Parkinson Disease: Beyond the Motor Features

Iracema Leroi
Institute of Brain, Behaviour and Mental Health
Parkinson’s Disease in the 19th century

- PD = *paralysis agitans* (shaking palsy).
- The term "Parkinson's disease" was coined several decades later by French neurologist Charcot
The Stages of motor symptoms in PD

• Pre-motor stage
• (Prodromal stage)
• Early motor stage
• Advanced stage
Parkinson’s Disease in the 21st century: Non-motor symptoms (‘NMS’)

• Pain syndromes
• Parathesias
• RLS
• Fatigue
• Skin symptoms
  • Seborrhoea
  • facial oiliness
• Dysautonomia
  • bladder instability,
  • altered thermal regulation
  • orthostatic hypotension

Prof Ray Chaudhuri
Other non-motor PD features

- **Psychiatric Symptoms**
  - depression
  - anxiety
  - sleep disturbance
  - psychosis

- **Cognitive Symptoms**
  - executive dysfunction
  - mild cognitive impairment
  - dementia
Cognitive and Psychiatric NMS

Depression, anxiety, psychosis and apathy have been well characterised in PD = ‘NPS’ (Neuropsychiatric Syndromes)

How are NPS related to the cognitive changes in PD?
Aim of the talk

• NPS in PD from the perspective of stage of cognitive decline.
• Impact of NPS and cognitive impairment
• Effect of cognitive enhancers on NPS in PD
• Non-pharmacological strategies for cognitive impairment in PD
The motor and cognitive stages of PD

PRE-MOTOR

PD normal cognition

EARLY-MOD

PD-mild cognitive impairment

ADVANCED

Dementia in PD
Mild cognitive impairment in Parkinson Disease (MCI-PD)

• 25% of people with PD
• MCI-PD may convert to PDD (Janvin 2006; Williams-Grey 2010)
Definition of mild cognitive impairment in PD (MCI-PD): MDS Task Force proposal
(Litvan 2012)

• Level I:
  • abbreviated assessment of global cognition
  • limited neuropsychological test batteries
  • classification of “possible PD-MCI”.

• Level II:
  • extensive neuropsychological testing
  • tests in five domains
  • impairment on at least 2 tests in one or more domain
  • classification of PD-MCI subtypes.
MCI-PD: MDS Task Force proposal: 5 key cognitive domains

- attention and working memory
- executive dysfunction
- language
- memory
- visuospatial function
Cognitive profile of MCI-PD
(Aarsland 2011)

• Range of cognitive domains affected

• 11% non-amnestic, single-domain impairment
• 9% amnestic single-domain
• 5% amnestic multiple domain
• 1.3% non-amnestic multiple domain
Clinical correlates of MCI-PD

(Joinvin 2007; Alves 2009)

• Older age
• Longer duration of disease
• More advanced disease
Dementia in PD (PDD)
Advanced stage PD

• Motor symptoms more severe
• Falls more common
• “on-off” complications and fluctuations/freezing
• Tremor may be less obvious
• Marked bradykinesia
• Gait assisted
• Less responsive to dopamine replacement therapy
“The Sydney Multicentre Study”
(Hely 2008)

Longitudinal observational study
• N=136 PD participants
• Followed at 10, 15, and 20 years
• At 20 years, 100 died
• *PDD in 83% of 20-year survivors
“The Sydney Multicentre Study”  
(Hely 2008)

• Mean age at PDD diagnosis 71.6 years
• Mean time to onset after dx 10.9 years
• After PDD diagnosis, mean survival 54 months
Post-mortem PDD: heterogeneous pathology

<table>
<thead>
<tr>
<th></th>
<th>Hughes 1993 (n=31)</th>
<th>Hely 2008 (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD-changes</td>
<td>9 (29%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Vascular</td>
<td>2 (6%)</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>Cortical Lewy bodies</td>
<td>3 (10%)</td>
<td>8 (47%)</td>
</tr>
<tr>
<td>Other</td>
<td>17 (55%)</td>
<td>Pick bodies, FTD 1(6%)</td>
</tr>
</tbody>
</table>
# Neuropsychology of AD vs PDD

(Bronnick 2007)

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>PDD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Memory</strong></td>
<td>encoding</td>
<td>recall</td>
</tr>
<tr>
<td><strong>Orientation</strong></td>
<td><em>poor</em></td>
<td><em>fair</em></td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td><em>poor</em></td>
<td><em>fair</em></td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td><em>fair</em></td>
<td><em>poor</em></td>
</tr>
<tr>
<td><strong>ECF</strong></td>
<td><em>fair</em></td>
<td><em>poor</em></td>
</tr>
<tr>
<td><strong>Visuoperceptual function</strong></td>
<td><em>fair</em></td>
<td><em>poor</em></td>
</tr>
</tbody>
</table>

Can predict AD vs PDD on cognitive profile alone with 74.7% accuracy.
Severe Cholinergic Deficiency in PDD

ACh loss in DLB, PDD and AD
Operationalized MDS Criteria for PDD: simple 5 step algorithm
(Dubois et al, 2007)

• 1. diagnosis of iPD
• 2. PD prior to dementia
• 3. PD with ↓ global cognitive efficiency

• 4. Cognitive ↓ impairs ADL

• 5. Impairment of >1 cognitive domain

• Queen’s Square
• History/records

• MMSE < 26
• Carer interview/pill questionnaire

• Domains: attention, ECF, visuospatial, memory
Why should we examine NPS in PD relative to stages of cognitive change?

- In *non-PD* populations → strong association between NPS and cognitive impairment
- Similar relationship may exist in PD
- May have prognostic role to predict cognitive decline
- With dementia, a ‘neuropsychiatric slippery slope’ may appear, heralding the onset of a more rapid global decline in health and quality of life and a step-up in caregiver burden.
- Focus on complications of cognitive impairment and the need for added intervention.
Neuropsychiatric symptoms in non-PD cognitive impairment

Dementia:

• **Cache County Study:** >60% of a community sample of people over the age of 65 with dementia had *at least one NPS.*
  
  • Of these, > 50% had ‘clinically significant’ NPS (‘moderate to severe’ severity) on the Neuropsychiatric Inventory (NPI).⁵
Neuropsychiatric symptoms in non-PD cognitive impairment

Mild cognitive impairment (MCI):

• Cardiovascular Health Study (CHS)
  • n=824
  • NPS in 43%, with 29% having ‘clinically significant’ symptoms
  • Thus, NPS may be a precursor to subsequent cognitive decline and may therefore have a predictive role
Relation of NPS to progression of neurodegenerative stages in PD

Braak stages in PD

Neurodegeneration of brainstem nuclei

- neuropsychiatric (e.g. raphe nuclei and locus coeruleus)
- cognitive (e.g. nucleus basalis of Meynert)
Non-motor symptoms correspond to the orderly progression of LB pathology (Braak stages)

- olfactory bulb
- Dorsal motor nucleus of the vagus nerve (DMNX)
- Rostral along brain stem
  - Locus coerulceus
  - Dorsal raphe nucleus
- Midbrain substantia nigra
NPS and stages of cognitive impairment in PD:

*Intact cognition in PD*

  - >50% positive in at least one NPI domain vs HC
    - Of these, nearly 35% ≥2 NPI items;
    - most prevalent NPS: apathy and depression.
Neuropsychiatric Symptoms in Parkinson's Disease with Mild Cognitive Impairment and Dementia

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Manchester Study of Neuropsychiatric Symptoms of PD-MCI

(Leroi, Pantula, et al 2012)

• Aim:
  • (1) compare the frequency, magnitude of NPS in PD, PD-MCI and PDD
  • (2) explore the relationship of NPS with motor and cognitive profiles

• Study design:
  • cross sectional, case control

• Participants (n=127):
  • PD-NC (normal cognition): n=54
  • PD-MCI (Litvan 2012): n=48
  • PDD (Emre 2007): n=25
Frequency & severity of NPI symptoms in PD, PDMCI and PDD

(Leroi & Pantula 2011)
Proportion of clinically significant NPI domains (≥ 4)

- **PD NC vs PD MCI**: differed only on apathy
- **PDD vs PD NC and PD MCI**: more frequently on delusions, hallucinations, aggression, depression, irritability, aberrant motor

*P*=0.001 for PD-NC vs. PD-MCI; *P*=0.01 for PD-MCI vs. PDD; *P*=0.001 for PD-NC vs. PDD
Correlation between apathy, depression and anxiety and cognitive scores in PD NC and PD MCI (*rho*)

<table>
<thead>
<tr>
<th>Cognitive Test</th>
<th>Apathy</th>
<th>Depression</th>
<th>Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global (MMSE total)</td>
<td>-0.33*</td>
<td>-0.21*</td>
<td>-0.07</td>
</tr>
<tr>
<td>Verbal fluency (FAS)</td>
<td>-0.23*</td>
<td>-0.20*</td>
<td>0.18</td>
</tr>
<tr>
<td>Attention (Trials B-A)</td>
<td>0.23*</td>
<td>-0.19</td>
<td>-0.12</td>
</tr>
<tr>
<td>Memory (word list recall)</td>
<td>-0.21*</td>
<td>-0.14</td>
<td>0.00</td>
</tr>
<tr>
<td>Executive function (WCST)</td>
<td>-0.27*</td>
<td>-0.016</td>
<td>0.08</td>
</tr>
<tr>
<td>Working memory (n-back)</td>
<td>-0.29*</td>
<td>-0.23*</td>
<td>0.08</td>
</tr>
</tbody>
</table>
Apathy is the *only* NPS that distinguishes PD from MCI-PD
Apathy and Emotional Blunting in Parkinson’s Disease

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3South Essex Partnership University NHS Trust, UK
4University of Leeds, UK
5CollTeK & Memory Centre, University of Nice Sophia, Antipolis, France

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Abstract

Background: Apathy is common in Parkinson’s disease (PD), even in the absence of dementia. In general, apathy has three key dimensions: emotional blunting, diminished initiative, and diminished interest. The objective of this study was to evaluate the clinical profile and impact of apathy in PD with particular emphasis on emotional blunting.

Methods: 91 PD participants free of dementia were evaluated with the Apathy Inventory (IA). Those with clinically significant apathy (n=32) were compared to those without apathy (n=59) on clinical variables, level of disability, quality of life and caregiver burden. Within the apathy group, a subsequent comparison of those with apathy and emotional blunting (EB+; n=22) to those with apathy but no blunting (EB−; n=10) was undertaken.

Results: In PD, compared to those without apathy, apathy sufferers were significantly more depressed, and had more impaired executive function, quality of life, and greater disability and caregiver burden. The EB+ group had worse quality of life and greater caregiver burden compared to the EB− group despite the EB− group being associated with older age and more advanced disease.

Conclusion: In PD without dementia, apathy with emotional blunting has a greater adverse impact on the affected person and their caregiver than apathy without emotional blunting.
Apathy in PD:
\[ n=91 \text{ without dementia} \]

**Emotional blunting** domain

Each rated on the Apathy Inventory (IA; Robert et al 2007)

Within the apathy group:
Compared emotional blunting (EB+; \( n=22 \)) vs no blunting (EB-; \( n=10 \))
Apathy: emotional blunting
(indicates worse function)

<table>
<thead>
<tr>
<th>Impact variables:</th>
<th>EB-</th>
<th>EB+</th>
<th>( t )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disability (UPDRS-ADL)</td>
<td>13.20 (5.30)</td>
<td>17.44 (4.06)</td>
<td>3.92</td>
<td>&lt;0.001 (-6.34; -2.07)</td>
</tr>
<tr>
<td>Disability (Schwab and England)</td>
<td>81.43 (9.76)</td>
<td>68.28 (14.73)</td>
<td>5.12</td>
<td>&lt;0.001 (8.13; 18.46)</td>
</tr>
<tr>
<td>Quality of life (PDQ-8)</td>
<td>16.67 (10.07)</td>
<td>25.13 (10.07)</td>
<td>3.76</td>
<td>&lt;0.001 (-12.70; -3.92)</td>
</tr>
<tr>
<td>Zarit Burden Inventory</td>
<td>18.06 (12.77)</td>
<td>29.03 (14.43)</td>
<td>3.45</td>
<td>&lt;0.001 (-17.32; -4.62)</td>
</tr>
</tbody>
</table>

**Table 2:** Comparison of means (SD) and proportions of demographic and clinical characteristics of the apathy and the non-aphathy PD groups.
Most commonly reported neuropsychiatric symptoms
(in **over 20%** of each group, excluding sleep & appetite)

<table>
<thead>
<tr>
<th></th>
<th>PD NC</th>
<th>PD MCI</th>
<th>PDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>In order of frequency</td>
<td>Anxiety Depression</td>
<td>Anxiety Depression Apathy</td>
<td>Anxiety Depression Apathy Agress/agitat Hallucinations Delusions Aberrant motor</td>
</tr>
</tbody>
</table>

- Anxiety
- Depression
- Apathy
- Aggress/agitat
- Hallucinations
- Delusions
- Aberrant motor
Non-motor symptoms in advanced PD

- **Depression:**
  - Greater frequency and severity
  - Many patients are on antidepressants
  - Less tolerant of dopamine agonists so cannot use them for their antidepressant effect
  - May contribute to cognitive impairment

- **Psychosis:**
  - Confusional episodes, visual hallucinations, frank delusions (misidentifications, morbid jealousy)
  - Key factor in institutionalisation

- **Anxiety:**
  - May be related to motor fluctuations (freezing/ “off” stages)

- **Apathy:**
  - Loss of initiative, loss of interest, emotional blunting
  - Very common
  - Significant impact on QOL, carer burden, disability
  - May have physical implications due to inactivity
  - Limits ability to participate in activity programs
Impact of NPS associated with cognitive impairment in PD
The negative impact of NPS associated with cognitive impairment in PD

• Most PwPD live in their own homes with family members who provide care
  • household chores
  • physical help
  • personal needs
• As PD progresses, caregivers take on more tasks....supporting decision-making and managing finances.
• As a result, the burden of care increases significantly as cognition declines
Predictors of Carer burden

- Parkinson’s UK Member’s cross-sectional survey (2007):
  - n=14089 caregivers’ self-completion survey
    - financial strain
    - caregiver health burden
Manchester Couples’ Study of Carer Burden in PD with behavioural disturbances

(Leroi et al 2012)

- n=71 people with PD and their non-professional carers
- normal cognition
- Zarit Burden Inventory
- Compared 3 groups:
  - ICD
  - Apathy
  - Neither

Results:
- presence of any behavioural disturbances caused significant burden to caregivers
- Apathy resulted in the greatest burden of care, followed by ICD
- Controlled for depression and motor function
Manchester Study on QoL and Disability in PD with cognitive impairment
Leroi et al. (2012)

• Impact of cognitive stage in PD on QoL
• Parkinson’s Disease Questionnaire (PDQ-8)
  • 8 dimensions: mobility; activities of daily living (ADL); emotional well-being; stigma; communication; social support; cognitions; and bodily discomforts.
• PD-NC (n=54)
• PDD (n=25)
• PD-MCI (n=48)
Impact of cognitive impairment in PD
(Leroi and Pantula 2011)
Management of NPS and cognitive impairment/dementia in PD
## Cognitive enhancers in PDD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil (Aricept)</td>
<td>5mg daily → 10mg daily</td>
<td>Leroi et al, 2004 (RCT); Ravina et al 2005 (RCT); EDON Trial</td>
</tr>
<tr>
<td>Rivastigmine (Exelon)</td>
<td>1.5 mg daily/BD → 6mg BD; Patch once daily</td>
<td>Emre et al, 2004 (RCT)*</td>
</tr>
<tr>
<td>Galantamine XL (Reminyl)</td>
<td>8mg daily → 24 mg daily</td>
<td>Aarsland et al, 2004</td>
</tr>
<tr>
<td>Memantine (Ebixa)</td>
<td>5mg daily → 10mg BD</td>
<td>Leroi 2010 Aarsland 2011 Emre 2011</td>
</tr>
</tbody>
</table>
MUSTARDD study in mild PDD

- No long-term data on efficacy of ACHEI in PDD
- 2 year study
- Donepezil vs placebo
- UK sites

- May give guidance about when to discontinue therapy
Memantine improves goal attainment and reduces caregiver burden in PDD

$p=0.007^{**}$  
$p=.04^*$

- % GAS improved
- Carer burden
## Side Effects of All Cholinesterase Inhibitors in PDD

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Concern in PDD</th>
<th>Anti-PD drug side effects</th>
<th>Weight loss; mechanical difficulties eating</th>
<th>Sleep fragmentation; insomnia; nocturia; EDS</th>
<th>Prodrome to hallucinations; REM problems</th>
<th>Common in PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>*GI (nausea, vomiting, diarrhea)</td>
<td></td>
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<tr>
<td>Anorexia</td>
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<tr>
<td>Insomnia</td>
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<tr>
<td>Nightmares</td>
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<tr>
<td>Hypersalivation</td>
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</table>
## Side Effects of Cholinesterase Inhibitors in PDD

<table>
<thead>
<tr>
<th>Concern in PDD</th>
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<tbody>
<tr>
<td>↓ motor function/tremor*</td>
</tr>
<tr>
<td>? Ach ↑ DA↓</td>
</tr>
<tr>
<td>Leg cramps</td>
</tr>
<tr>
<td>wearing off; dystonia</td>
</tr>
<tr>
<td>Orthostatic hypotension/falls</td>
</tr>
<tr>
<td>gait ↓; ANS failure; impaired righting reflex</td>
</tr>
<tr>
<td>Agitation</td>
</tr>
<tr>
<td>YES</td>
</tr>
<tr>
<td>Paradoxial psychosis</td>
</tr>
<tr>
<td>PD-related psychosis</td>
</tr>
</tbody>
</table>
ABSTRACT

Parkinson’s disease (PD) is known to cause neuropsychiatric symptoms (NPS). It has been established that the more advanced the motor stage of PD is, the more frequent and severe the NPS may be. However, the relationship between NPS and stage of cognitive decline is less well understood. This is important because the majority of people with PD will experience some degree of cognitive decline during the course of their disease, and there is a high risk of developing dementia (PDD). In non-PD populations there is a strong association between NPS and cognitive impairment and the same association may apply in PD. Consequently, the aim of this article is to provide a brief overview of NPS in PD from the perspective of stage of cognitive decline. We highlight studies that have demonstrated the increasing prevalence and severity of NPS with increasing cognitive impairment in PD. We point out the importance of apathy as a possible precursor to PDD. We also describe the negative impact of NPS and cognitive impairment on caregiver distress and quality of life. Finally, we have summarised findings from key studies of cognitive enhancers in PDD which have examined the effect of these treatments on NPS.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Author</th>
<th>Study Design</th>
<th>Neuropsychiatric Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Ishikawa et al.⁴</td>
<td>Donepezil in PDD; prospective open-label exploratory study over 12 weeks; n=9</td>
<td>NPI (primary outcome) showed improvements in predominantly aberrant motor behaviour, anxiety and hallucinations by 1.7, 1.6, and 1.3 points, respectively</td>
</tr>
<tr>
<td>Aarsland et al.³⁵</td>
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<td>Donepezil vs placebo in PD with cognitive impairment; randomised double-blind crossover study over 10 weeks; n=14</td>
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<td>Leroi et al.³⁶</td>
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<td>Donepezil vs placebo in PD with cognitive impairment; randomised double-blind study over 18 weeks in 2 centres; n=16</td>
<td>NPI (secondary outcome) total score dropped 40.9% in the donepezil group compared to 26.4% reduction in final visit in the placebo group</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Aarsland et al.³⁸</td>
<td>Galantamine in PDD; multi-centre open-label study over 8 weeks; n=13</td>
<td>NPI (primary outcome) used to assess hallucination; 7 out of 9 (78%) improved from baseline</td>
</tr>
<tr>
<td></td>
<td>Grace et al.³⁷</td>
<td>Galantamine vs placebo in PD without dementia; randomised double-blind study over 16 weeks; n=69</td>
<td>NPI (secondary outcome) showed improvements by 1.14 points but no significant difference between groups</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Emre et al.³³</td>
<td>Rivastigmine vs placebo in PD with cognitive impairment; randomised multi-centre double-blind study over 24 weeks; n=541</td>
<td>NPI (secondary outcome) showed significant improvement in treatment group (p=0.02), with over 40% having at least 30% improvement in NPI scores</td>
</tr>
<tr>
<td>Memantine</td>
<td>Leroi et al.⁴¹</td>
<td>Memantine vs placebo in PDD; randomised double-blind study over 22 weeks; n=25</td>
<td>NPI (secondary outcome) showed no significant difference between groups (p=0.70)</td>
</tr>
<tr>
<td></td>
<td>Aarsland et al.⁴²</td>
<td>Memantine vs placebo in PDD; randomised multi-centre study over 24 weeks; n=72</td>
<td>NPI (secondary outcome) showed no significant difference between groups</td>
</tr>
<tr>
<td></td>
<td>Emre⁴³</td>
<td>Memantine vs placebo in PDD and DLB; randomised double-blind multicentre study; n=199</td>
<td>NPI (secondary outcome) showed no significant difference between groups at any point in PDD contrary to LBD: delusions (p=0.02), hallucinations (p=0.02), and sleep behaviour (p=0.04)</td>
</tr>
</tbody>
</table>
Table 3: Response of neuropsychiatric symptoms to cognitive enhancers in key Parkinson’s disease dementia trials.

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<td>Donepezil vs placebo in PD with cognitive impairment; randomised double-blind study over 18 weeks in 2 centres; n=16</td>
<td>NPI (secondary outcome) total score dropped 29% in the donepezil group compared to 26.4% reduction in first visit in the placebo group.</td>
<td></td>
</tr>
<tr>
<td>Galantamine</td>
<td>Aarsland et al.³⁸</td>
<td>Galantamine in PDD; multi-centre open-label study over 8 weeks; n=13</td>
<td>NPI (primary outcome) used to assess hallucinations; 7 out of 9 (78%) improved from baseline.</td>
</tr>
<tr>
<td>Grace et al.³⁷</td>
<td>Galantamine vs placebo in PD without dementia; randomised double-blind study over 16 weeks; n=69</td>
<td>NPI (secondary outcome) showed improvements of 14 points but no significant difference between groups.</td>
<td></td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Emre et al.³³</td>
<td>Rivastigmine vs placebo in PD with cognitive impairment; randomised multi-centre double-blind study over 24 weeks; n=541</td>
<td>NPI (secondary outcome) showed significant improvement in treatment group (p=0.02), with over 40% having at least 30% improvement in NPI scores.</td>
</tr>
<tr>
<td>Memantine</td>
<td>Leroi et al.⁴¹</td>
<td>Memantine vs placebo in PDD; randomised double-blind study over 22 weeks; n=25</td>
<td>NPI (secondary outcome) showed no significant difference between groups (p=0.70).</td>
</tr>
<tr>
<td>Aarsland et al.⁴²</td>
<td>Memantine vs placebo in PDD; randomised multi-centre study over 24 weeks; n=72</td>
<td>NPI (secondary outcome) showed no significant difference between groups at any point in PDD contrary to LBD: delusions (p=0.02), hallucinations (p=0.02), and sleep behaviour (p=0.04).</td>
<td></td>
</tr>
<tr>
<td>Emre⁴³</td>
<td>Memantine vs placebo in PDD and DLB; randomised double-blind multicentre study; n=199</td>
<td>NPI (secondary outcome) showed no significant difference between groups at any point in PDD contrary to LBD: delusions (p=0.02), hallucinations (p=0.02), and sleep behaviour (p=0.04).</td>
<td></td>
</tr>
</tbody>
</table>
Treatment of PDD: Non Pharmacological interventions

• Principles of basic dementia care
  • Education and financial planning (wills, POA)
  • Driving
  • Caregiver support, support groups, respite
  • Memory cueing techniques (OT)
  • Safety and ease in the home setting (OT)
  • Monitoring medical condition
  • Improving sensory deprivation
## Non-pharmacological therapies for cognitive enhancement in dementias not related to Parkinson’s disease

<table>
<thead>
<tr>
<th>Therapy type</th>
<th>Target group</th>
<th>Method</th>
<th>Objective/outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive stimulation therapy (CS)</td>
<td>Mild to moderate dementia</td>
<td>Active stimulation/engagement</td>
<td>Cognitive and psychosocial function</td>
</tr>
<tr>
<td>Cognitive rehabilitation therapy (CR)</td>
<td>Cognitive impairment due to Alzheimer disease, stroke or traumatic brain injury</td>
<td>Metacognitive strategies</td>
<td>Daily living skills to improve self-efficiency and coping</td>
</tr>
<tr>
<td>Cognitive training (“brain training”)</td>
<td>Mild cognitive impairment due to various causes</td>
<td>Stimulating active (e.g. puzzle solving, crosswords) and passive (e.g. listening to poetry or watching a play) mental activities</td>
<td>Enhances cognitive performance and effective against functional deterioration.</td>
</tr>
<tr>
<td>Reminiscence therapy (RT)</td>
<td>Mild memory impairment</td>
<td>Two types that are effective: Integrative and instrumental.</td>
<td>Recall of past experiences and provide a sense of continuity of events in their lives.</td>
</tr>
<tr>
<td>Reality orientation (RO)</td>
<td>Memory loss with Impaired orientation to time, place or person.</td>
<td>Reminds individuals facts about themselves and their environment</td>
<td>Reduce distress by improving orientation about surrounding and situation.</td>
</tr>
<tr>
<td>Validation therapy (VT)</td>
<td>Moderate dementia</td>
<td>Accepts, acknowledges and respects opinions and beliefs through non-confrontational listening.</td>
<td>Improvement in interaction and reduction in negative emotions.</td>
</tr>
<tr>
<td>Behavioural approaches and memory retraining programme</td>
<td>Moderate to severe dementia</td>
<td>Aims to use strategies aimed at eliminating challenging behavior; based on conditioning and learning theory principles</td>
<td>Optimizes retained abilities</td>
</tr>
</tbody>
</table>
## Selected un-controlled non-pharmacological studies designed to enhance cognition in PD

<table>
<thead>
<tr>
<th>Therapy type</th>
<th>Study design/purpose</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Training (CT)</td>
<td>Feasibility &amp; acceptance [42]; (n=14)</td>
<td>CT in PD was feasible and acceptable</td>
<td>Small sample size</td>
</tr>
<tr>
<td></td>
<td>Computer based; to improve motor executive function [43]; (n=30)</td>
<td>Improvement in sequence initiation</td>
<td>Small sample size; effects of CT in unimpaired people not described</td>
</tr>
<tr>
<td>Exercise and physical therapies</td>
<td>Case study of aerobic exercise[44]; (n=1)</td>
<td>Improved dual task combined cognitive and motor performance</td>
<td>Non-comparative</td>
</tr>
<tr>
<td></td>
<td>Case series of passive exercise[45]; (n=19)</td>
<td>Improved executive function</td>
<td>Level of cognitive impairment not specified</td>
</tr>
<tr>
<td>Combined therapies</td>
<td>Motor and cognitive training in early PD with MCI [46]; (n=20)</td>
<td>Improved abstract reasoning, visuospatial ability and verbal fluency</td>
<td>Intervention not well explained</td>
</tr>
<tr>
<td></td>
<td>Case study of virtual reality gait training [47]; (n=20)</td>
<td>Improved gait, dual task performance, and executive function</td>
<td>Small sample size; non-comparative</td>
</tr>
<tr>
<td>Brain stimulation</td>
<td>Case series of one session of tDCS [48]; (n=18)</td>
<td>Improved working memory task</td>
<td>One treatment session only</td>
</tr>
<tr>
<td></td>
<td>Case series of one session of rTMS [49]; (n=10)</td>
<td>No improvement in cognitive function or motor features</td>
<td>One treatment session only</td>
</tr>
<tr>
<td></td>
<td>Case series of one session of sequential rTMS [50]; (n=10)</td>
<td>All components of Stroop test improved</td>
<td>One treatment session only</td>
</tr>
</tbody>
</table>
## Controlled non-pharm studies designed to enhance cognition in PD

<table>
<thead>
<tr>
<th>Therapy type</th>
<th>Study design/purpose</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Training</td>
<td>Effect of daily Sudoku [51]; (n=20)</td>
<td>Improved executive functions (inhibition/set shifting, logical reasoning)</td>
<td>Small sample size; no active control; assessors not blind</td>
</tr>
<tr>
<td></td>
<td>RCT of ten sessions of CT [52]; (n=26)</td>
<td>Improved executive function in the executive training group</td>
<td>Small sample size; cognitive status was not stated; follow up only during the stay; assessors not blinded</td>
</tr>
<tr>
<td></td>
<td>Blind multicentre RCT of the efficacy of CT [53]; (n=28)</td>
<td>Improved various domains</td>
<td>Small sample size</td>
</tr>
<tr>
<td>Exercise and physical therapies</td>
<td>Multimodal exercise program on executive function [54]; (n=10)</td>
<td>Improved executive function</td>
<td>Control group was not an active control but derived from a previous study</td>
</tr>
<tr>
<td></td>
<td>Controlled trial of exercise [55]; (n=28)</td>
<td>Improved verbal fluency, spatial working memory and possibly semantic fluency.</td>
<td>Small sample size; Non blinded assessments</td>
</tr>
<tr>
<td>Combined therapies</td>
<td>Parallel, single blind RCT of Nintendo Wii™ cognitive stimulation and balance exercises [56]; (n=32)</td>
<td>No added benefit of Wii™</td>
<td>Wii™cogn task unclear</td>
</tr>
<tr>
<td></td>
<td>Large complex RCT with three interventions [57]; (n=222)</td>
<td>All groups showed improvement on ADASCOG</td>
<td>No other active or inactive control group</td>
</tr>
<tr>
<td>Brain stimulation</td>
<td>RCT of rTMS with placebo and sham rTMS with Fluoxetine [58]; (n=25)</td>
<td>Improved cognition in both groups, independent of improvement in mood.</td>
<td>Small sample size; unclear randomization method; no placebo control</td>
</tr>
<tr>
<td></td>
<td>A placebo controlled double blind RCT of rTMS was used</td>
<td>Improved depression with treatment; accuracy of Stroop test improved</td>
<td>Small sample size</td>
</tr>
</tbody>
</table>
Exercise Therapy for Cognition in PD
(Murray 2014)

• Exercise promotes neuronal proliferation, neuroprotection & neurogenesis in basal ganglia (MPTP mice models)
• PRISM report of 14 studies
• Includes 6 pre-clinical studies
• Various interventions
• Non-randomised designs of trials
• Some ‘weak’ evidence – positive effect of aerobic resistance and dance exercise on executive function
Cognitive Stimulation Therapy in Parkinson’s Disease: INVEST Study

Psychosocial Therapy to Benefit Patients with Parkinson’s-related Dementia: A Feasibility and Exploratory Pilot Study.
Thank you.