses 1

- L-dopa
  - $T_{1/2}$ = 60-90 min
  - Short-duration effect,
    - Parallel to the rise & fall of plasma LD concentrations



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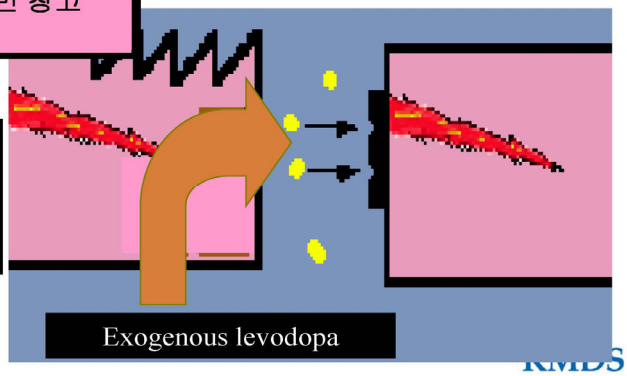
Loss of buffering function (proper adjustment of striatal vesicular dopamine concentration/ storage) in nigrostriatal dopaminergic neuron

- Dependent to exogenous L-dopa
- Circulating L-dopa level = intrasynaptic DA level



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Short-duration Responses 2

- Responsible for **motor fluctuations** and **dyskinesia**
- **Pharmacokinetics**
  - Short half-life (60-90 min)
  - Erratic absorption (second to erratic gastric emptying)
  - Variable transport to brain (secondary to saturated BBB LNAA transport)

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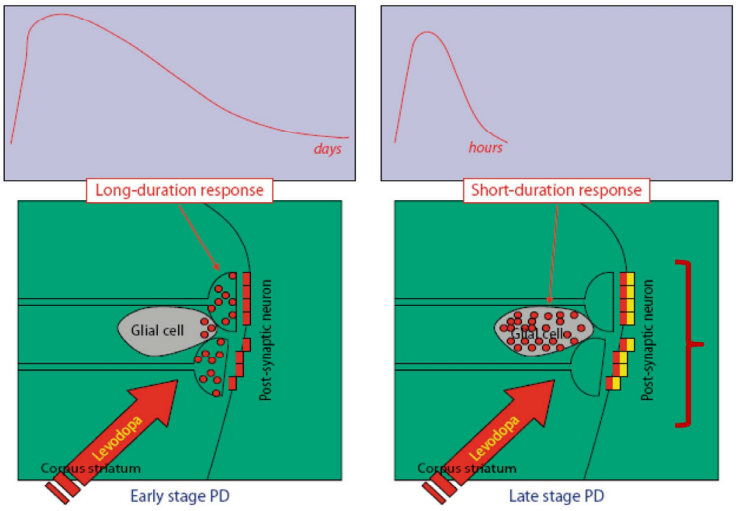
Postsynaptic mechanism



Supersensitive DA receptors

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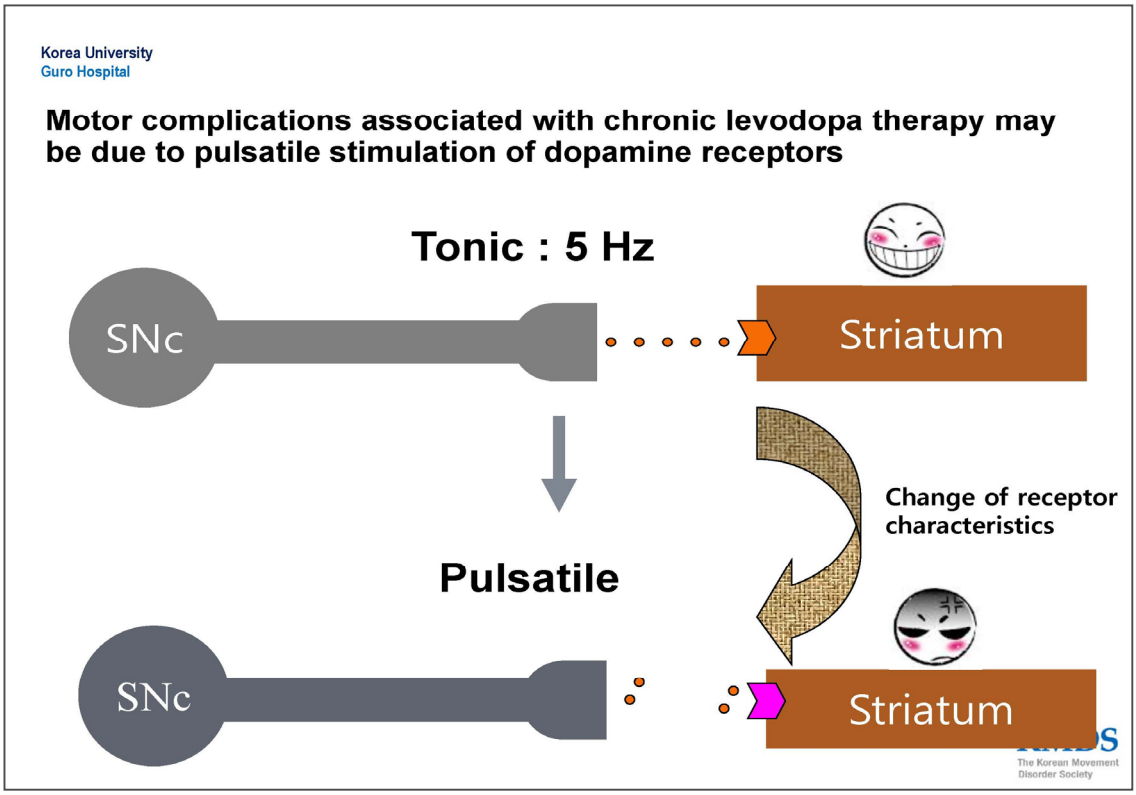
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Motor complications associated with chronic levodopa therapy may be due to pulsatile stimulation of dopamine receptors
Tonic : 5 Hz
SNc
Striatum
Change of receptor characteristics
Pulsatile
SNc
Striatum
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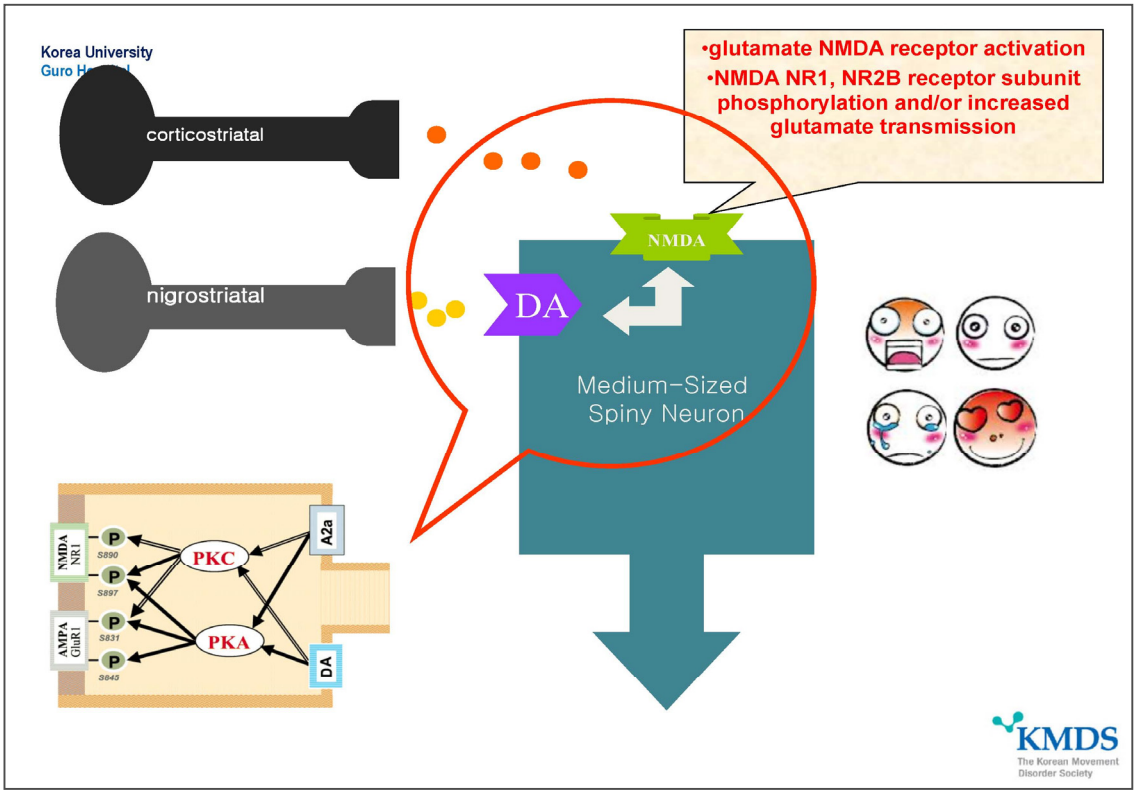
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•glutamate NMDA receptor activation
•NMDA NR1, NR2B receptor subunit phosphorylation and/or increased glutamate transmission
corticostriatal
nigrostriatal
NMDA
DA
Medium-Sized Spiny Neuron
NMDA NR1
AMPA GluR1
P
S890
S897
S831
S845
PKC
PKA
A2a
DA
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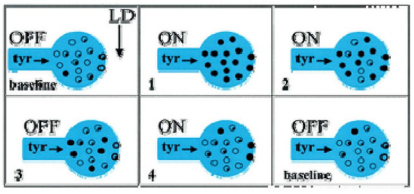
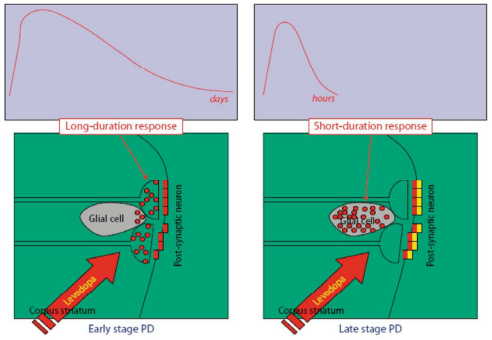
Random on-off

Presynaptic mechanism



Postsynaptic mechanism



Brain 2004;127:888-899

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Factors influencing MF in PD

- Age onset of PD: YOPD
- Disease duration and severity of PD

✓ Earlier initiation and longer duration of levodopa exposure ?

✓ Dosage of levodopa

➢ Pharmacogenomics (Precision medicine)

❖ Motor fluctuations were influenced more likely with greater disease duration and levodopa dose.

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Principles

treatment of motor fluctuation

1. Patient education: fluctuations generally can**not** be **eliminated** but may be made ***bearable***.
2. Determine **what** fluctuates and what causes disability
3. Make response **predictable** by controlling *pharmacokinetic factors* and administrating *adequate dose*
4. Make the response to *each dose* sufficiently **long** such that it is useful to the patient.
5. **Reduce** *"off" disability*
6. Avoid drug toxicity and tolerance by **limiting** cumulative doses of antiparkinsonian drugs

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1. Determining what fluctuates

- Physician: carful history taking or close observation of "on" & "off"
- The response to first dose cycle may be **different** from the response to dose cycle later in the day.
- Motor fluctuation accompanied with anxiety, mood, autonomic function, and sensation. Anxiety and depression are frequently major contributors to distress.
- Alternate method: home video, diary (motor & nonmotor), monitoring techniques

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2. Making Responses Predictable

- **Unpredictable** L-dopa responses are generally related to **pharmacokinetic causes**.
- Most important L-dopa pharmacokinetics: short plasma half life, variable absorption and distribution
- Most common cause: **small doses of L-dopa**
  - Duration of response to each dose: proportional to the **size of the dose** (sometimes dose failure)
  - Controlled release L-dopa preparations: (1) *lower* plasma concentrations, (2) more *erratic* absorption → more *erratic* response

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DRT adjustment (1)
to overcome wearing off

- Strategy
  - *Adequate dosage* for controlling symptoms
  - Good strategy: converting CR form → IR form (3-4 hour interval)
  - Focus of schedule: **L-dopa**

- The efficient **peripheral pharmacokinetics**
  (consider **meal**, **gastric emptying** and **bowel passage**, **protein diet**)
  - Before meal (avoid with meal, ferrous sulfate), dissolving with carbonated water
  - Add antiacid, dompheridone
  - Sometimes: reconsider using anticholinergics for delaying gastric emptying or eliminating anticholinergics
  - Protein redistribution diet (protein rich diet: only for dinner)
  - Eradicating gastric *Helicobacter pyroli*

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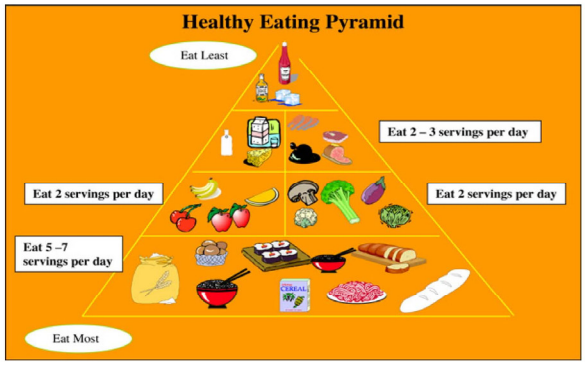

성분명	약품명	성분명	약품명
아클라토니움 (aclatonium)	아크라톤정,아크라톤캡슐	브로모프라이드 (bromopride)	벤트릴캅셀, 벤트릴정
클레보프라이 (clebopr	정, 크레보릴정	메토클로프라 (metoclopr	란정, 멕소롱정, 로프라미드정 등
돔페리돈 (domperidon)	돔페리돈정, 모타리돈정, 무비돈정, 돔페닐정, 마라돈정, 모타딘정, 칸치딘정, 돔페리만정, 모티리움엠정 등	레보설프 (levosulprid	보엠정, 레보필정, 정, 레보스틴정, 라이드정, 레보탈정, 엘프라이드정, 레보프라이드정 등
이토프라이드 (itopride)	이토벨정, 가스트론정, 가나톤정, 미라드정, 가나메드정, 이토메드정, 가프리드정 등	모사프라이드 (mosapride)	가스틴정, 나모티정, 모사핀정, 가스프린정, 모사달정, 가스모틴정, 나모틴정 등

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3. Making Responses Usable

- ***Predictable*** L-dopa responses is **not *enough*** to patient, the ***response*** must be ***useful***.
- If the response is not useful, we should consider **adding** other drugs (dopamine agonist, MAO-B inhibitor, COMT inhibitors and sometimes amantadine).
- **"Weak response at end of day"**
  - Usually ***not*** useful by **increasing the dosage** of afternoon & evening levodopa (sometimes develop drowsiness)
  - 2nd option: adding LD-SR, supplemental DA, anticholinergics or amantadine

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DRT adjustment (2)
to overcome wearing off

- maintaining more **constant plasma LD concentrations** which is stimulating many efforts to improve delivery systems
  - Add long acting dopamine agonists
  - controlled release preparations (?)
  - Add COMT inhibitor: entacapone, opicapone
  - Add MAO-B inhibitor: rasagiline, salfinamide

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4. Other strategies

- Reduce "off" disability
  - Dopamine agonists
  - Deep brain stimulation
- Reducing cumulative drug intake
  - Increase anti-PD drugs during long-term treatment will reduce "off" time. However, this benefit wanes over weeks to months, necessitating a further increase in levodopa.
  - Sometimes it is possible to get as good or better control of fluctuations with lower doses of levodopa, with less adverse effects. (restrict the highest dosage per day)
  - Give the patient a comfortable night's sleep.

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Zonisamide

multicenter, randomized, double-blind, parallel-group, placebo-controlled study

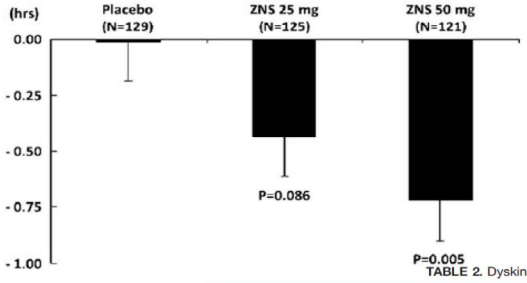

FIG. 2. Change from ba
standard error) at the f
daily "off" time significa
mide 50-mg group (esti
square mean ± standard
group.

TABLE 2. Dyskinesia at the final assessment (FAS)

			ZNS	
		Placebo (N = 129)	25 mg/d (N = 125)	50 mg/d (N = 121)
Dyskinesia duration, h/d (mean ± SD)	Baseline	0.693 ± 1.599	0.548 ± 1.286	0.581 ± 1.194
	Final assessment	0.665 ± 1.570	0.746 ± 1.707	0.719 ± 1.489
	Changes	−0.027 ± 0.945	0.197 ± 1.200	0.138 ± 0.907
	vs. placebo[a]	—	$P = 0.103$	$P = 0.235$
UPDRS Part IV, No. 33 (Disability caused by dyskinesia) (no. of patients)	Improved	3	6	5
	Unchanged	11	7	9
	Worsened	6	6	1
	Zero	109	106	106
UPDRS Part IV, No. 34 (Painful dyskinesia) (no. of patients)	Improved	1	1	2
	Unchanged	1	1	3
	Worsened	3	1	3
	Zero	124	122	113

Mov Disord 2015;30:1343-1350

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Treatment of PD

DYSKINESIA

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1. Adjustment of DRT

- Consider:
  - Discontinuing MAO-B inhibitor, COMT inhibitor
  - Levodopa dose reduction (투약 시간 별로 다른 용량도 고려) with or without increase dosage of dopamine agonist

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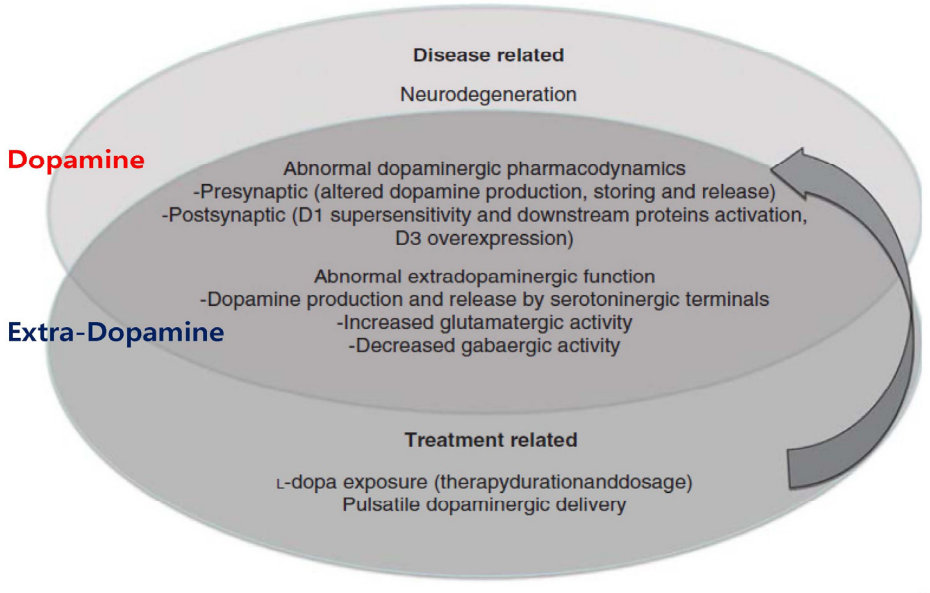
2. Anti-dyskinetic agent



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NMDA antagonist

- amantadine (350 mg/ day)
  - N = 14
  - dyskinesia : 60% reduction in amantadine group compared to placebo group without change in motor function

(Metman LV. Et al. *Neurology* 1998; 50:1323)

- NMDA antagonist dextromethorphan
  - average/maximal dyskinesia score : 50% reduction

(Metman LV. Et al. *Neurology* 1998; 51:203)

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- Short-term anti-dyskinetic effect: RCT (PDRD 2005;11:449-452)
  - Before/ after amantadine *vs* placebo
  - Reduced dyskinesia on CDRS, UPDRS IV (p<0.05)
  - No change on UPDRS part III
- Long-term antidyskinetic efficacy of amantadine in Parkinson's Disease (Mov disord 2010;10:1357-1363)
  - Subjects: Stable LID with amantadine over 1 year
  - Switched to amantadine & placebo for 3 weeks
  - Placebo group: significant increase in UPDRS IV 32+33
  - No differences on UPDRS part III between two groups

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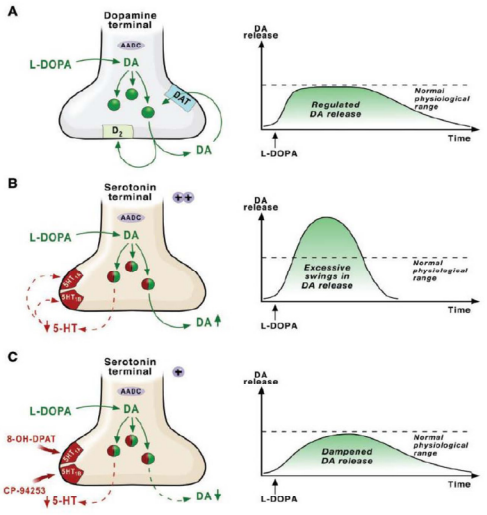
Non-dopaminergic : 5-HT$_{1A/1B}$ agonist for LID

1. DA accumulating in the storage vesicles of serotonin nerve terminal
2. lack of normal auto-regulatory feedback
3. DA released from serotonin terminals will be poorly regulated
4. uncontrolled, excessive swings in DA release
   → dyskinesia.

- The 5-HT1A and 5-HT1B receptor agonists
  - dampening the excessive swings in L-DOPA-derived DA release from the striatal serotonergic terminals.
  - Buspar (2004, 2007, 2014)
  - Eltoprazine, anpirtoline (2007,2008, 2015 Brain)



Carta M. et al. Brain. 2006;130:1819

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Serotonin, Adenosine

Serotonergic drugs (5HT$_{1A}$ agonist)

Clozapine: 50mg/day, significant reduction of LID

Buspirone: 20-30mg/day, reduction in AIM, ***risk of increase of 'off' time***

Eltoprazine: ongoing clinical trial (Phase 2)

Adenosine $_{2A2}$ antagonist

Tozadenant: ongoing clinical trial

Fipamezole: ongoing clinical trial (Phase 2b)

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Practical management for dyskinesia

- **Adjustment of DRT**
  1. Optimization of levodopa dose: minimal tolerable dosage (Risk for worsening of motor symptoms)
  2. Add or use of DA agonist (long-acting DA agonist)
  3. Use of CR form (may exacerbate dyskinesia in biphasic dyskinetic pts)
- **Anti-dyskinetic agents**
  1. Clozapine (5HT2A/2C antagonism; S/E: eosinophilia, neutropenia, apalstic anemia, myocarditis) or atypical neuroleptics
  2. Glutamate antagonist : amantadine (limitation : transient < 1yr & rebound pheunomenon), IV amantadine therapy
- **Surgery**
  - STN/GPi-DBS in PD

❖ **Dyskinesia *versus* OFF (immobile)**

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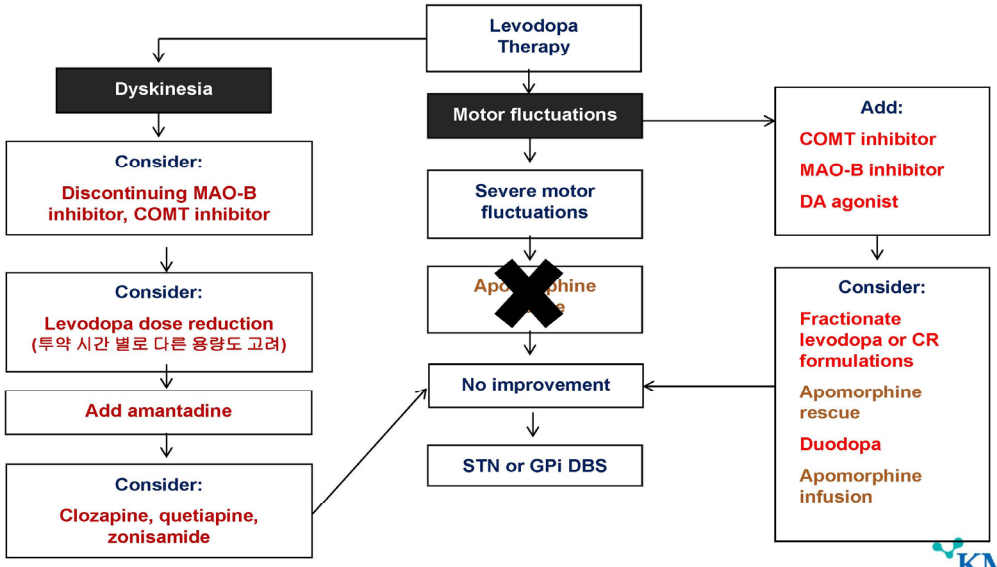
Management of motor complications in PD



Jankovic J, Poewe W Curr Opin Neurol 2012

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Surgical treatment
Targets for DBS in PD

Globus pallidus interna

- Direct anti-dyskinetic effect
- Direct anti-dystonic
- Mild anti-PD effect

Subthalamic nucleus

- Direct anti-PD effect
- Indirect anti-dyskinetic effect by lowering dosage of levodopa
- Mild direct anti-dyskinetic effect
- More frequent neuropsychiatric complications

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MDS TFT 2018 review

- **To prevent motor fluctuations**
  - Pramipexole-IR, cabergoline: clinically useful
  - Ropinirole-IR: investigational
  - Entacapone: not useful
- **To prevent dyskinesia**
  - Pramipexole-IR, ropinirole-IR, cabergoline: clinically **useful**
  - selegiline, entacapone : ***not*** useful

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MDS TFT 2018 review

- **For the treatment of motor fluctuations**
  - Dopamine agonist
    - PPX-IR/ER, ROP-IR/ER, rotigotine: clinically useful
  - Levodopa preparation
    - Standard formulation, extended form, duodopa: clinically useful
    - CR form, rapid onset form: insufficient evidence
  - COMT inhibitor
    - Entacapone, opicapone: clinically useful
  - MAO B inhibitor
    - Rasagiline: clinically useful
    - Selegiline: insufficient evidence
  - MAO-B inhibitor + channel blocker
    - Zonisamide, salfinamide: clinically useful

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MDS TFT 2018 review

- **For the treatment of dyskinesia**
  - Amantadine, Clozapine: clinically useful
  - Duodopa: possibly useful
  - Pramipexole, Zonisamide, levetiracetam: insufficient

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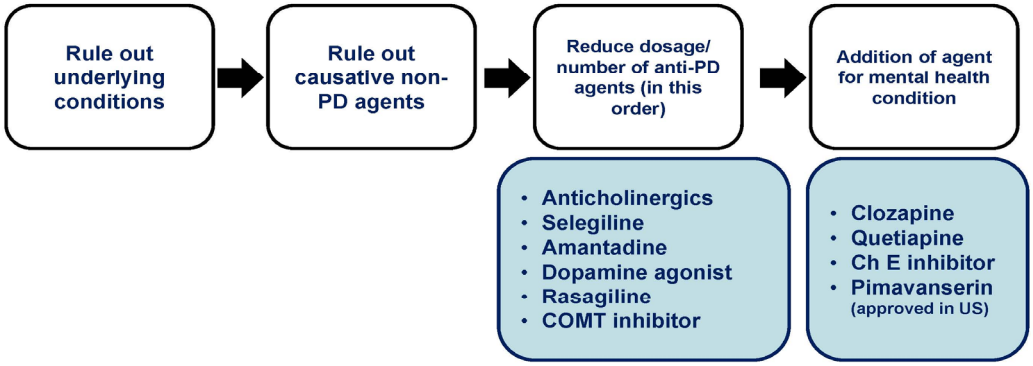
Management of
Parkinson's Disease & comorbid Mental Health Disorder

Stepwise approach for treating PDF patients with a comorbid mental health disturbance (2001, 2015 Guidelines)



Goldman JG, Holden S. Treatment of psychosis and dementia in Parkinson's disease. *Curr Treat Options Neurol.* 2014;16:281.
Bountouni I, Zis P, Chaudhuro KR, Schrag A. Psychosis in Parkinson's disease. In Neuropsychiatric symptoms of Movemement disorders. Springer. 2014
Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. *Neurology.* 2001;56(11 suppl 5):S1-S88.

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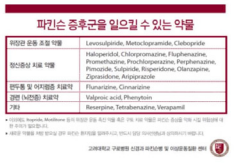
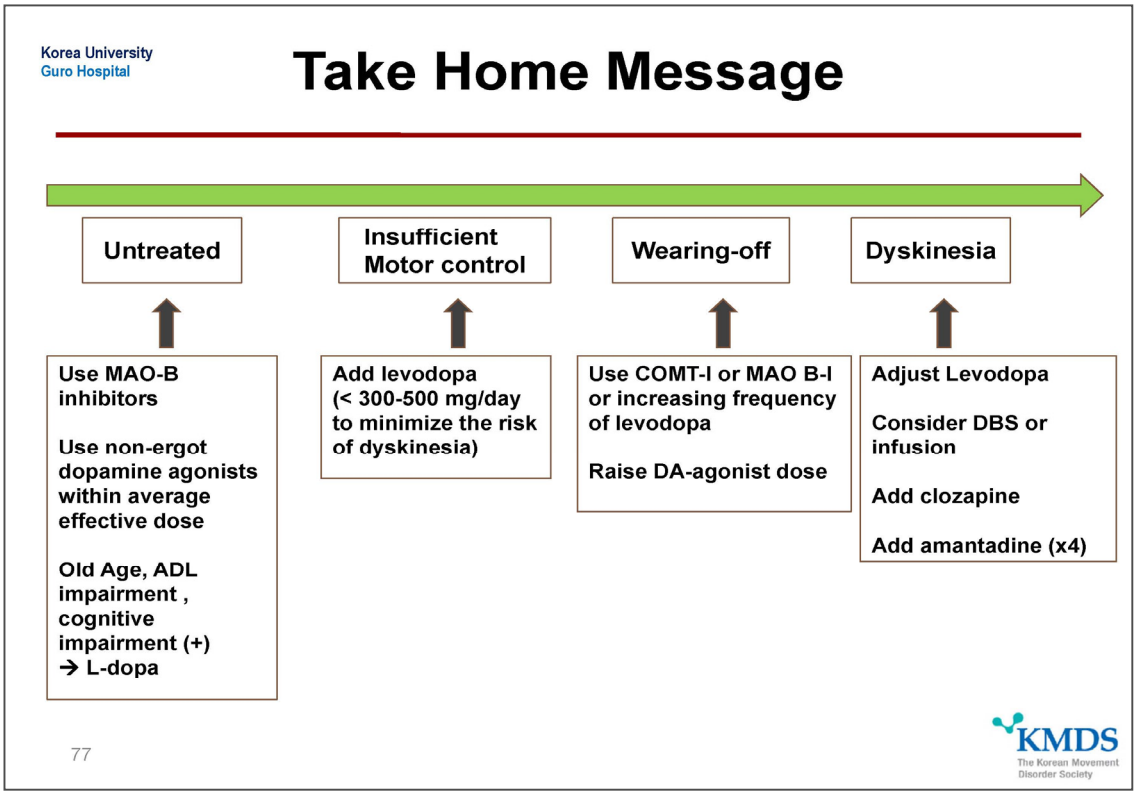


파킨슨 증후군을 일으킬 수 있는 약물

위장관 운동 조절 약물	Levosulpiride, Metoclopramide, Clebopride
정신증상 치료 약물	Haloperidol, Chlorpromazine, Fluphenazine, Promethazine, Prochlorperazine, Perphenazine, Pimozide, Sulpiride, Risperidone, Olanzapine, Ziprasidone, Aripiprazole
편두통 및 어지럼증 치료약	Flunarizine, Cinnarizine
경련 (뇌전증) 치료약	Valproic acid, Phenytoin
기타	Reserpine, Tetrabenazine, Verapamil

▸ 이외에도 Itopride, Motilitone 등의 위장관 운동 촉진 약물 혹은 구토 치료 약물은 파킨슨 증상을 악화 시킬 위험성에 대한 주의가 필요합니다.
▸ 새로운 약물을 처방 받으실 경우 파킨슨 환자임을 알려주시고, 반드시 담당 의사선생님과 상의하시기 바랍니다.

고려대학교 구로병원 신경과 파킨슨병 및 이상운동질환 센터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Take Home Message
Untreated
Insufficient Motor control
Wearing-off
Dyskinesia
Use MAO-B inhibitors
Use non-ergot dopamine agonists within average effective dose
Old Age, ADL impairment , cognitive impairment (+)
→ L-dopa
Add levodopa (< 300-500 mg/day to minimize the risk of dyskinesia)
Use COMT-I or MAO B-I or increasing frequency of levodopa
Raise DA-agonist dose
Adjust Levodopa
Consider DBS or infusion
Add clozapine
Add amantadine (x4)
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