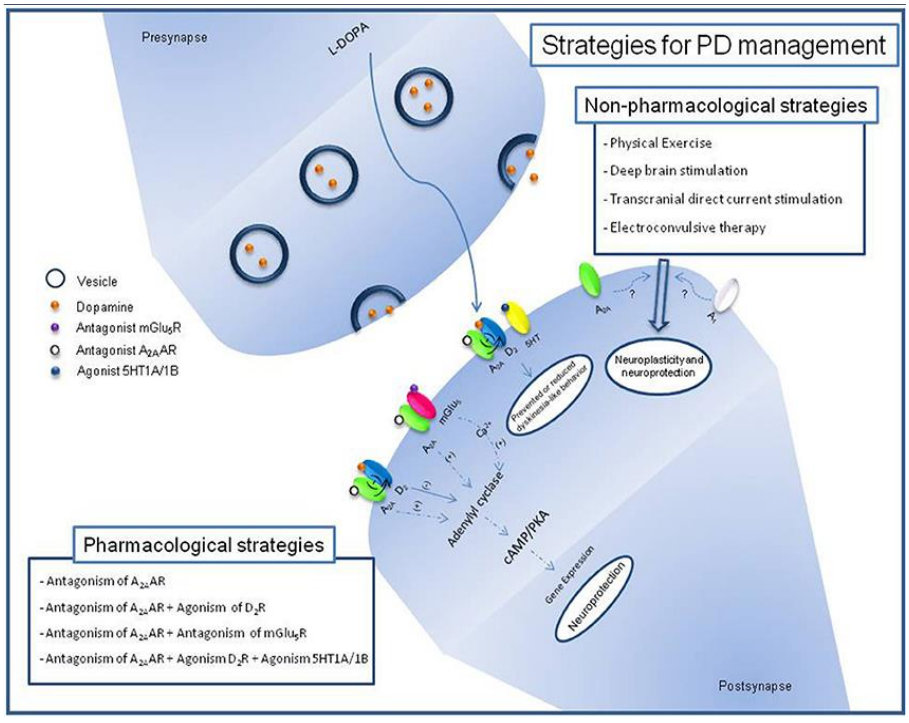
MANAGEMENT OF PARKINSON'S DISEASE

ODINACHI OGUH M.D

OBJECTIVES

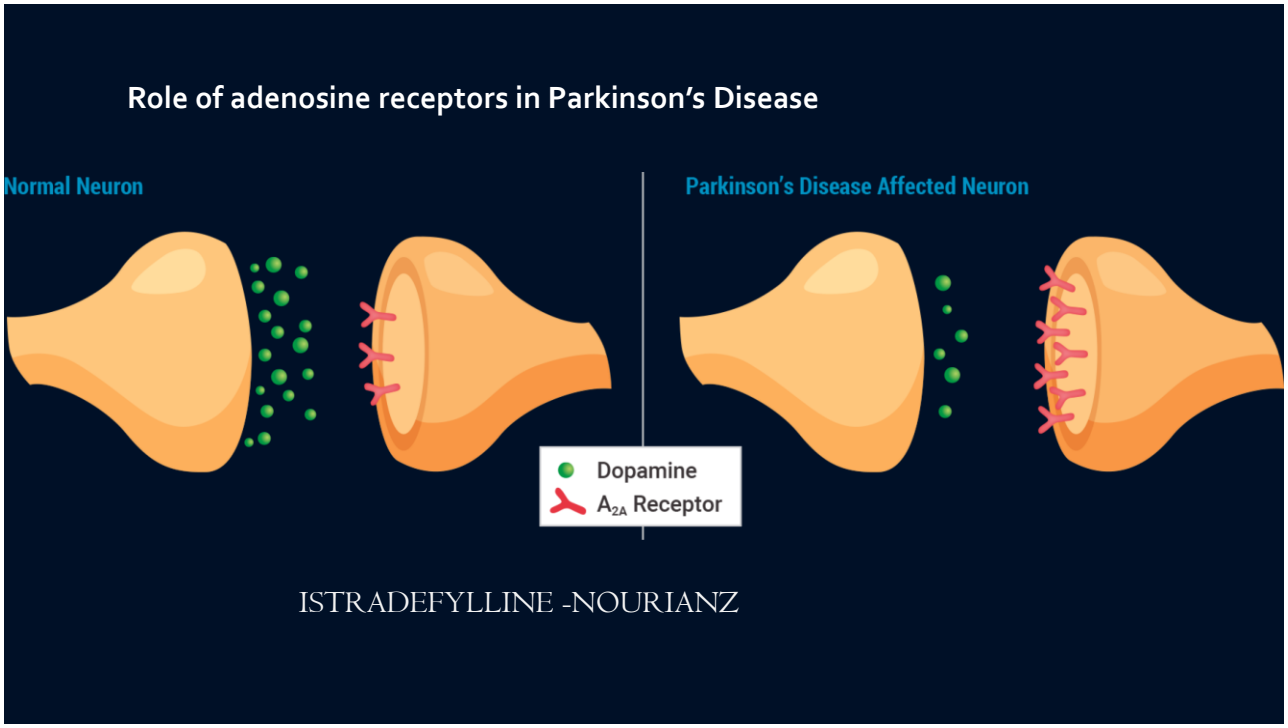
- Pharmacological therapies in the management of PD
- Considering Advanced therapies in PD
- Choosing what is best treatment.

WHAT'S NEW IN PHARMACOLOGICAL THERAPIES



Levodopa	Dopamine agonist	MAO-B inhibitors	Anticholinergics	COMT inhibitors	Amantadine	A2A
Sinemet IR (levodopa/ carbidopa)	Pramipexole (Mirapex®)	Rasagiline (Azilect®)	Trihexyphenidyl (Artane®)	Stalevo (carbidopa-levodopa and entacopone	(Symmetrel®, generics	ISTRADEFYLLINE - NOURIANZ
Sinemet CR	Ropinirole (Requip®)	Selegiline (Eldepryl® Zelapar®)	Benztropine (Cogentin®)	Entacopone	Gocovri	
Rytary (IR/CR)	Rotigotine (Neupro® patch)	Safinamide Xadago		opipacone	Osmolex	
Parcopa orally disintegrating tablet)	Apomorphine (Apokyn®)					
DUOPA						

what's new in pharmacological treatment



ISTRADEFYLLINE -NOURIANZ

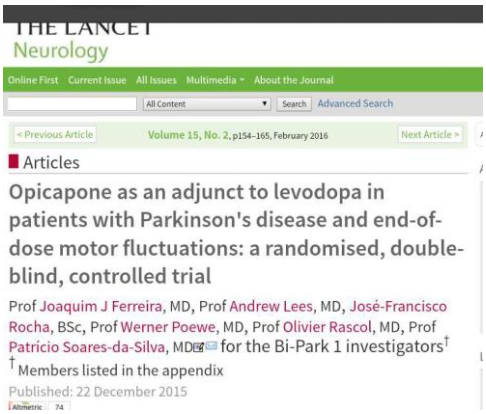
- The adenosine A2A receptor in humans
- Does not affect other receptors (e.g. dopamine, serotonin, norepinephrine)
- Almost exclusively in the striatum
- Also in the "nucleus accumbens" that appears to play a role in mood.
- Adenosine antagonists: enhance levodopa without worsening dyskinesias
- In a recent study effectively improves "off" time
- Istradefylline: approved in Japan, USA ; FDA approved.

- NET EFFECT of these medications: Block of A2AAR by antagonist induces reduction of positive effects over Adenylyl cyclase and negative effects over D2R signaling.

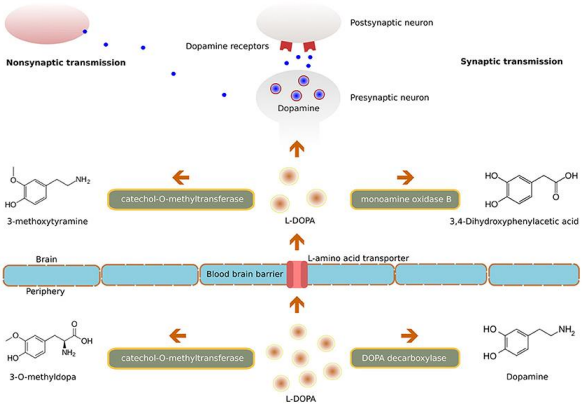
BI-PARK I STUDY

- 600 PD patients 30-83 year age, on levodopa with
- end of dose motor fluctuations were randomized to
- receive opicapone (5 mg, 25 mg or 50 mg OD),
- placebo or entacapone (200 mg with every levodopa
- dose).
- Mean “off” time was significantly reduced with
- opicapone 25 mg and 50 mg OD.
- Opicapone was non-inferior to entacapone

BI-PARK I STUDY



OPICAPONE – COMT INHIBITOR

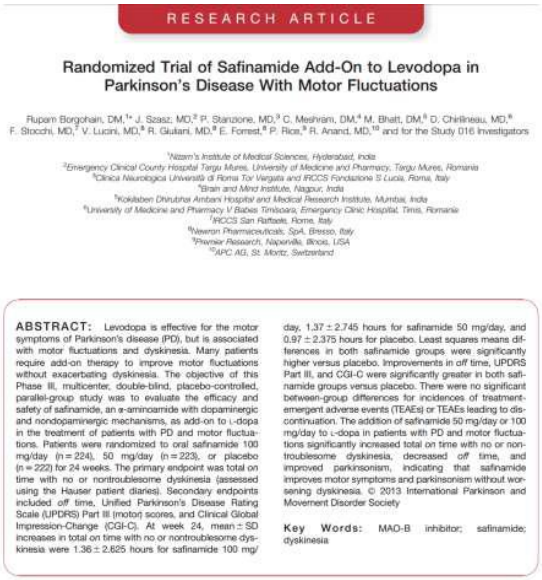


Opicapone: clinical considerations in Parkinson’s Disease
Improves EoD motor fluctuations (↓ OFF time and ↑ ON time); benefits maintained over 1 year in OLEs.
Better efficacy than placebo and noninferior to entacapone in pivotal phase 3 trials.
In the real-world setting, patients experience clinically meaningful improvements.
Generally well tolerated.

SUBLINGUAL APOMORPHINE CURRENTLY APPROVED .

- Many people do not like injections; moreover, sublingual route is easier to administer,
- Sublingual apomorphine (APL-130277) tested in 2/phase 3 studies, Dose: 10-30 mg during OFF phase,
- ON state achieved in 15-30 min of dose in about of patients,
- Mean duration of ON phase is 50 min and 60% remain ON for >90 min
- Common side effects are dizziness, somnolence and nausea.

KYNMOBI™
(apomorphine HCl) sublingual film
10 mg • 15 mg • 20 mg • 25 mg • 30 mg



RESEARCH ARTICLE

Randomized Trial of Safinamide Add-On to Levodopa in Parkinson's Disease With Motor Fluctuations

Rupam Borgohain, DM,[1]* J. Szasz, MD,[2] P. Stanzione, MD,[3] C. Meshram, DM,[4] M. Bhatt, DM,[5] D. Chirilineau, MD,[6] F. Stocchi, MD,[7] V. Lucini, MD,[8] R. Giuliani, MD,[8] E. Forrest,[8] P. Rice,[9] R. Anand, MD,[10] and for the Study 016 Investigators

[1]Nizam's Institute of Medical Sciences, Hyderabad, India
[2]Emergency Clinical County Hospital Targu Mures, University of Medicine and Pharmacy, Targu Mures, Romania
[3]Clinica Neurologica Universita di Roma Tor Vergata and IRCCS Fondazione S Lucia, Roma, Italy
[4]Brain and Mind Institute, Nagpur, India
[5]Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Mumbai, India
[6]University of Medicine and Pharmacy V Babes Timisoara, Emergency Clinic Hospital, Timis, Romania
[7]IRCCS San Raffaele, Rome, Italy
[8]Newron Pharmaceuticals, SpA, Bresso, Italy
[9]Premier Research, Naperville, Illinois, USA
[10]APC AG, St. Moritz, Switzerland

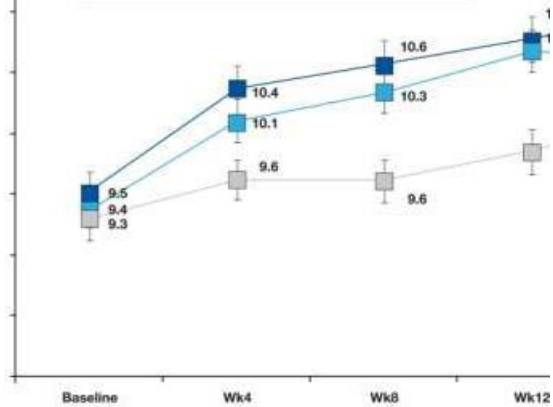
ABSTRACT: Levodopa is effective for the motor symptoms of Parkinson's disease (PD), but is associated with motor fluctuations and dyskinesia. Many patients require add-on therapy to improve motor fluctuations without exacerbating dyskinesia. The objective of this Phase III, multicenter, double-blind, placebo-controlled, parallel-group study was to evaluate the efficacy and safety of safinamide, an α-aminoamide with dopaminergic and nondopaminergic mechanisms, as add-on to L-dopa in the treatment of patients with PD and motor fluctuations. Patients were randomized to oral safinamide 100 mg/day (n = 224), 50 mg/day (n = 223), or placebo (n = 222) for 24 weeks. The primary endpoint was total on time with no or nontroublesome dyskinesia (assessed using the Hauser patient diaries). Secondary endpoints included off time, Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor) scores, and Clinical Global Impression-Change (CGI-C). At week 24, mean ± SD increases in total on time with no or nontroublesome dyskinesia were 1.36 ± 2.625 hours for safinamide 100 mg/day, 1.37 ± 2.745 hours for safinamide 50 mg/day, and 0.97 ± 2.375 hours for placebo. Least squares means differences in both safinamide groups were significantly higher versus placebo. Improvements in off time, UPDRS Part III, and CGI-C were significantly greater in both safinamide groups versus placebo. There were no significant between-group differences for incidences of treatment-emergent adverse events (TEAEs) or TEAEs leading to discontinuation. The addition of safinamide 50 mg/day or 100 mg/day to L-dopa in patients with PD and motor fluctuations significantly increased total on time with no or nontroublesome dyskinesia, decreased off time, and improved parkinsonism, indicating that safinamide improves motor symptoms and parkinsonism without worsening dyskinesia. © 2013 International Parkinson and Movement Disorder Society

Key Words: MAO-B inhibitor; safinamide; dyskinesia

SAFINAMIDE

- Patients aged 30-80 years, with mid-late-stage PD of
- 3 or more yrs duration, having motor fluctuations
- (>1.5 hours off time/day) on levodopa and other
- dopaminergic medications, were included
- Randomized into 3 groups: 50 mg/d, 100 mg/d or
- placebo, OD dose, treated for 24 weeks

	Safinamide 50 mg	Safinamide 100 mg
LS Mean	1.23	1.28
LS Difference vs. placebo	0.51	0.55
95% CI of LS Difference	(0.07, 0.94)	(0.12, 0.99)
p-value vs. placebo	0.0223	0.0130



N time = ON time without dyskinesia + ON time with minor dyskinesia

SAFINAMIDE

- On" time without troublesome dyskinesia
- significantly increased
- "Off" time significantly reduced,
- No significant treatment related adverse events were noted.
- 100 mg/d was better than 50 mg/d, but both doses of safinamide were better than placebo.

LOOKING TO THE FUTURE

- PUMP DEVICES continues Levodopa infusion
- One device delivers apomorphine through a subcutaneous pump and has been available in Europe for several years. (APO-GO)
- Two trials working on this;
  - NEURODERM TRIAL
  - ABBIVE TRIAL

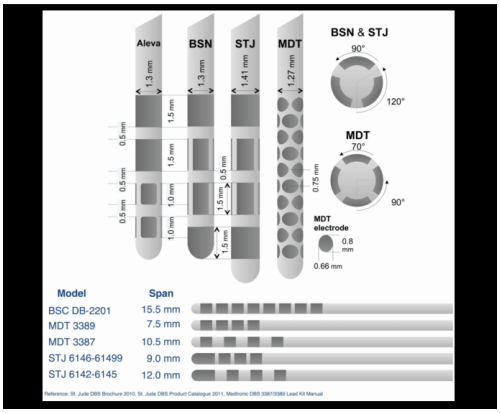
CURRENT DEEP STIMULATION DEVICES

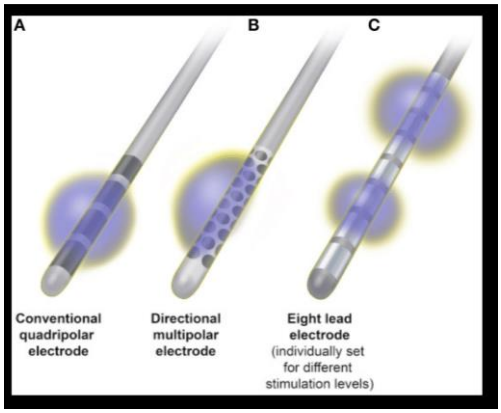
Medtronic

St. Jude's infinity device

Boston Scientific Vesice

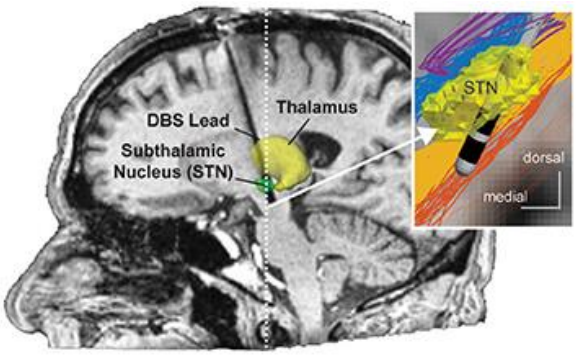
DBS LEADS

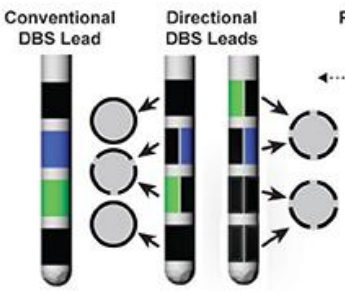


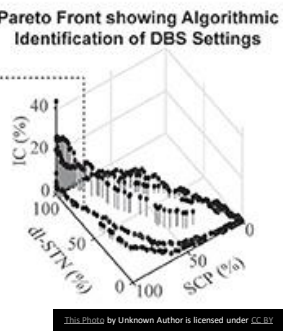


THE TWO LEADS IN THE MARKET WITH DIRECTIONAL LEAD TECHNOLOGY

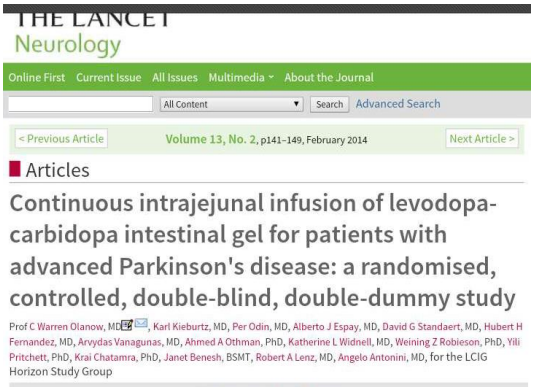
- St. Jude infinity device
- Boston Scientific vesice device
- Medtronic DBS lead is Directional Lead system







DUOPA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Articles

Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study

Prof C Warren Olanow, MD, Karl Kieburtz, MD, Per Odin, MD, Alberto J Espay, MD, David G Standaert, MD, Hubert H Fernandez, MD, Arvydas Vanagunas, MD, Ahmed A Othman, PhD, Katherine L Widnell, MD, Weining Z Robieson, PhD, Yili Pritchett, PhD, Krai Chatamra, PhD, Janet Benesh, BSMT, Robert A Lenz, MD, Angelo Antonini, MD, for the LCIG Horizon Study Group

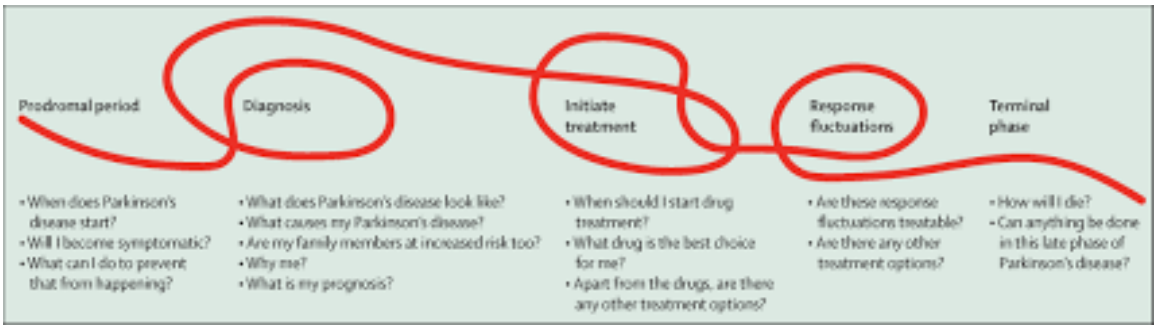
- 71 patients with advanced PD were randomized to receive LCIG infusion (n=37) with LC IR placebo or LC IR with LCIG infusion placebo (n=34) for 12 weeks, LCIG infusion was given by PEG-J tube for 16 waking hours, and stopped overnight
- Mean reduction in off time with LCIG infusion was 4 hours (1.9 hours more than LC IR tablets) Mean increase in on time with LCIG infusion was 4 hours (1.86 hours more than LC IR tablets)

DUOPA

DUOPA: Indication

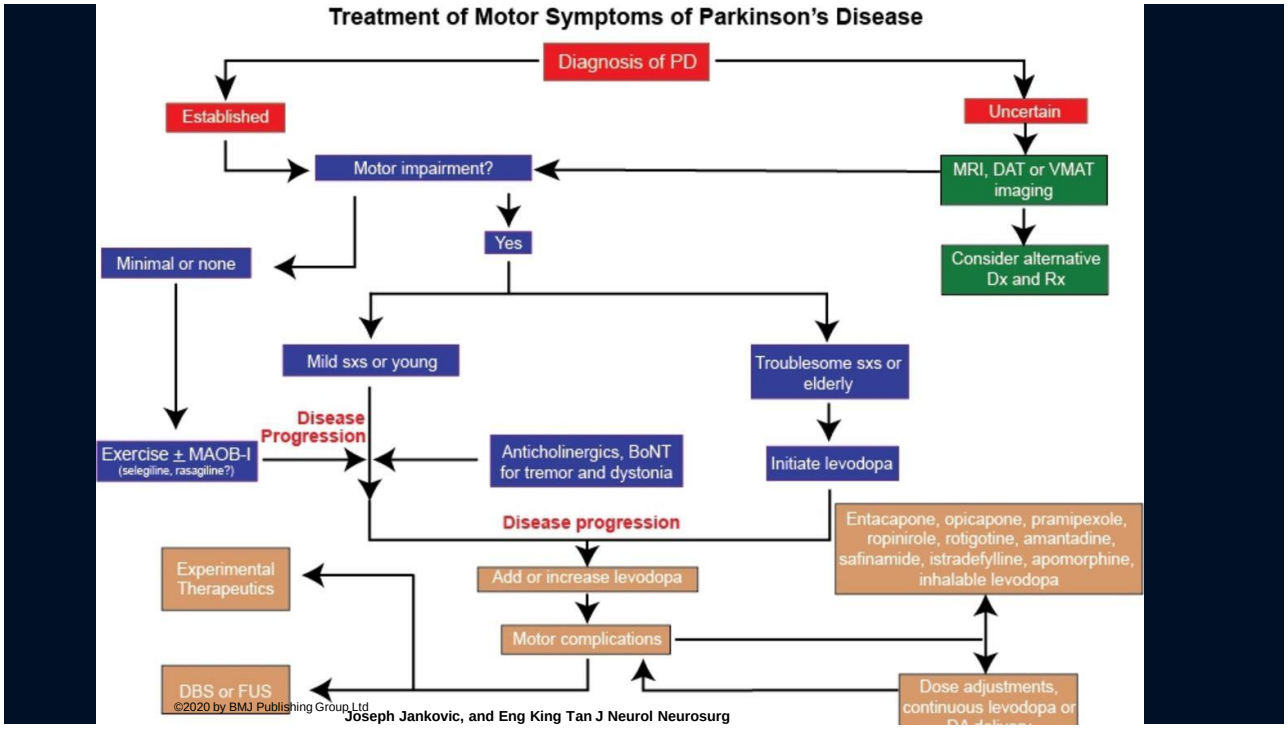
DUOPA is indicated for the treatment of motor fluctuations in patients with advanced Parkinson's disease

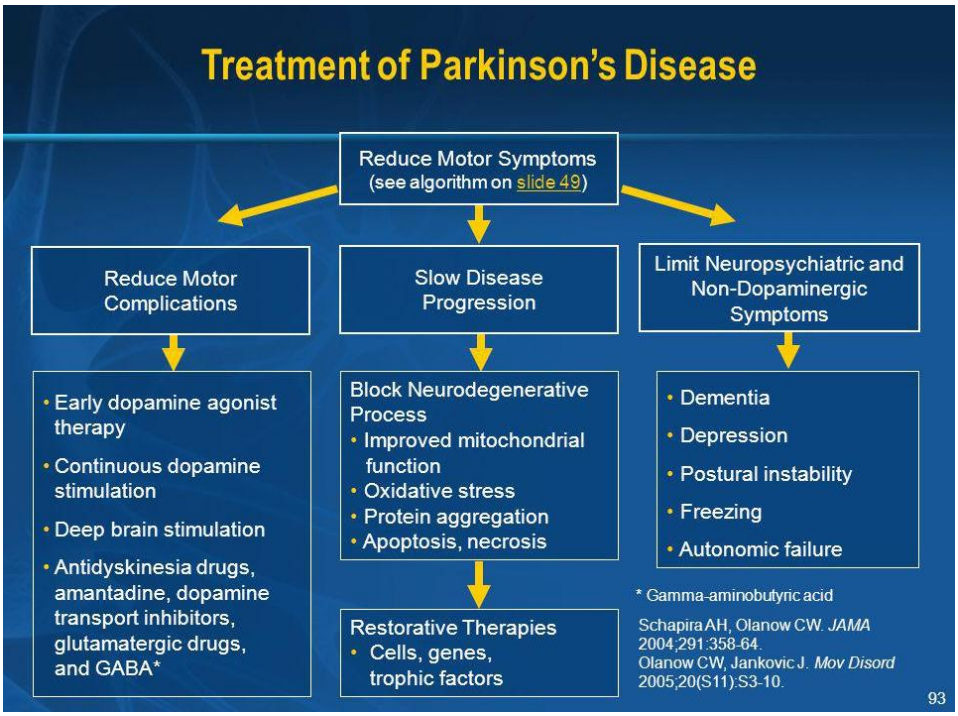
HOW DO WE MAKE DOSE THERAPY DECISIONS



CONSIDERATIONS WHEN MAKING THERAPY DECISIONS

1. Age of onset young vs. old
2. Duration of disease >> symptomatic burden mild symptoms v.s troublesome symptoms , extent of functional impairment
3. History of side effects to dopaminergic medications
4. When do you consider Advanced therapies - motor fluctuations , increase pill burden , DBS vs. DUOPA




Treatment of Parkinson's Disease
Reduce Motor Symptoms
(see algorithm on slide 49)
Reduce Motor Complications
Slow Disease Progression
Limit Neuropsychiatric and Non-Dopaminergic Symptoms
• Early dopamine agonist therapy
• Continuous dopamine stimulation
• Deep brain stimulation
• Antidyskinesia drugs, amantadine, dopamine transport inhibitors, glutamatergic drugs, and GABA*
Block Neurodegenerative Process
• Improved mitochondrial function
• Oxidative stress
• Protein aggregation
• Apoptosis, necrosis
Restorative Therapies
• Cells, genes, trophic factors
• Dementia
• Depression
• Postural instability
• Freezing
• Autonomic failure
* Gamma-aminobutyric acid
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Olanow CW, Jankovic J. Mov Disord 2005;20(S11):S3-10.
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Any
Questions