Modern therapy of Parkinsons disease

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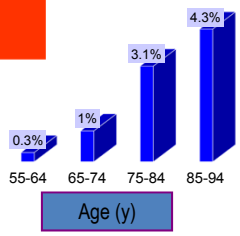
Epidemiology of Mb. Parkinson

4 million patients worldwide
20.000 - 30.000 in Austria

Age of 62 – 65y
< 40y: 5 - 10 %

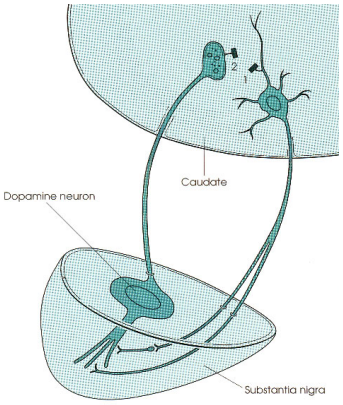


Increasing prevalence with age

Causes and Risk Factors of Ideopathic Parkinson Syndrome (IPS)

- Age
- Gene analysis
  - α - Synuclein, Parkin
- Neurotoxins
  - environment
  - Methyl - Phenyl - Tetrahydro - Pyridine (MPTP)
  - Carbonmonoxid, Mangan, Cyanid

Pathogenetic basis

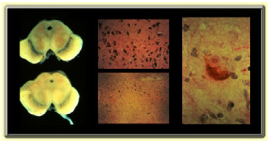


Loss of Dopamine

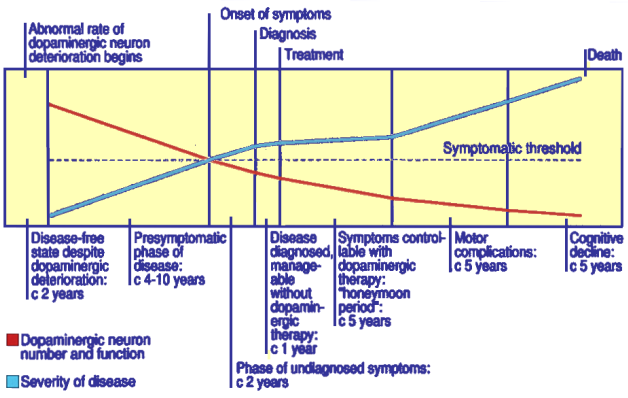
Post mortem:
> 90 %

Main symptoms:
70 - 80 %

“ asymptomatic “ :
< 50 %



Phases and Course of IPS



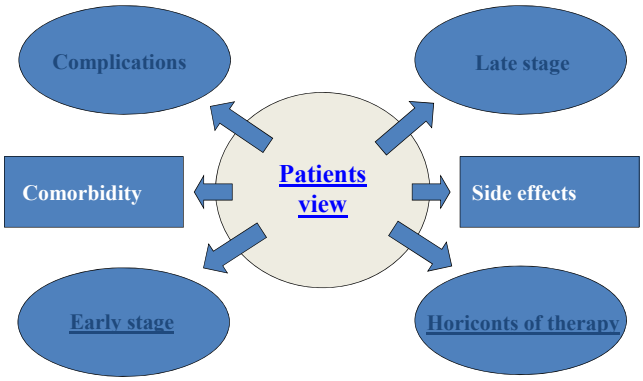
Clinical Aspects of IPS

Preliminary sympt.
Emotional lability
Memory dysfunction
Mood disorder
Performance brake

Early sympt.
Depression, fear
Vegetative disorder
Vigilance disturbance
Posture abnormality
hypokinesis
Pain in vertebral
Spine, headaches

Full stage
Rigidity
Tremor
Akinesia
Bradyphrenia
Disturbance in postural reflexes

Decision in therapy program

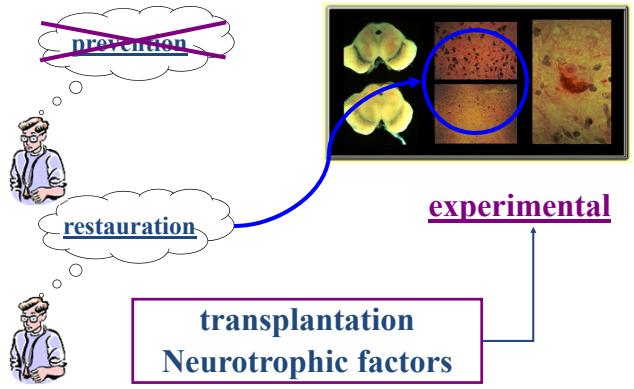


Principles of Therapy - Objectives

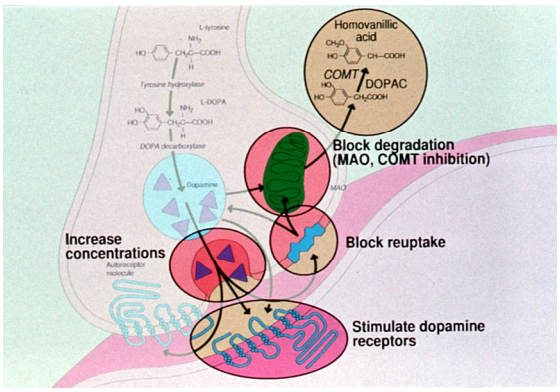
- Prevention
- Restauration of premorbid neuronal integrity and function

  Prevention of neuron decline (neuroprotection)
- Compensation of symptoms
- Amelioration of Quality of Life

Principal aims of therapy



Strategies of medical treatment



Classes of substances

- Dopaminergic drugs
  - L - Dopa
  - Dopamin - agonists (DA)
- COMT Inhibitors
- MAO - B Inhibitors
- Non-dopaminergic drugs
  - Amantadine
  - Anticholinergics

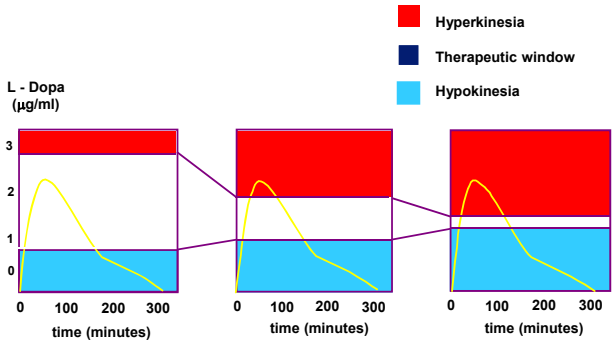
L - Dopa & Benserazid / Carbidopa

Advanteges	Disadvantages
Gold standard	No neuroprotection
Good response of all patients	L - Dopa – long time syndrome
Influence to all main symptoms	SE: nausea, vomiting, postural hypotension, psychotic symptoms, sleepyness
Monotherapy	

L - Dopa & Benserazid / Carbidopa

	Start of effect (minutes)	Duration of effect (hours)	Dosage (mg / day)
Madopar ® Sinemet ®	20 - 40	2 - 4	150 - 600
Madopar CR ® Sinemet ret. ®	30 - 60	3 - 6	200 - 600
Madopar ® Water solutable	10 - 20	0.5 - 1	150 - 600

Effect of progression on the therapeutic window



Disadvanteges of L - Dopa therapy

Loss of effectiveness in 75 % of the patients after 2 - 5 years

Central pharmakodynamic mechanisms	On - Off Dyskinesias
Peripheral pharmakodynamic mechanisms	Delayed - On No - On

Dopamin agonists receptor affinity

	D_1	D_2	D_3	D_4	D_5
Dopamin	++	+++	++++	-	-
Bromocriptin	-	++	++	+	+
Cabergolin	-	+++	?	?	?
Pergolid	+	++++	++++	+	+
Ropinirol	-	+++	++++	+	-
Pramipexol	-	+++	++++	++	?
Apomorphin	++	++	?	?	?

mod. n. Tolosa & Marin, 1997; P. Jenner, 2002

Distribution of dopamine receptors in basal ganglia

	D_1	D_2	D_3	D_4	D_5
Striatum	+	+	+	+	+
Gpe		+		+	
STN	+	+	+		
Gpi / $Sn_{ret.}$	+			+	
$Sn_{comp.}$	+	+	+		

Dopaminagonists

(J.P.Hubble, 2002)

	HT (h)	PD (m)	Dosage (mg/d)
Bromocriptin (**Umprel**)	6	70-100	7.5 - 30
Lisurid (**Dopergin**)	2 - 4	60 - 80	1 - 5
Cabergolin (**Cabaseril**)	65 +	60 - 80	2 - 6
Pergolid (**Permax**)	15-27	60-120	1.5 - 12
Pramipexol (**Sifrol**)	8 - 12	60-180	1.5 - 4.5
Ropinirol (**Requip**)	4 - 6	90	9 - 24

Dopaminagonists (DA)

- Advanteges
  1. neuroprotection (?)
     Monotherapy
     After 3y 30 - 40 %
     After 5y 30 - 35 %
     No L-Dopa longtime syndrome
     L - Dopa: Dyskinesia later and minor
     L- Dopa saving effect
- Disadvanteges
  ? Minor effect compared to L-Dopa
  Risk factors for incompatibility
  SE: nausea, dizzyness, psychotic symptoms, sleepyness

Monotherapy with Dopamin-Agonists

- Start with low dosages
- Slow titration (within 3 weeks) until maximum of effectiveness under care of SE
- Try to reach maximal dosages

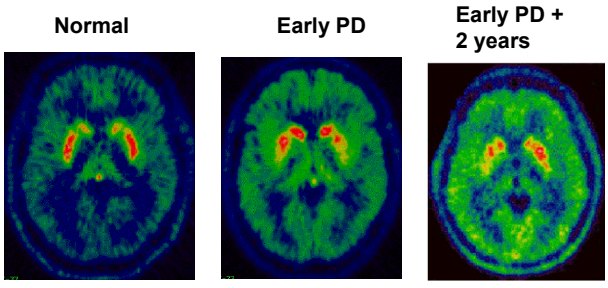
Indication for combination treatment

- Loss of effectiveness of L - Dopa / DA;
- Increasing side effects under L – Dopa monotherapy (fluctuation, dyskinesia);
- Beginn when patient is allready disabled

Progredience of IPS

Annual progredience of extrapyramidal symptoms 1.5 %

^{18}F - Dopa PET



The progressive reduction of ^{18}F-Dopa-uptake in the striatum shows the loss of dopaminergic functions, a biomarker of progression of PD

Neuroprotective (?) properties of dopamin-agonists

	PET	ß - CIT	time
L - Dopa[1,2]	- 20 %	- 25 %	3 years
Ropinirol[1]	- 14 %		3 years
Pramipexol[2]		- 11 %	3 years
Pergolid[3]	- 11 %		3 years

[1]REAL-PET $p < 0.02$; [2]CALM-PD $p < 0.01$; [3]PELMOPET $p < 0.08$;
Ref.: AAN, 2002.

COMT – Antagonists (Comtan®)

- Advantages
  - Improved bioavaliability
  - Smoothing of fluctuations
  - Improvements of activities of daily life (ADL)
- Disadvantages
  - Dyskinesia
  - Diarrhea
  - Monitoring of blood analysis

Selegilin (Jumex® 10 mg / d)

- Advantages
  - Neuroprotection (?)
  - in combination with L - Dopa reduced fluctuation
  - In early treatment delay of L - Dopa - need
- Disadvantages
  - reduced antiparkinson effectiveness
  - No influence to the progression of PD
  - SE: Insomnia, psychotic reactions

Amantadine

Substance	Preparate	Dosage
Amantadin-Sulfate	PK-Merz	300-600mg po
	Hofcomant	200-400mg iv

Amantadine

- Advantage
  - Possible parenteral application
  - Good effect on rigor, tremor, akinesia
  - High anti-dyskinesia potential
- Disadvantages
  - Livedo reticularis
  - Edema of the legs
  - Psychotic reactions

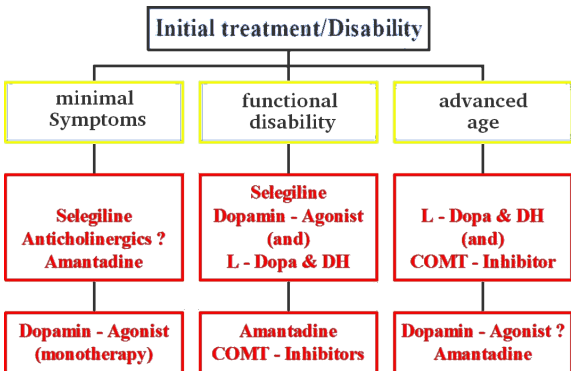
Anticholinergics

- Advantages
  - Good effect against tremor
- Disadvantages
  - Antiparkinson effect only minimal
  - Cognitive dysfunctions
  - SE: hallucination, psychotic reaction

Frequent problems in therapy

Problem	Solution
Fluctuation of effectiveness	COMT-Inhibitors Dopamine-Agonists
On – Off	Apomorphine pause in therapy (?)
L – Dopa Dyskinesia	L – Dopa reduction Fraction of dosage Dopamine-Agonists Amantadine
Akinetic states	Amantadine - infusion
psychosis	Dosis reduction Last in – first out atypical neuroleptics

What, when ?



How ?

- Individual treatment program
- optimal dosage = maximal clinical effect with low side effects
- Experience of the neurologist with the drugs used
- Additional modificating factors

Individual treatment program

- age
- Profession, hobby, partner
- Characteristic of symptoms / Disability
- Dominant symptom(s)
- Costs (?)

Layers of initial treatment

Symptoms:	Strategy:
No functional disability	no treatment (?)
minor symptoms, Tremor	Pramipexol, Anticholiner-gics (?)
Minimal symptoms	Selegiline, Amantadine, Dopamine-agonists monotherapy
Functional handicap	L - Dopa, dopamine-agonists, COMT - inhibitors
Depression, anxiety	SSRI, Trizyclics, Benzo-diazepine

Therapeutical horizont in younger age

- Long treatment duration
  - Profession, hobby, partner
- High risk of long period complication
  - ⇒ Dopamin-agonist - monotherapy
  - ⇒ L - Dopa saving
  - ⇒ Neuroprotection

Therapeutical horizont in higher age

- Shorter treatment duration
- Diminished risk of long period complications of dopaminergic substances -> L - Dopa
- Higher comorbidity risk
  - Drugs
  - Brain circulation disturbances