TC 24: MOVEMENT DISORDERS:
Emerging diagnostic and treatment aspects in Parkinson's disease and related disorders

Recent challenges of medical treatment of PD

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Major issues

- Control of motor symptoms – monotherapy
- Control of motor symptoms as an adjunct to levodopa
- Treatment of motor complications:
  - For the treatment of motor fluctuations
  - For the treatment of dyskinesia
- Treatment of non-motor symptoms
- Prevention/delay of clinical progression

Major players in PD therapy

- Levodopa
- Dopamine agonists
- COMT inhibitors
- MAO-B inhibitors
- Anticholinergics
- Amantadine
- *Others (e.g. clozapine, zonisamide)*

TABLE 2. Conclusions on dopamine agonists (presented in alphabetical order)

Dopamine agonists		Prevention/delay of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention/delay of motor complications	Treatment of motor complications
Nonergot dopamine agonists						
Piribedil	Efficacy	Insufficient evidence	*Efficacious*	Efficacious	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	*Clinically useful*	Clinically useful	Investigational (F, D)	Investigational (F, D)
Pramipexole	Efficacy	Insufficient evidence	Efficacious	Efficacious	*Efficacious (F, D)*	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	Clinically useful	*Clinically useful (F, D)*	Clinically Useful (F)
Pramipexole extended release	Efficacy	*Insufficient evidence*	*Efficacious*	*Insufficient evidence*	*Insufficient evidence (F, D)*	*Insufficient evidence (F, D)*
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	*Investigational*	*Clinically useful*	*Investigational*	*Investigational (F, D)*	*Investigational (F, D)*
Ropinirole	Efficacy	Insufficient evidence	*Efficacious*	*Efficacious*	Insufficient evidence (F) Efficacious (D)	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	*Clinically useful*	*Clinically useful*	Investigational (F) Clinically useful (D)	Clinically useful (F) Investigational (D)
Ropinirole prolonged release	Efficacy	*Insufficient evidence*	*Likely efficacious*	*Efficacious*	*Insufficient evidence (F)* *Efficacious (D)*	*Efficacious (F)* *Insufficient evidence (D)*
	Safety	*Acceptable risk without specialized monitoring*				
	Practice implications	*Investigational*	*Possibly useful*	*Clinically useful*	*Investigational (F)* *Clinically useful (D)*	*Clinically useful (F)* *Investigational (D)*
Rotigotine	Efficacy	*Insufficient evidence*	*Efficacious*	*Efficacious*	*Insufficient evidence (F, D)*	*Efficacious (F)* *Insufficient evidence (D)*
	Safety	*Acceptable risk without specialized monitoring*				
	Practice implications	*Investigational*	*Clinically useful*	*Clinically useful*	*Investigational (F, D)*	*Clinically useful (F)* *Investigational (D)*
Parenteral nonergot dopamine agonist						
Apomorphine	Efficacy	Insufficient evidence	Insufficient evidence	Efficacious	Insufficient evidence (F, D)	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk without specialized monitoring when used as parenteral therapy.				
	Practice implications	Investigational	Investigational	Clinically useful	Investigational (F, D)	Clinically useful (F) Investigational (D)
Ergot dopamine agonists						
Bromocriptine	Efficacy	Insufficient evidence	Likely efficacious	Efficacious	Insufficient evidence (F) Likely efficacious (D)	Likely efficacious (F) Insufficient evidence (D)
	Safety	*Acceptable risk with specialized monitoring*				
	Practice implications	Investigational	Possibly useful	Clinically useful	Investigational (F) Possibly useful (D)	Possibly useful (F) Investigational (D)
Cabergoline	Efficacy	Insufficient evidence	*Efficacious*	Efficacious	*Efficacious (F, D)*	Likely efficacious (F) Insufficient evidence (D)
	Safety	*Acceptable risk with specialized monitoring*				
	Practice implications	Investigational	*Clinically useful*	Clinically useful	*Clinically useful (F, D)*	Possibly useful (F) Investigational (D)
Dihydroergocryptine	Efficacy	Insufficient evidence	Efficacious	Insufficient evidence	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	*Acceptable risk with specialized monitoring*				
	Practice implications	Investigational	Clinically useful	Investigational	Investigational (F, D)	Investigational (F, D)
Lisuride	Efficacy	Insufficient evidence	Likely efficacious	Likely efficacious	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	*Acceptable risk with specialized monitoring*				
	Practice implications	Investigational	Possibly useful	Possibly useful	Investigational (F, D)	Investigational (F, D)
Pergolide	Efficacy	*Unlikely efficacious*	Efficacious	Efficacious	*Insufficient evidence (F)* *Likely efficacious (D)*	Efficacious (F) Insufficient evidence (D)
	Safety	*Acceptable risk with specialized monitoring*				
	Practice implications	*Unlikely useful*	Clinically useful	Clinically useful	*Investigational (F)* *Possibly useful (D)*	Clinically useful (F) Investigational (D)

Treatments with new efficacy conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds.
F, motor fluctuations; D, dyskinesia.

TABLE 3. Conclusions on levodopa

Levodopa		Prevention/delay of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention/delay of motor complications	Treatment of motor complications
Standard formulation	Efficacy	Insufficient evidence	Efficacious	N/A	Nonefficacious (F, D)	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	N/A	Not useful (F, D)	Clinically useful (F) investigational(D)
Controlled-release formulation	Efficacy	Insufficient evidence	Efficacious	N/A	Nonefficacious (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	N/A	Not useful (F, D)	Investigational (F, D)
Rapid-onset oral formulation	Efficacy	*Insufficient evidence*	*Insufficient evidence*	*Insufficient evidence*	*Insufficient evidence (F, D)*	*Insufficient evidence (F)* *Insufficient evidence (D)*
	Safety	*Acceptable risk without specialized monitoring*				
	Practice implications	*Investigational*	*Investigational*	*Investigational*	*Investigational (F, D)*	*Investigational (F)* *Investigational (D)*
Infusion formulations	Efficacy	*Insufficient evidence*	*Insufficient evidence*	*Insufficient evidence*	*Insufficient evidence (F, D)*	*Likely efficacious (F, D)*
	Safety	*Acceptable risk without specialized monitoring*				
	Practice implications	*Investigational*	*Investigational*	*Investigational*	*Investigational (F, D)*	*Investigational (F, D)*

Treatments with new conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds.
F, motor fluctuations; D, dyskinesia; N/A, not applicable.

TABLE 4. Conclusions on COMT inhibitors

COMT inhibitors		Prevention/delay of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention/delay of motor complications	Treatment of motor complications
Entacapone	Efficacy	Insufficient evidence	N/A	Efficacious[a] *Nonefficacious*[b]	*Nonefficacious (F, D)*	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	N/A	Clinically useful[a] *Not useful*[b]	*Not useful (F, D)*	Clinically useful (F) Investigational (D)
Tolcapone	Efficacy	Insufficient evidence	N/A	Efficacious	Insufficient evidence (F, D)	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk with specialized monitoring				
	Practice implications	Investigational	N/A	Possibly useful	Investigational (F, D)	Possibly useful (F) Investigational (D)

[a]In PD subjects *with* motor complications;
[b]in PD subjects with respect to motor function in nonfluctuating patients; both without prior use of levodopa or already on levodopa.
Treatments with new conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds.
F, motor fluctuations; D, dyskinesia; N/A, not applicable.

TABLE 5. Conclusions on MAO-B inhibitors

MAO-B inhibitors		Prevention/delay of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention/delay of motor complications	Treatment of motor complications
Selegiline	Efficacy	Insufficient evidence	Efficacious	Insufficient evidence	Insufficient evidence (F) Nonefficacious (D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	investigational	Investigational (F) Not useful (D)	Investigational (F, D)
Oral disintegrating selegiline	Efficacy	*Insufficient evidence*	*Insufficient evidence*	*Insufficient evidence*	*Insufficient evidence (F, D)*	*Insufficient evidence (F, D)*
	Safety	*Acceptable risk without specialized monitoring*				
	Practice implications	*Investigational*	*Investigational*	*Investigational*	*Investigational (F, D)*	*Investigational (F, D)*
Rasagiline	Efficacy	Insufficient evidence	Efficacious	*Efficacious*	Insufficient evidence (F, D)	*Efficacious (F)* *Insufficient evidence (D)*
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	*Clinically useful*	Investigational (F, D)	*Clinically useful (F)* *Investigational (D)*

Treatments with new conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds.
F, motor fluctuations; D, dyskinesia.

TABLE 6. Conclusions on anticholinergics, amantadine, clozapine, and zonisamide

Drug		Prevention of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention of motor complications	Treatment of motor complications
Anticholinergics	Efficacy	Insufficient evidence	Likely efficacious	Likely efficacious	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	Clinically useful	Investigational (F, D)	Investigational (F, D)
Amantadine	Efficacy	Insufficient evidence	Likely efficacious	Likely efficacious	Insufficient evidence (F, D)	Insufficient evidence (F) Efficacious (D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Possibly useful	Possibly useful	Investigational (F, D)	Investigational (F) Clinically useful (D)
Clozapine	*Efficacy*	*Insufficient evidence*	*Insufficient evidence*	*Insufficient evidence*	*Insufficient evidence (F, D)*	*Insufficient evidence (F)* *Efficacious (D)*
	Safety	*Acceptable risk with specialized monitoring*				
	Practice implications	*Investigational*	*Investigational*	*Investigational*	*Investigational (F, D)*	*Investigational (F)* *Possibly useful (D)*
Zonisamide	*Efficacy*	*Insufficient evidence*	*Insufficient evidence*	*Efficacious*	*Insufficient evidence (F, D)*	*Insufficient evidence (F, D)*
	Safety	*Acceptable risk without specialized monitoring*				
	Practice implications	*Investigational*	*Investigational*	*Clinically useful*	*Investigational (F, D)*	*Investigational (F, D)*

Treatments with new conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds.
F, motor fluctuations; D, dyskinesia.

TABLE 8. Conclusions on nonpharmacological treatments

Therapy		Prevention of clinical progression	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention of motor complications	Treatment of motor complications
Physical therapy	Efficacy	Insufficient evidence	Insufficient evidence	*Likely efficacious*	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Investigational	*Possibly useful*	Investigational (F, D)	Investigational (F, D)
Speech therapy	Efficacy	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient (F, D) data	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Investigational	*Possibly useful*	Investigational (F, D)	Investigational (F, D)
Occupational therapy	Efficacy	Insufficient evidence	Insufficient evidence	insufficient evidence	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Investigational	Possibly useful	Investigational (F, D)	Investigational (F, D)
Acupuncture	Efficacy	*Insufficient evidence*	*Insufficient evidence*	*Insufficient evidence*	*Insufficient evidence (F, D)*	*Insufficient evidence (F, D)*
	Safety	*Acceptable risk without specialized monitoring*				
	Practice implications	*Investigational*	*Investigational*	*Investigational*	*Investigational (F, D)*	*Investigational (F, D)*

Treatments with new conclusions have gray backgrounds and italicized text, and those with no changes have white backgrounds.
F, motor fluctuations; D, dyskinesia.

Control of motor symptoms – monotherapy/1

- Efficacious
  - Piribedil, pramipexole, pramipexole ER, ropinirole, rotigotine, cabergoline, dihydroergocryptine, pergolide
  - Standard and controlled released (CR) formulations of levodopa
  - Selegiline, rasagilin

Control of motor symptoms – monotherapy/2

- Likely efficacious
  - Ropinirole PR, bromocriptine, lisuride
  - Anticholinergics
  - Amantadine
- Insufficient evidence
  - Rapid onset oral formulations, infusion formulation of levodopa
  - Orally disintegrating selegiline
  - All other

Control of motor symptoms as an adjunct to levodopa

- Efficacious
  - the dopamine agonists piribedil, pramipexole, pramipexole PR, ropinirole, rotigotine, apomorphine, bromocriptine, cabergoline, pergolide
  - Tolcapone, rasagiline, zonisamide
  - Entacapone (only in PD patients with motor fluctuations
- Likely efficacious
  - Lisuride, anticholinergics, amantadine

Treatment of motor complications/1 motor fluctuations

- Efficacious
  - pramipexole, ropinirole, ropinirole ER, rotigotine, apomorphine, pergolide, standard oral levodopa, entacapone, tolcapone, rasagiline
- Likely efficacious
  - Bromocriptine, cabergoline, infusion formulations of levodopa
- Insufficient evidence
  - For all other interventions
    (including piribedil, pramipexole ER, dihydroergocryptine, lisuride, rapid onset oral levodopa, CR levodopa, selegiline, oral disintegrating selegiline, zonisamide)

Treatment of motor complications/2 dyskinesias

- Efficacious
  - Clozapine
  - Amantadine
  - (DBS)
- Likely efficacious
  - Infusion formulation of levodopa
- Insufficient evidence
  - For other therapies

Non-motor symptoms in PD

- Depression, mood disorders, anxiety disorders, apathy, and fatigue
- Cognitive dysfunction and dementia
- Psychosis
- Medication-related impulse controls disorders and other compulsive behaviors
- Autonomic dysfunction
  - Orthostatic hypotension
  - Sexual dysfunction
  - Gastrointestinal dysfunction
  - Sialorrhea
  - Sweating
- Disorders of sleep and wakefulness
  - RBD
  - Sleep fragmentation and insomnia
- Daytime Sleepiness and sudden onset of sleep

TABLE 3. Conclusions on drugs to treat depression including depressive symptoms[a] in PD

	Efficacy	Safety	Practice implications
Dopamine agonists			
Pramipexole	*Efficacious*	*Acceptable risk without specialized monitoring*	*Clinically useful*
Pergolide	*Insufficient evidence*	*Acceptable risk with specialized monitoring*	*Not useful*
TCA			
Nortriptyline	*Likely efficacious*	*Acceptable risk without specialized monitoring*	*Possibly useful*
Desipramine	*Likely efficacious*	*Acceptable risk without specialized monitoring*	*Possibly useful*
Amitriptyline	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*[b]
SSRIs			
Citalopram	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*[b]
Sertraline	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*[b]
Paroxetine	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*[b]
Fluoxetine	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*[b]
MAO-Inhibitors			
Moclobemide	Insufficient evidence	Insufficient evidence[c]	Investigational[d]
Selegeline	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Newer antidepressants			
Atomoxetine	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
Nefazodone	*Insufficient evidence*	*Unacceptable risk*	*Not useful*
Alternative therapies			
Ω-3 fatty acids	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
Nonpharmacological interventions			
rTMS	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
ECT	Insufficient evidence	Insufficient evidence	Investigational

TABLE 4. Conclusions on drugs to treat fatigue in PD

	Efficacy	Safety	Practice implications
Methylphenidate	*Insufficient evidence*	*Insufficient evidence*	*Investigational*
Modafinil	*Insufficient evidence*	*Insufficient evidence*	*Investigational*

TABLE 5. Conclusions on drugs to treat pathological gambling in PD

	Efficacy	Safety	Practice implications
Amantadine	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*

TABLE 6. Conclusions on drugs to treat dementia in PD

	Efficacy	Safety	Practice implications
Acetylcholinesterase inhibitors			
Donepezil	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
Rivastigmine	*Efficacious*	*Acceptable risk without specialized monitoring*	*Clinically useful*
Galantamine	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
NMDA Receptor Antagonists			
Memantine	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*

TABLE 7. Conclusions on drugs to treat psychosis in PD

	Efficacy	Safety	Practice implications
Clozapine	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
Olanzapine	*Unlikely efficacious*	*Unacceptable risk*	*Not useful*
Quetiapine	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*

TABLE 8. Conclusions on drugs to treat autonomic dysfunction in PD

	Efficacy	Safety	Practice implications
Orthostatic hypotension			
Fludrocortisone	Insufficient evidence	Insufficient evidence	Investigational
Domperidone	Insufficient evidence	Insufficient evidence	Investigational
Midodrin	Insufficient evidence	Insufficient evidence	Investigational
Dihydroergotamine	Insufficient evidence	Insufficient evidence	Investigational
Etilefrine hydrochloride	Insufficient evidence	Insufficient evidence	Investigational
Indomethacine	Insufficient evidence	Insufficient evidence	Investigational
Yohimbine	Insufficient evidence	Insufficient evidence	Investigational
L-threo-3.4-dihydroxyphenylserine	Insufficient evidence	Insufficient evidence	Investigational
Sexual dysfunction			
Sildenafil	*Insufficient evidence*	*Insufficient evidence*	*Investigational*
Gastrointestinal motility problems (Constipation)			
Macrogol	*Likely efficacious*	*Acceptable risk without specialized monitoring*	*Possibly useful*
Gastrointestinal motility problems (Anorexia, nausea and vomiting associated with levodopa and/or dopamine agonist treatment)			
Domperiodone	Likely efficacious	Acceptable risk without specialized monitoring	Possibly useful
Metoclopramide	Insufficient evidence	Unacceptable risk	Not useful
Sialorrhea			
Ipratropium bromide spray	*Insufficient evidence*	*Insufficient evidence*	*Investigational*
Glycopyrrolate	*Efficacious*[a]	*Insufficient evidence*	*Possibly useful*
Botulinum toxin B	*Efficacious*	*Acceptable risk with specialized monitoring*	*Clinically useful*
Botulinum toxin A	*Efficacious*	*Acceptable risk with specialized monitoring*	*Clinically useful*
Urinary frequency, urgency, and/or urge incontinence			
Oxybutynin	Insufficient evidence	Insufficient evidence	Investigational
Tolteradine	Insufficient evidence	Insufficient evidence	Investigational
Flavoxate	Insufficient evidence	Insufficient evidence	Investigational
Propiverine	Insufficient evidence	Insufficient evidence	Investigational
Prazosin	Insufficient evidence	Insufficient evidence	Investigational
Desmopressin	Insufficient evidence	Insufficient evidence	Investigational

TABLE 9. Conclusions on drugs to treat disorders of sleep and wakefulness in PD

	Efficacy	Safety	Practice implications
Insomnia			
Controlled-release formulation of levodopa/carbidopa	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
Pergolide	*Insufficient evidence*	*Acceptable risk with specialized monitoring*	*Not useful*
Eszopiclone	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
Melatonin 3–5 mg	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
Melatonin 50 mg	*Insufficient evidence*	*Insufficient evidence*	*Investigational*
Excessive daytime somnolence and the sudden onset of sleep			
Modafinil	*Insufficient evidence*	*Insufficient evidence*	*Investigational*

Prevention/delay of clinical progression

- Unlikely efficacious:
  - Pergolide
- Insufficient evidence:
  - Any other treatment

TABLE 1. Failed clinical trials of disease-modifying therapies for PD from 2013 to 2015

Study	Drug	Mechanism of Action	Trial Design	Subjects	Follow-up Period	Primary Outcome Measure(s)	Results
Olanow et al., 2015[6]	AAV2-Neuturin (injection into bilateral SNpc and putamen)	Neurotrophic factor	Multi-center, randomized, double-blind, sham surgery-controlled, phase 2 trial	Advanced PD subjects (n = 51)	15-24 months	Change in UPDRS part 3 in practically defined "off"-state	No statistically significant difference between treated and control groups
PSG et al., 2014 (QE3)[8]	Coenzyme Q10 (1200 mg/d or 2400 mg/d) + vitamin E (1200 IU/d)	Bioenergetic; Antioxidant	Multi-center, randomized, double-blind, placebo-controlled, phase 3 trial	Early PD subjects not requiring dopaminergic therapy (n = 600)	16 months (or until requiring dopaminergic therapy if sooner)	Change in total UPDRS score	Prematurely terminated due to futility
NET-PD et al., 2015 (LS1)[9]	Creatine (10 g/d)	Bioenergetic	Multi-center, randomized, double-blind, placebo-controlled, phase 3 trial	Early PD subjects receiving dopaminergic therapy (n = 1741)	4 years (median)	Difference in decline of clinical status defined by 5 outcome measures	Prematurely terminated due to futility
Schapira et al., 2013 (PROUD)[13]	Pramipexole (1.5 mg/day)	D2/D3 dopamine receptor agonist	Multi-center, randomized, double-blind, placebo-controlled, delayed-start trial	Early PD subjects not requiring dopaminergic therapy (n = 535)	15 months	Change in total UPDRS score	No statistically significant difference between early-start and delayed-start groups
NET-PD, 2015 (FS-ZONE)[15]	Pioglitazone (15 mg/d or 45 mg/d)	PPAR-γ agonist	Multi-center, randomized, double-blind, placebo-controlled, futility trial	Early PD subjects on rasagiline or selegiline (n = 210)	44 weeks	Change in total UPDRS score	Futility

Abbreviations: AAV2, adeno-associated virus serotype 2; LS1, Long-term Study 1; PD, Parkinson's disease; PPAR, peroxisome proliferator-activated receptor; PROUD, Pramipexole On Underlying Disease; QE3, Coenzyme Q10 in Early Parkinson Disease; SNpc, substantia nigra pars compacta; UPDRS, Unified Parkinson's Disease Rating Scale.

Ongoing clinical trials of disease-modifying therapies for PD in 2015

Study	Drug	Mechanism of Action	Trial Design	Estimated Enrollment	Follow-up Period	Primary Outcome Measure(s)	Status
NCT02216188	PD01A + adjuvant (subcutaneous injection; 15μg or 75μg booster x 1)	Active immunization against α-synuclein	Single-center (Austria), randomized, single-blind, follow-up, phase 1 trial	PD subjects who previously received PD01A and untreated controls (n = 32)	6 months	Safety and tolerability	Enrolling by invitation
NCT01885494	PD01A + adjuvant (subcutaneous injection; 15 μg or 75 μg × 4)	Active immunization against α-synuclein	Single-center (Austria), observational, follow-up, phase 1 extension trial	PD subjects who previously received PD01A and untreated controls (n = 32)	52 weeks	Safety and tolerability	Active but not recruiting
NCT02267434	PD03A + adjuvant (subcutaneous injection; 15 μg or 75 μg × 4)	Active immunization against α-synuclein	Dual-center (Austria), randomized, single-blind, placebo-controlled, phase 1 trial	Early PD subjects (n = 36)	52 weeks	Safety and tolerability	Recruiting
NCT02157714	PRX002 (intravenous infusion)	Passive immunization against α-synuclein	Multi-center (United States), randomized, double-blind, placebo-controlled, phase 1 trial	PD subjects (n = 60)	6 months	Safety and tolerability; several pharmacokinetic parameters	Recruiting
NCT01738178	Caffeine (400 mg/d)	Nonspecific adenosine receptor antagonist	Multi-center (Canada, Brazil), randomized, double-blind, placebo-controlled, phase 3 trial with delayed-start component	PD subjects (n = 250)	5 years	MDS-UPDRS score	Recruiting
NCT01621581	AAV2-GDNF (convection enhanced delivery to bilateral putamen)	Neurotrophic factor	Single-center (United States), open-label, phase 1 trial	Advanced PD subjects (n = 24)	5 years	Safety and tolerability; several clinical measures	Recruiting

Ongoing clinical trials of disease-modifying therapies for PD in 2015 (contd.)

NCT02168842 (STEADY-PD III)	Isradipine (immediate release; 10 mg/d)	Dihydropyridine calcium channel blocker	Multi-center trial (United States, Canada), randomized, double-blind, placebo-controlled, phase 3 trial	Early PD subjects not requiring dopaminergic therapy (n = 336)	36 months	Change in total UPDRS score	Recruiting
NCT01560754 (NIC-PD)	Nicotine (transdermal patch; 7-28 mg/d)	Nicotinic acetylcholine receptor agonist	Multi-center (Germany, United States), randomized, double-blind, placebo-controlled, phase 2 trial with washout period	Early PD subjects not requiring dopaminergic therapy (n = 160)	12 months followed by 2-month washout period	Change in total UPDRS score	Recruiting
NCT02424708	GSH (intranasal; 300 mg/d or 600 mg/d)	Antioxidant	Dual-center (United States), randomized, double-blind, placebo-controlled, phase 2 trial	PD subjects (n = 45)	12 weeks	Change in total UPDRS score	Recruiting
NCT01470027	N-acetylcysteine (1800 mg/d or 3600 mg/d)	GSH precursor	Single-center (United States), randomized, double-blind, placebo-controlled, phase 1/2 trial	PD subjects on no medications for PD (n = 60)	4 weeks	Change in cerebral GSH levels measured by proton magnetic resonance spectroscopy	Recruiting
NCT01882010	Sagramostim (subcutaneous injection; 6 μg/kg/d)	GM-CSF	Dual-center (United States), randomized, double-blind, placebo-controlled phase 1 trial	PD subjects and non-PD controls (n = 32)	52 weeks	Safety and tolerability	Recruiting
NCT01453803	Adipose-derived stromal stem cells (intraarterial and intravenous infusion)	Multiple	Single-center (Mexico), open-label, phase 1/2 trial	PD subjects with motor complications (n = 10)	6 months	Safety and tolerability; UPDRS scores	Recruiting

Abbreviations: AAV2, adeno-associated virus serotype 2; GDNF, glial cell-line derived neurotrophic factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GSH, glutathione; MDS-UPDRS, Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale.

Levodopa-based approaches in development

	DRUG	MECHANISM	TRIAL STATUS
NOVEL LD FORMULATION	IPX 066	LD-ER	Phase 3, completed
	XP21279	ER LD-prodrug	Phase 2, ongoing
	AP CD/LD	prolonged gastric retention	Phase 2
	DM-1992	Combined IR/ER gastric retention	Phase 2
COMT-INHIBITORS	Opicapone	COMT-inhibition	Phase 3,ongoing
	0DM-101	novel LD/CD/ENT combination	Phase 2, ongoing
LD DELIVERY	LD/CD intestinal gel	cont. jejunal delivery	Phase 3, completed
	ND0612/0650	s.c. LD/CD delivery	Phase *1/2*, ongoing
	CVT-301	LD inhaler	Phase 3 planned

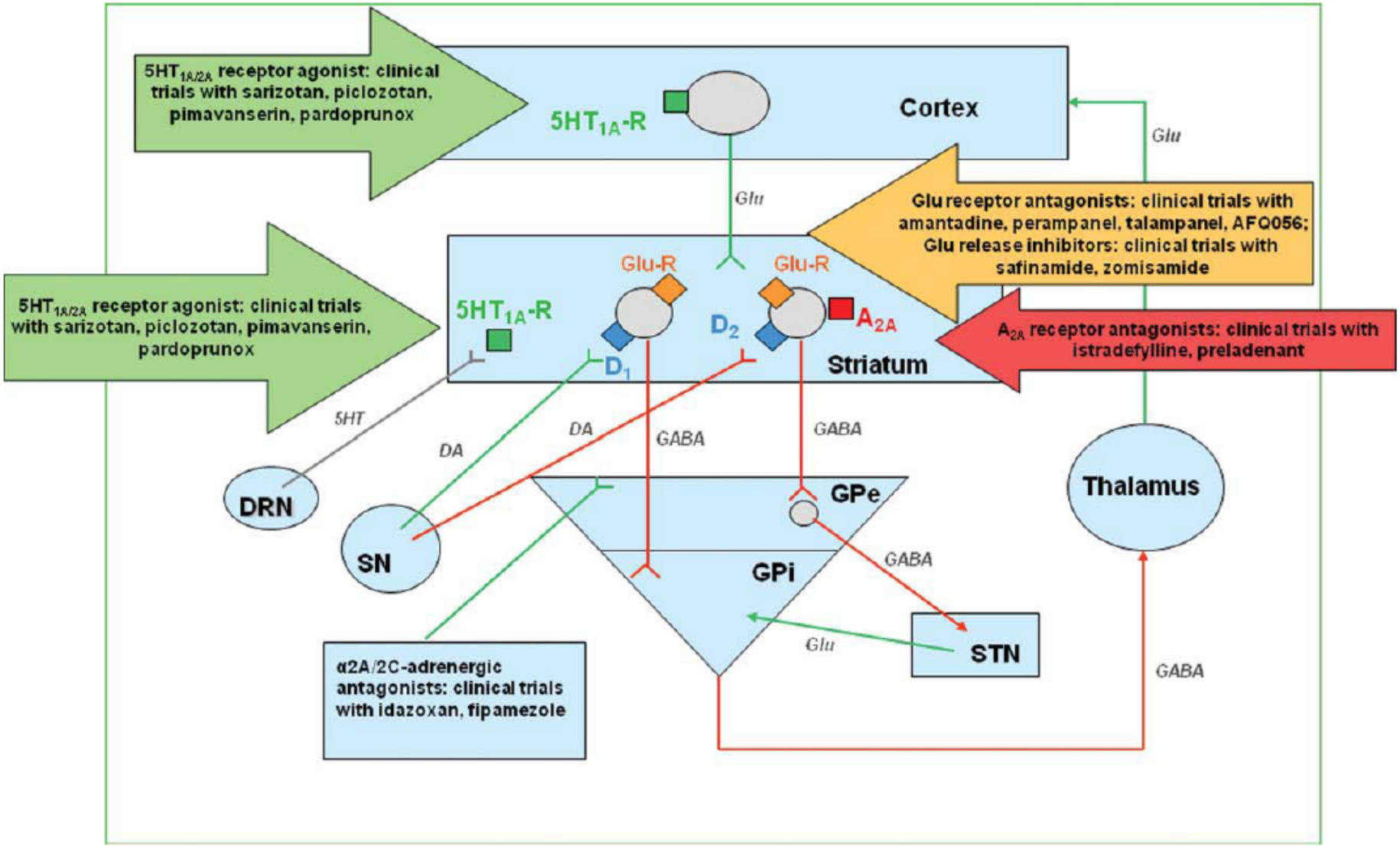
R = immediate relase CR = *controlled release* LD = levodopa *CD=carbidopa* ENT = entacapone

REVIEW

Novel Formulations and Modes of Delivery of Levodopa

Poewe & Antonini, *Mov. Disord. 2015*

Non-dopamine targets and candidate drugs



Rascol et al., *Mov Disord 2011*

New drugs or formulations for the treatment of motor complications 2013-2015

Drug and formulation	New studies in the period 2013-2015	Main results	Safety	Development/ marketing status
New formulations of levodopa				
Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel	1 R, DB, DD trial vs levodopa IR[12]	Reduced daily OFF-time, increased "good" ON-time	Related to the device or infusion	Commercialized in USA and Europe
IPX066	1 R, DB, DD vs levodopa IR[20] 1 R, DB, CO, DD trial vs entacapone[21]	Reduced daily OFF-time, increased "good" ON-time	Same as L-dopa IR	Commercialized in USA
XP21279	1 R, DB, DD, CO vs levodopa IR[25]	No effects on OFF-time, reduced percentage deviation from the mean L-dopa concentration	Same as L-dopa IR	In Phase II
Melevodopa	1 OL, CS, vs levodopa IR[26]	Shorter onset of motor benefit after an oral dose	Same as L-dopa IR	In Phase II
New COMT or MAO-B inhibitors				
Opicapone	2 R, DB vs placebo or entacapone[32,33]	Increased L-dopa exposure, reduced off-time	Dyskinesia, insomnia, dizziness, nausea	In Phase III
Safinamide	1 R, DB vs placebo[38]	Increased "good" ON-time	Dyskinesia, worsening of PD, cataract, back pain, depression, headache, and hypertension	Commercialized in Europe. NDA submitted to FDA
New formulation of apomorphine				
Inhaled apomorphine	3 R, DB, vs placebo[42-44]	Greater motor improvements after a single dose	Somnolence, yawning, flushing, dysgeusia, dizziness, orthostatic hypotension	In Phase III

New drugs or formulations for the treatment of motor complications 2013-2015 (contd.)

New formulation of amantadine				
Extended-release amantadine	1 R, DB vs placebo[56]	Reduced dyskinesia frequency/severity	Constipation, hallucinations, dizziness, dry mouth	In Phase III
New A2A antagonists				
Istradefylline	1 R, DB vs placebo[47]	Reduced OFF-time	Dyskinesia	Marketed in Japan and USA
Tozadenant	1 R, DB vs placebo[64]	Reduced daily OFF-time	Dyskinesia, nausea, dizziness	In Phase III
Caffeine	1 Exploratory cohort study[63]	Less frequent dyskinesia in consumers of 12 oz/d	—	Worldwide available in supermarket
New glutamatergic antagonists				
Mavoglurant	1 R, DB vs placebo[57] 1 R, DB vs placebo[58]	Reduced dyskinesia frequency/severity, NS reduction in OFF-time	Dizziness, hallucination, fatigue, nasopharyngitis, diarrhea, insomnia	In Phase III
New serotoninergic drugs				
Eltoprazine	1 R, DB vs placebo[62]	Reduction of dyskinesia frequency/severity	Nausea, dizziness	In Phase III
Other drugs				
Tetrabenazine	1 OL, UC[65]	Reduced dyskinesia frequency/severity	—	Available worldwide for hyperkinetic disorders
Simvastatin	1 n-of-1 trial[66]	No effects on dyskinesia	—	Available worldwide for hypercholesterolemia
Topiramate	1 R, DB, CO vs placebo[67]	No effects on dyskinesia	Dry mouth, cognitive, breathing problems	Available worldwide for epilepsy

References

Fox et al, Mov Disord 2011; 26/S3:S2

Seppi et al, Mov Disord 2011; 26/S3:S42

Poewe & Antonini, Mov Disord 2015; 30:114

Kalia et al, Mov Disord 2015; 30:1442

Rascol et al, Mov Disord 2015; 30:1451

Goldman & Weintraub, Mov Disord 2015; 30:1471