Novità terapeutiche nel morbo di Parkinson

Giuseppe Bellelli
The history of PD treatment

- 1817, James Parkinson provided the first detailed description in his monography “An essay on the Shaking Palsy”
- 1960, Ehringer discovered dopamine deficiency in corpus striatum and SN
- 1961, Hornykiewicz & Birkmayer and the antiparkinsonian effect of L-Dopa
- 1967, Cotzias et al. efficacy of oral L-dopa for the treatment of chronic Parkinsonism
New pharmacologic horizons in the treatment of Parkinson disease

• Parkinsons’ disease (PD) is a progressive neurodegenerative condition characterized by resting tremor, bradykinesia, rigidity and postural instability as result of loss of dopaminergic neurons in the substantia nigra pars compact (SN pc; area A-9)

• As the disease progresses, neuron degeneration continues, involving other systems, including mesocortical dopaminergic cells (area A-10), noradrenergic (locus coeruleus), serotonergic (dorsal raphe nuclei), cholinergic (nucleus basalis of Meynert), histaminergic, and peptidergic systems

Bonuccelli U et al, Neurology 2006
New pharmacologic horizons in the treatment of Parkinson disease

- According to the staging proposed by Braak et al, at first pathology is confined to the medulla (dorsal motor nucleus of the vagus and intermediate reticular region of the medulla).
- SN degeneration represents an intermediate stage.
- Later there is involvement of the forebrain and ultimately of the neocortex.

- Widespread multisystem nature of the neurodegenerative process of PD and explains the appearance of new motor (gait disturbances, disequilibrium, falls, camptocormia, swallowing, and speech difficulties) and non motor (autonomic dysfunction, sleep disorders, pain, depression, dementia) symptoms that are only partially responsive to or nonresponsive to dopaminergic treatment.

Bonuccelli U et al, Neurology 2006
Sommario

• Motor symptoms
  – Neuroprotective agents
  – Symptomatic therapy
  – DBS
  – Rehabilitation

• Non motor symptoms
  – Depression
  – Cognitive deficits
## Potential neuroprotective drugs (CI NAPS)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>Adenosine antagonist</td>
</tr>
<tr>
<td>Coenzyme Q 10</td>
<td>Antioxidant/mitochondrial enhancer</td>
</tr>
<tr>
<td>Creatine</td>
<td>Mitochondrial enhancer</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Undetermined /multiple</td>
</tr>
<tr>
<td>GPI 1485</td>
<td>Trophic factor</td>
</tr>
<tr>
<td>GM-1 ganglioside</td>
<td>Trophic factor</td>
</tr>
<tr>
<td>Mynocycline</td>
<td>Anti-inflammatory/anti-apoptotic</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Unknown</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>Antioxidant/vesicular trafficking</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>Rasagiline</td>
<td>Antioxidant/anti-apoptotic</td>
</tr>
<tr>
<td>Selegiline</td>
<td>Antioxidant/anti-apoptotic</td>
</tr>
</tbody>
</table>
PD Neuroprotection: Vitamin E and Selegiline

• DATATOP trial (1993)
  - Randomized, double-blind, prospective
  - 800 patients randomized to a dose of 2,000 IU of vitamin E/day or placebo
  - Followed for 14 ± 6 months
  - Primary endpoint: onset of disability requiring use of levodopa
  - No difference between tocopherol and placebo groups in the average time to required levodopa (hazard ratio 0.91, 95% CI .74 to 1.12)
  - Selegiline was able to delay the requirement for levodopa by 9 months compared to placebo (symptomatic effect?)

AAN 2007
PD Neuroprotection: Rasagiline

- Irreversible and selective MAO-B inhibitor with a 5-10 greater potency than selegiline
- “Delayed-started” trial to assess the neuroprotective effect of rasagiline
- 371 subjects treated with rasagiline 2 and 1 mg/day for 12 months showed better UPDRS score than subjects whose treatment was delayed for 6 months (P=.001 and P=.005, respectively)
- Inconclusive results

*Parkinson Study Group 2004, NEJM*
Conclusions: Coenzyme Q$_{10}$ was safe and well tolerated at dosages up to 1200 mg/d. Less disability developed in subjects assigned to Coenzyme Q$_{10}$ than in those assigned to placebo, and the benefit was greatest in those receiving the highest dosage. Coenzyme Q$_{10}$ appears to slow the progressive deterioration of function in PD but these results need to be confirmed in a larger study.

Arch Neurol 2002; 59:1541-1550
Slowing Parkinson’s disease progression

Recent dopamine agonist trials

J. Eric Ahlskog, PhD, MD

Abstract—In recent clinical trials, chronic treatment of patients with PD with pramipexole or ropinirole was associated with a slower decline of imaged striatal dopaminergic signal, compared to levodopa monotherapy. Although this could reflect slowed progression of PD, equally plausible is a pharmacologic effect on proteins that interact with the imaging radioligands. To date, there is no compelling evidence favoring dopamine agonists over levodopa; either is an appropriate choice for initial treatment of PD.

NEUROLOGY 2003;60:381–389
Recommendations for Neuroprotection

- There is insufficient evidence for neuroprotection (Level U):
  - Amantadine
  - Ropinirole
  - Pramipexole
  - NMDA receptor antagonist
  - Riluzole

AAN, 2007
Symptomatic treatment of motor symptoms of PD
The efficacy of L-dopa is unsurpassed

- Double-blinded, RCT
- 361 PD patients to placebo or L-dopa (150mg/day, 300 mg/day, or 600 mg/day)
- Primary outcome: masked assessment of change in UPDRS from baseline after 40 weeks of treatment and 2-week washout
- Patients randomized to all L-Dopa doses: significantly better UPDRS scores than patients on placebo
- Highest doses greatest benefit

*PSG NEJM 2004; 351: 2498–508*
L-Dopa è più efficace dal punto di vista sintomatologico rispetto ai dopamino-agonisti (CALM-PD study)

- Improvement with levodopa:
  - 5.9 points vs pramipexole ($p=0.003$) on total UPDRS at 4 years
  - 4.48 points vs ropinirole ($p=0.008$) on UPDRS motor subscale at 5 years
  - 2.9 points vs cabergoline ($p<0.001$) on UPDRS motor subscale at 5 years

Holloway et al, Arch Neur 2004
Il trattamento con L-dopa ha significativamente ridotto la mortalità associata al PD dal 1960 ad oggi.

![Graph showing the impact of L-dopa treatment on mortality in PD patients over time.](image)

*Hoehn and Yahr, 1967; Hoehn, 1983*
I problemi connessi all’uso di L-Dopa

• L-Dopa è tossica?
• L-Dopa accellerà la perdita dei neuroni dopaminergici?
• L-Dopa favorisce la comparsa di fluttuazioni motorie e disciniesie?
• Problemi associati con il rilascio pulsatile di L-Dopa
**Levodopa**

**Is toxicity a myth?**

Y. Agid, MD, PhD

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**Article abstract**—Whether a drug such as levodopa, which is prescribed for long periods, may be toxic is a legitimate and even indispensable question. The problem is no different from that posed by other drugs—such as calcium antagonists, antihypertensives, or hormones—normally prescribed for chronic diseases. What, however, is meant in this context by “toxic” (from the Greek toxicon, meaning poison)? Irrevocable damage such as cell loss should not be confused with reversible side effects resulting from cell dysfunction. Clinically or experimentally, levodopa has not been shown to accelerate neurodegeneration or cause permanent impairment of cell function in a manner that would result in irreversible side effects. These data have been reasonably well established in vivo in animals and humans, although preliminary studies suggesting that levodopa is a trophic factor remain unconfirmed. Like oxygen or calcium, levodopa can be toxic in vitro when it is present in high concentrations or in the absence of glial cells. However, glial cells are much more numerous than neurons in vivo, so these conditions cannot simply be extrapolated to three-dimensional brain structures in which protective interactions with the cellular environment abound. Because levodopa remains the most effective treatment available for Parkinson’s disease, questions regarding timing or manner of administration of the drug should arise not because levodopa is toxic to nerve cells, but because it causes reversible side effects. When the elementary rules of substitutive therapy to provide maximum comfort while limiting side effects are followed, we need not fear that levodopa is dangerous unless the contrary is proven.
Dyskinesias are related to L-dopa use?

- Chronic L-dopa is not toxic for remaining dopamine neurons, but instead promotes their recovery, in rats with moderate nigrostriatal lesions
  

- ELLDOPA study
La risposta a L-Dopa varia con il progredire della patologia.

**Early disease**
- Smooth, long duration of clinical benefit
- Low incidence of dyskinesias

**Mid-stage disease**
- Diminished duration of clinical benefit
- Increased incidence of dyskinesias

**Advanced disease**
- Clinical response mirrors levodopa plasma pharmacokinetic profile
- ‘On’ time is associated with dyskinesias

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Obeso et al, Neurology 2000
Meccanismi che determinano l’insorgenza di complicanze motorie

La degenerazione progressiva dei neuroni dopaminergici determina una riduzione delle capacità di “storage” dopaminergico nello striato

Fluttuazione dei livelli plasmatici di L-Dopa (perdita della capacità di buffer)

Stimolazione pulsatile dei recettori domaminergici dello striato
Continuous delivery of levodopa by infusion reverses motor complications.

MA L’INFUSIONE NON SEMPRE E’ PRATICABILE

Oral levodopa
After 6 months levodopa infusion

Plasma levodopa concentration (ng/ml)

Time of day

Off-time (h/day) Dyskinesia score (AIMS)

AIMS=Abnormal Involuntary Movement Score

Stocchi et al, 2005
Complicanze motorie nel PD

• Fluttuazioni motorie
  – End of dose (wearing off)
  – Fluttuazioni motorie imprevedibili (fenomeni on-off)
  – Doses failure
  – Episodi di freezing

• Discinesie
  – Discinesie di picco dose
  – Discinesie difasiche D-I-D
  – Distonie

Olanow et al, 2001
La L-Dopa fobia

“Levodopa phobia”: A new iatrogenic cause of disability in Parkinson disease

Roger Kurlan, MD

Two recent research directions have raised question about the role of levodopa in treating Parkinson disease (PD). First is evidence that levodopa is toxic in nigral neuronal cell cultures. Second are clinical trials showing that compared to beginning therapy with a dopamine agonist, initial treatment with levodopa is associated with earlier appearance of dyskinesias and wearing-off fluctuations. There has been much publicity about these potential negative aspects of levodopa. I report two patients with PD who became disabled because their treating neurologists were fearful of prescribing levodopa because of the widespread publicity.

Case reports. Case 1. A 72-year-old man had been diagnosed with PD 3 years earlier. He was initially treated with ropinirole and required steadily increasing dosages up to 24 mg/day. Due to ongoing bradykinesia and gait difficulties, amantadine 300 mg/day and deprenyl 10 mg/day were added. Visual hallucinations and episodes of confusion developed but resolved after discontinuation of amantadine and deprenyl. The patient was functionally disabled by unsteady gait with freezing, overall slowness, and impaired dexterity for daily activities such as dressing and eating and was referred to the University of Rochester PD Program by the treating neurologist “since there are no other medication op-
Insorgenza di discinesie nel PD

Le discinesie insorgono approssimativamente nel 50-75% dei pazienti con PD dopo 5-10 anni di trattamento con L-Dopa

Rascol et al PSG 2000
Clinical Questions

1. Quali farmaci riducono i fenomeni off e che efficacia hanno?
2. Quali farmaci riducono le discinesie?
3. Il DBS riduce il time off, le discinesie, l’uso dei farmaci e migliora la funzione motoria?
4 options + 1

- Dopamine agonists
- MAO B inhibitors
- COMT inhibitors
- Sustained release Carbidopa/Levodopa

- Amantadine
## Evidence: Dopamine Agonists

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug</th>
<th>Class</th>
<th>N</th>
<th>Study Duration</th>
<th>Decrease Off time Active</th>
<th>Decrease Off time Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanow</td>
<td>Pergolide</td>
<td>I</td>
<td>189/187</td>
<td>24 week</td>
<td>32% (1.8 h)*</td>
<td>4% (0.2 h)</td>
</tr>
<tr>
<td>Lieberman</td>
<td>Pramipexole</td>
<td>I</td>
<td>181/179</td>
<td>32 week</td>
<td>31%*</td>
<td>7%</td>
</tr>
<tr>
<td>Guttman</td>
<td>Pramipexole</td>
<td>II</td>
<td>79/83</td>
<td>40 week</td>
<td>15% (2.5 h)*</td>
<td>3%</td>
</tr>
<tr>
<td>Rascol</td>
<td>Ropinirole</td>
<td>II</td>
<td>23/23</td>
<td>12 week</td>
<td>23%*</td>
<td>4%</td>
</tr>
<tr>
<td>Lieberman</td>
<td>Ropinirole</td>
<td>II</td>
<td>95/54</td>
<td>26 week</td>
<td>11.7%*</td>
<td>5%</td>
</tr>
<tr>
<td>Dewey</td>
<td>Apomorphine</td>
<td>II</td>
<td>20/9</td>
<td>4 week</td>
<td>34% (2 h)*</td>
<td>0%</td>
</tr>
<tr>
<td>Guttman</td>
<td>Bromocriptine</td>
<td>II</td>
<td>84/83</td>
<td>40 week</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Steiger</td>
<td>Cabergoline</td>
<td>III</td>
<td>19/10</td>
<td>24 week</td>
<td>40% (2 h)*</td>
<td>18% (0.7 h)</td>
</tr>
<tr>
<td>Ahlskog</td>
<td>Cabergoline</td>
<td>III</td>
<td>17/10</td>
<td>24 week</td>
<td>59% (3.3 h)*</td>
<td>NS</td>
</tr>
</tbody>
</table>

* AAN, 2007
# Evidence: MAO B Inhibitors

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug</th>
<th>Class</th>
<th>N</th>
<th>Study Duration</th>
<th>Decrease Off time Active</th>
<th>Decrease Off time Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSG</td>
<td>Rasagiline (0.5 mg)</td>
<td>I</td>
<td>164/159</td>
<td>26 week</td>
<td>23% (1.4 h)*</td>
<td>15% (0.9 h)</td>
</tr>
<tr>
<td>PSG</td>
<td>Rasagiline (1.0 mg)</td>
<td>I</td>
<td>149/159</td>
<td>26 week</td>
<td>29% (1.8 h)*</td>
<td>15% (0.9)</td>
</tr>
<tr>
<td>Rascol</td>
<td>Rasagiline (1.0 mg)</td>
<td>I</td>
<td>231/229</td>
<td>18 week</td>
<td>21% (1.2 h)*</td>
<td>7% (0.4 h)</td>
</tr>
<tr>
<td>Waters</td>
<td>Orally Disintegrat</td>
<td>II</td>
<td>94/46</td>
<td>12 week</td>
<td>32% (2.2 h)*</td>
<td>9% (0.6 h)</td>
</tr>
<tr>
<td>Golbe</td>
<td>Selegiline</td>
<td>III</td>
<td>50/46</td>
<td>6 week</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

* NR = Not Reported

AAN, 2007
## Evidence: COMT Inhibitors

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug</th>
<th>Class</th>
<th>N</th>
<th>Study Duration</th>
<th>Decrease Off time Active</th>
<th>Decrease Off time Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSG</td>
<td>Entacapone</td>
<td>I</td>
<td>103/102</td>
<td>24 week</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rascol</td>
<td>Entacapone</td>
<td>I</td>
<td>227/229</td>
<td>18 week</td>
<td>21% (1.2 h)*</td>
<td>7% (0.4 h)</td>
</tr>
<tr>
<td>Poewe</td>
<td>Entacapone</td>
<td>II</td>
<td>197/104</td>
<td>24 week</td>
<td>25.8% (1.6 h)*</td>
<td>13.4% (0.9 h)</td>
</tr>
<tr>
<td>Rinne</td>
<td>Entacapone</td>
<td>II</td>
<td>85/86</td>
<td>24 week</td>
<td>23.6% (1.3 h)*</td>
<td>1.9% (0.1 h)</td>
</tr>
<tr>
<td>Fenelon</td>
<td>Entacapone</td>
<td>II</td>
<td>99/63</td>
<td>12 week</td>
<td>0.9 h</td>
<td>0.4 h</td>
</tr>
<tr>
<td>Rajput</td>
<td>Tolcapone (100 mg tid)</td>
<td>II</td>
<td>69/66</td>
<td>12 week</td>
<td>32% (2.3 h)</td>
<td>20% (1.4 h)</td>
</tr>
<tr>
<td>Rajput</td>
<td>Tolcapone (200 mg tid)</td>
<td>II</td>
<td>67/66</td>
<td>12 week</td>
<td>48% (3.2 h)*</td>
<td>20% (1.4 h)</td>
</tr>
<tr>
<td>Baas</td>
<td>Tolcapone (100 mg tid)</td>
<td>II</td>
<td>60/58</td>
<td>12 week</td>
<td>31.5%*</td>
<td>11%</td>
</tr>
<tr>
<td>Baas</td>
<td>Tolcapone (200 mg tid)</td>
<td>II</td>
<td>59/58</td>
<td>12 week</td>
<td>26.20%</td>
<td>11%</td>
</tr>
</tbody>
</table>

*AAN, 2006*
# Evidence: Sustained Release Carbidopa/Levodopa

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug</th>
<th>Class</th>
<th>N</th>
<th>Study Duration</th>
<th>Decrease Off time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jankovic</td>
<td>Carbidopa/levodopa CR/IR</td>
<td>III</td>
<td>20</td>
<td>16 week</td>
<td>NS</td>
</tr>
<tr>
<td>Hutton</td>
<td>Carbidopa/levodopa CR/IR</td>
<td>III</td>
<td>21</td>
<td>24 week</td>
<td>NS</td>
</tr>
<tr>
<td>Ahlskog</td>
<td>Carbidopa/levodopa CR/IR</td>
<td>III</td>
<td>28</td>
<td>16 week</td>
<td>NS</td>
</tr>
<tr>
<td>Lieberman</td>
<td>Carbidopa/levodopa CR/IR</td>
<td>III</td>
<td>24</td>
<td>16 week</td>
<td>NS</td>
</tr>
</tbody>
</table>
Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson’s Disease

Renzo Zanettini, M.D., Angelo Antonini, M.D., Gemma Gatto, M.D., Rosa Gentile, M.D., Silvana Tesei, M.D., and Gianni Pezzoli, M.D.

Pathological gambling in Parkinson's disease

Sui H Wong and Malcolm J Steiger

BMJ 2007;334:810-811
doi:10.1136/bmj.39176.363958.80
Recommendations for Patients with PD and Motor Fluctuations

- Entacapone and rasagiline should be offered to reduce off time in PD patients (Level A)*
- Pergolide, pramipexole, ropinirole, and tolcapone should be considered to reduce off time (Level B)*
  - Tolcapone (hepatotoxicity) and pergolide (valvular fibrosis) should be used with caution and require monitoring
- Apomorphine, cabergoline, and selegiline may be considered to reduce off time (Level C)*
- Sustained release carbidopa/levodopa and bromocriptine may be disregarded to reduce off time (Level C)*

*Strength indicates level of supporting evidence, not hierarchy of efficacy
Relative Efficacy of Medications in Reducing Off Time

- Rasagiline similar to entacapone
- Bromocriptine similar to pramipexole
- Tolcapone similar to pergolide
- Cabergoline similar to bromocriptine
- Tolcapone similar to entacapone
- Ropinirole possibly superior to bromocriptine

- Many of these studies not powered to demonstrate superiority of one drug over another
- Other than comparisons of ropinirole and bromocriptine, there is insufficient evidence to conclude which one agent is superior to another in reducing off time
Recommendations for Medications that Reduce Dyskinesia

• Amantadine may be considered for PD patients with motor fluctuations to reduce dyskinesia (Level C)

• Insufficient evidence to support or refute the efficacy of clozapine in reducing dyskinesia (Level U)
Randomized, Double-blind, Placebo-Controlled Trial on Symptomatic Effects of Coenzyme Q₁₀ in Parkinson Disease

Alexander Storch, MD; Wolfgang H. Jost, MD; Peter Vieregge, MD; Jörg Spiegel, MD; Wolfgang Greulich, MD; Joachim Durner, MD; Thomas Müller, MD; Andreas Kupsch, MD; Henning Henningsen, MD; Wolfgang H. Oertel, MD; Gerd Fuchs, MD; Wilfried Kuhn, MD; Petra Niklowitz, MD; Rainer Koch, PhD; Birgit Herting, MD; Heinz Reichmann, MD; for the German Coenzyme Q₁₀ Study Group

• Conclusions: Nanoparticular CoQ₁₀ at a dosage of 300 mg/d is safe and well tolerated and leads to plasma levels similar to 1200 mg/d of standard formulations. Add-on CoQ₁₀ does not display symptomatic effects in midstage Parkinson disease

Arch Neurol. 2007;64(7):938-944
Conclusions: Transdermal rotigotine significantly improved “off” time in subjects with Parkinson disease not optimally controlled with levodopa and was safe and well tolerated, with typical dopaminergic side effects and occasional application site reactions.
Il problema: molti pazienti richiedono levodopa per il controllo dei sintomi

Need for l-dopa in patients initiated with dopamine agonist (pramipexole)

Need for l-dopa in patients initiated with monoamine oxidase inhibitor (selegiline)

PSG, 1997; Holloway et al, 2004
I preparati combinati
L-Dopa + entacapone enhances the pharmacokinetics of levodopa

Plasma levodopa (µg/ml) vs. Time (h)

- Traditional levodopa
- L-Dopa entacapone

Time by which the half-life of l-dopa is extended

Ruottinen and Rinne, 1996
L-Dopa & entacapone: impatto sulle ADL

Poewe et al, Acta Neurol Scand, 2002

Diagram showing UPDRS-s ADL scores over time (months) for L-Dopa entacapone/LCE and Traditional levodopa plus placebo.
Deep Brain Stimulation
Panel 2: Proposed criteria for deep brain stimulation

Inclusion criteria
1. Clinically definite Parkinson’s disease
2. Hoehn and Yahr stage 2–4 (moderate to severe bilateral disease, but still ambulatory when on)
3. L-dopa responsive with clearly defined off and on periods
4. Persistent disabling motor fluctuations despite best drug treatment with some combination of
   • At least 3 h of off period daily
   • Unpredictable off periods
   • Disabling dyskinesia
5. Intact cognition as measured by neuropsychological testing and no active psychiatric disturbances
6. Strong social support system and commitment from patient and family members to keep follow-up appointments

Exclusion criteria
1. Parkinson-plus syndromes
2. Atypical parkinsonism—eg, vascular parkinsonism
3. Drug-induced parkinsonism
4. Medical contraindications to surgery or stimulation (serious comorbid medical disorders, chronic anticoagulation with warfarin, cardiac pacemakers, etc)
5. Dementia or psychiatric issues (untreated depression, psychosis, etc)
6. Intracranial abnormalities that would contraindicate surgery—eg, stroke, tumour, vascular abnormality affecting the target area
7. Severe brain atrophy on imaging (makes target localisation difficult)
8. Serious doubt about patient’s commitment to return for follow-up visits (several no-shows in the past, poor compliance record, etc)
Surgical and hardware complications of subthalamic stimulation

A series of 160 procedures

Kelly E. Lyons, PhD; Steven B. Wilkinson, MD; John Overman, BS, BEE; and Rajesh Pahwa, MD

Abstract—Objective: To assess the surgical and hardware complications in a series of 81 consecutive patients undergoing subthalamic (STN) deep brain stimulation (DBS) for Parkinson disease (PD). Methods: The authors prospectively documented surgical and hardware complications occurring at the time of surgery and at subsequent neurologic and surgical evaluations for an average of 17 months, ranging from 1 to 54 months. Results: No patient had a serious surgical complication resulting in death or permanent neurologic deficit. One patient had an intracranial hemorrhage but with no permanent deficit. In follow-up, 2.5% had infections requiring system removal, 3.7% had infections requiring implantable pulse generator (IPG) removal, 12.5% had misplaced leads, and 26.2% had hardware complications including lead migration, lead fracture, extension erosion, extension fracture, and IPG malfunction. Conclusion: Serious complications leading to permanent neurologic deficit are rare after STN DBS for advanced PD. However, long-term follow-up demonstrated that hardware complications are relatively common, having occurred in approximately 26% of these patients.

NEUROLOGY 2004;63:612–616
Evidence DBS

• DBS of the STN may be considered as a treatment option in PD patients to improve motor function and to reduce motor fluctuations, dyskinesia, and medication usage (Level C). Patients need to be counseled regarding the risks and the benefits of this procedure.

• There is insufficient evidence to make any recommendations about the effectiveness of DBS of the GPi or VIM nucleus of the thalamus in reducing motor complications or medication usage, or in improving motor function in PD patients (Level U).

Practice Parameter: Treatment of PD with motor fluctuations and dyskinesia (an evidence-based review) Neurology 2006
Exercise treatment & rehabilitation
Management of Parkinson’s Disease

- Parkinson’s disease
  - Nonpharmacologic
    - Education
    - Support
    - Exercise
    - Nutrition
  - Considerations
    - Age
    - Cognitive function
    - Comorbidity
  - Yes
  - Dopamine agonists
  - Dopamine agonist + Levodopa (+/- COMT inhibitor)
  - Add COMT inhibitor
  - Motor complications
    - See section on control of motor complications

- Pharmacologic
  - Neuroprotection
    - Selegiline
  - Functional impairment
  - No
  - Levodopa (+/- COMT inhibitor)
  - Unacceptable control with medical therapies
    - Consider surgery
  - Continue to monitor

### Exercise Therapy in PD

<table>
<thead>
<tr>
<th>Author</th>
<th>Cohort size</th>
<th>Outcome variable</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wade et al 2003</td>
<td>144</td>
<td>PDQ-39, SC-36, peg test, walking</td>
<td>multidisciplinary rehab vs. placebo</td>
<td>1 x per week x 6 weeks, FU 48 weeks</td>
</tr>
<tr>
<td>Marchese et al 2000</td>
<td>20</td>
<td>UPDRS</td>
<td>cued vs. non-cued exercises</td>
<td>3 x per week x 6 weeks, FU 12 weeks</td>
</tr>
<tr>
<td>Miyai et al 2000</td>
<td>10</td>
<td>UPDRS, ambulation</td>
<td>BWSTT vs. physiotherapy</td>
<td>3 x per week x 4 weeks, FU 8 weeks</td>
</tr>
</tbody>
</table>
# Exercise Therapy in PD

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<tr>
<td>Miyai et al 2002</td>
<td>24</td>
<td>UPDRS, ambulation</td>
<td>BWSTT vs. physiotherapy</td>
<td>3 x per week x 4 weeks, FU 6 months</td>
</tr>
<tr>
<td>Hirsch et al 2003</td>
<td>18</td>
<td>balance, falls, strength</td>
<td>Balance/resistance vs. balance</td>
<td>3 x per week x 10 weeks, FU 14 weeks</td>
</tr>
<tr>
<td>Pachetti et al 2000</td>
<td>32</td>
<td>UPDRS, PDQualif</td>
<td>Music therapy vs. physical therapy</td>
<td>1 x per week x 3 months, FU 5 months</td>
</tr>
<tr>
<td>Comella et al 1994</td>
<td>18</td>
<td>UPDRS, depression</td>
<td>General exercise vs. placebo</td>
<td>3 x per week x 1 month, FU 12 months</td>
</tr>
</tbody>
</table>
Recommendation for Exercise Therapy in PD

• Exercise therapy may be considered to improve function (Level C)
  - Results in improvement in UPDRS
  - Decrease in falls

• No specific exercise program shown to be superior to another

• Benefit not sustained after exercise is discontinued
Possibili ragioni della ridotta provata efficacia della riabilitazione nel PD

- Eterogeneità della popolazione (durata e gravità malattia)
- Misure di outcomes variabili
  - Intervento adattativo
  - Intervento sulla plasticità neuronale
  - Qualità della vita
- Collaborazione del paziente / interventi educativi (non sempre valutati)
Non motor symptoms
I sintomi non motori sono spesso il primo segno di wearing off

- In addition to the motor-related symptoms of PD, non-motor complications can also be a significant burden for patients.
- Many of these symptoms are associated with PD itself; however, recent evidence suggests that non-motor symptoms such as anxiety, tingling, coldness of limbs and unclear thinking may frequently occur before motor symptoms emerge, highlighting the importance of their recognition in clinical practice.
Background

• Prospective survey n=99 (Shulman et al., 2001)
  - 88% had at least one of
    • Anxiety, depression, sensory disturbance, fatigue, pain, or sleep disturbance
  - 11% had 5 or more

• Low physician recognition of nonmotor features in PD

• Many PD symptoms overlap with features of depression and dementia

• Validated criteria for depression, psychosis and dementia in PD do not exist

AAN, 2007
Evidence: pharmacological treatment of depression in PD

• Amitriptyline may be considered for depression associated with PD (Level C)
  – Not necessarily the first choice for treatment

• Citalopram and sertraline (no benefit underpowered)

• Insufficient evidence to make recommendations for other pharmacologic depression treatments in PD (Level U)
Recommendations for Psychosis Treatment

• For patients with PD and psychosis
  – Clozapine should be considered (Level B)
    • Associated with agranulocytosis that may be fatal
    • Absolute neutrophil count must be monitored
    • Monitoring requirements may vary by country
  – Quetiapine may be considered (Level C)
  – Olanzapine should not be routinely considered (Level B)
    • Worsens motor function
Conclusioni

• IL PD è una sindrome più che una malattia e deve dunque essere trattata farmacologicamente di conseguenza
• Non vi sono attualmente preparati che svolgano una provata azione neuronoprotettiva
• La L-Dopa è il più potente agente antiparkinsoniano ancora in uso ma è gravato da alcuni problemi
• I farmaci dopaminoagonisti, I-MAO e COMT sono efficaci per le complicanze del PD (fluttuazioni)
• DBS efficacia limitata ed in casi selezionati
• Riabilitazione?