Not Just a Movement Disorder:
Cognitive Dysfunction in Parkinson’s Disease

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Approved/Unapproved Uses

This talk describes use of medications for purposes that are not approved by the FDA for the treatment of cognitive dysfunction in Parkinson’s disease.
Cognitive Dysfunction in PD

I. Prevalence

II. Pathophysiology

III. Clinical Characteristics

IV. Treatment
Parkinson’s Disease

- Affects ~ 1 million Americans
  ~ 0.3% general population
  ~ 1% of the population over age 50
  ~ 2.5% > 70 years; ~ 4% > 80 years

- All races, ethnicities

- Affects Men > Women

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace; the senses and intellects being uninjured.

James Parkinson
1755 - 1828
Cognitive Disturbances in PD

“I’m right there in the room, and no one even acknowledges me.”

*The New Yorker, 9/18/06*
When I woke up at 7:45 this morning my priority was to finish making a card for a sick friend and then work on finishing my Christmas cards from last seasons... But FIRST I needed to get my shower and get dressed.

Before I got out of bed though I wanted to go through a pile of catalogs and yesterday’s mail. At 9:30 I was interrupted by a phone call for information that made me come downstairs. And I never went back up to get ready for the day.”
Case Example - # 2

76 year old MWM, retired computer programmer and technology teacher
10-year history of PD

• Progressive cognitive changes X 4 years
  • Progressive comprehension deficits and trouble formulating ideas x 2 years
  • No behavioral difficulties, retained manners
  • More passive, less likely to initiate activities or engage in conversations
  • Independent with physical ADLs-dressing, eating
  • Impaired instrumental ADLs

• Executive and Memory Dysfunction
  • Forgets details and needs prompts to follow through on things.
  • Follows the calendar carefully, but wife maintains all scheduling and helps him plan things in advance.
  • Has great difficulty learning new things or following a series of instructions and has to ask for help, such as task on the computer, worse with complex attentional, strategic or processing tasks, e.g., can call a cab, but forgets details, can’t manage finances or track his schedule

• Bradyphrenia
  • All tasks take a long time. He persists but can’t process all elements
  • Says things intended to be funny, but timing is off
Prevalence of Cognitive Dysfunction in PD
Defining cognitive dysfunction in PD

• No consistent or validated definitions of PD-CD
  – Assessment methods affect diagnosis and diagnostic rates
    • Cognitive tests versus clinical exam
  – Archetype for cognitive dysfunction is Alzheimer’s disease
    • ‘Alzheimerization’ of terms

• Dx schemes based on prevailing memory deficits
  – e.g., DSM-IV dementia, Mild Cognitive Impairment (MCI)
    Cognitive impairment/Not Dementia (CIND)
Types of Cognitive Impairment

- Selective Cognitive Impairment
- Global intellectual deterioration (dementia)
Selective Cognitive Impairment

- Evident early in PD

- Affects >90% of patients

- Disruption of selective higher-order intellectual processes (‘Cognition’)
  - Executive
  - Memory (Procedural, explicit)
  - Visuospatial
  - Attentional deficits

## Selective Cognitive Impairments - Newly diagnosed PD

<table>
<thead>
<tr>
<th>No. of tests impaired</th>
<th>Patients with Parkinson disease, %</th>
<th>Healthy controls, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>37.4</td>
<td>68.6</td>
</tr>
<tr>
<td>1</td>
<td>24.3</td>
<td>20.0</td>
</tr>
<tr>
<td>2</td>
<td>14.8</td>
<td>7.1</td>
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<tr>
<td>3</td>
<td>8.7</td>
<td>2.9</td>
</tr>
<tr>
<td>4</td>
<td>3.5</td>
<td>1.4</td>
</tr>
<tr>
<td>≥5</td>
<td>11.3</td>
<td>~24%</td>
</tr>
</tbody>
</table>

### Table 2: Number of impaired tests and percentages of Parkinson disease patients and healthy controls demonstrating impairments

- **Age**: 66.2 (10.1) 63.7 (7.3)
- **Education**: 11.7 (2.4) 12.4 (2.2)
- **N**: 115 70
Cognitive Profile of Cognitively Impaired Subgroup

N=27 PD
Defining Mild Cognitive Impairment in Parkinson’s Disease

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A. PD Subjects

- 62% cognitively normal (PD-CogNL)
- 21% PD-MCI
- 17% dementia (PD-D)

B. PD-MCI

- 39% single domain - frontal/executive
- 22% multiple domains - without amnestic deficit
- 11% multiple domains - with amnestic deficit
- 6% single domain - language deficit
- 22% single domain - amnestic deficit

PD-CogNL (N = 53)  PD-MCI (N = 18)  PD-D (N = 15)

Caviness et al., 2007
### Cognitive Complaints in PD
% Yes Responses by Group
(Caviness et al., 2007)

<table>
<thead>
<tr>
<th>Complaint</th>
<th>PD-CogNL (N = 53)</th>
<th>PD-MCI (N = 18)</th>
<th>PD-D (N = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive cognitive decline</td>
<td>57%</td>
<td>67%</td>
<td>80%</td>
</tr>
<tr>
<td>Forgetfulness</td>
<td>53%</td>
<td>72%</td>
<td>87%</td>
</tr>
<tr>
<td>Disorientation</td>
<td>19%</td>
<td>22%</td>
<td>80%</td>
</tr>
<tr>
<td>Personality change</td>
<td>21%</td>
<td>33%</td>
<td>47%</td>
</tr>
<tr>
<td>Decreased work performance</td>
<td>38%</td>
<td>50%</td>
<td>87%</td>
</tr>
<tr>
<td>Getting lost</td>
<td>11%</td>
<td>6%</td>
<td>27%</td>
</tr>
<tr>
<td>Word finding deficits</td>
<td>75%</td>
<td>89%</td>
<td>93%</td>
</tr>
<tr>
<td>Withdrawal from activity</td>
<td>57%</td>
<td>50%</td>
<td>87%</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>21%</td>
<td>39%</td>
<td>60%</td>
</tr>
<tr>
<td>Delusions</td>
<td>2% **(p&lt;.01)</td>
<td>28%</td>
<td>67%</td>
</tr>
</tbody>
</table>
Range of Cognitive Dysfunction in PD patients with ‘normal’ MMSE (≥24)

Mean (SD) Age=58.7 (12.8); Duration PD=7.5 (6.0)
Awareness of Cognitive Dysfunction in PD patients with ‘normal’ MMSE (≥24)

- No Dx (n=43)
- Changes (n=49)
- Symptoms (n=38)
- Cog DO NOS (n=57)
- Dementia (n=13)
Dementia in PD (PD-D)

• No consistent definition
  – Global cognitive impairment
  – >r Memory, executive, attentional, language deficits
  – ‘Transition’ to dementia --- Dependence of others

• Epidemiology
  – 20-40% cross-sectional prevalence
  – Varied course ~10 years to onset
  – Overlap with dementia with Lewy bodies

• Risk factors
  – AGE!
  – More severe parkinsonism - PIGD Subtype
  – Mild cognitive impairment at baseline

Cumulative Prevalence of Dementia (Prospective Studies)

- Rajput 1987, Canada
  - 21.1% after 5 years

- Mayeux 1990, New York
  - 16% after 5 years, 65% after age 85

- Hughes 2000, Leeds
  - 38% cumulative prevalence over 5.5 years

  - 29% after ~3.6 years, increased risk with age, PD severity

- Aarsland 2003, Norway
  - 3-fold increased prevalence over 8 years (from 26% to 78%)
Cognitive Dysfunction: Longitudinal Course

- **Sydney Multi-center Study**
  - **15-year Follow-up**
    - $n=149$; 52 surviving ($71 \pm 8$; 55-86 years)
    - Most disabling long term symptoms
      - Cognitive decline - 84%
      - Dementia - 48%
      - “MCI” – 36%
      - Hallucinations – 50%
      - Depression – 39%
  - **20-year follow-up**
    - $n=149$, 36 surviving, 83% with dementia

Pathophysiology of Cognitive Dysfunction
Neuropathology of Parkinson’s Disease

A Dopamine Deficiency Disease

- Substantia Nigra pars compacta Neuronal Loss
- Substantia Nigra Lewy bodies
Role of Functional Dopaminergic Circuits

Dopaminergic Systems
Mesostriatal
Mesolimbic
Mesocortical

Cortico-striatal-thalamic circuits

Dopaminergic Circuits
Motor function
Reinforcement
Higher order cognitive processes

Figure 1 - Frontal-striatal connections.
DL: dorsolateral; DM: dorsomedial; VL: ventrolateral; VA: ventroanterior; VM: ventromedial.
Dopamine (DA) systems in the human brain

- Cognition
- Movement
- ADHD
- Reward & Motivation
- LIMBIC
- Drug Abuse

**THE DOPAMINERGIC PATHWAYS**

A. Substantia nigra
B. Ventral tegmental area
C. To amygdala
D. Tubero-infundibular DA system
E. Nucleus accumbens (ventral striatum)
F. To the striatum (caudate nucleus, putamen and globus pallidus)
G. Frontal cortex
Non-dopaminergic Neuropathology

- Neuronal loss
  - Locus Coeruleus – NE
  - Midbrain raphe – 5HT
  - Nucleus basalis – Ach

Alzheimer-type Changes

- Lewy Body Pathology
Glutamateric overactivity in PD

Dopaminergic depletion leads to overactive glutamatergic activity from the Subthalamic nucleus
Everyday Clinical Features of Cognitive Dysfunction
Executive Function

Mental processes involved in the elaboration and control of cognitive and behavioral tasks and responses to novel or challenging situations, e.g., complex social and purposeful, goal-directed behaviors

Pillon et al., Curr Op Neurology 2003; 16 (S2): S17-S22; Dubois 2004; Dubois et al., 2007
Domains of Executive Function

- Working memory
- Planning
- Decision-making/Problem-solving
- Coordinating
- Set-shifting
- Sequencing
- Processing and Monitoring relevant information
- Generativity
- Abstract reasoning
- Attention/distractibility

Pillon et al., Curr Op Neurology 2003; 16 (S2): S17-S22; Dubois 2004; Dubois et al., 2007
Processes Accomplished by Executive Functions

- Select, maintain, and monitor information to be processed
- Actively retrieve information
- Shift mental set
- To find a rule
- Self-direct, plan ahead, and follow-through on a series of actions
- Resist cognitive interference
- Share attentional resources

Pillon et al., Curr Op Neurology 2003; 16 (S2): S17-S22; Dubois 2004; Dubois et al., 2007
Executive Dysfunction in PD

- Precise nature of executive impairment not defined
- Set-shifting deficits are salient
- Executive dysfunction is context dependent
  - Psychometric tests may not reveal deficits
  - Dysfunction becomes apparent with greater task demands
  - Natural unstructured settings reveal disordered behavior

Pillon et al., Curr Op Neurology 2003; 16 (S2): S17-S22; Dubois 2004; Dubois et al., 2007
Effects of Executive Dysfunction on Everyday Function

“Let’s have tea!” Study
- Influence of task and attentional demands during an everyday functional activity contribute to clinical symptoms and gait disturbances

Study
- 20 mild to moderate PD, 10 Controls
- 4 Tasks
  - Simple walking: Walk to kitchen
  - Dual-motor: Walk and carry tray
  - Dual-cognitive: Walk and recall a memory
  - Multiple motor-cognitive task: Walk, carry tray, and recall a memory

Results
- Increased task complexity $\rightarrow$ gait speed
- Gait speed $\alpha$ cognition, depression, physical fatigue, balance
- Dual Motor and Dual cognitive $\alpha$ fatigue and cognition
- Multi-task: $\alpha$ Fatigue

Practical Implications of “Let’s have tea” Study

• Supports theory of attention as a capacity model
  – When resources are shared, performance declines at a critical level of task complexity

• Illustrates interactions between mood, motor, and cognitive functions in PD
  – Mental challenges result in fatigue, distress, worse motor function
  – Treatments of mood, motor, and cognitive dysfunction need to take into account the influence of related variables
Other Examples of Executive Difficulties

- **Response inhibition/selective attention**
  - Ability to ignore distractions and respond to environment

- **Set-shifting/Flexibility**
  - Shifting from one category of information or specific goal to another
  - Response monitoring and adjustments to environmental changes
  - Paying bills, taking part in group conversations, driving

- **Strategic planning**
  - Requires formulation of series of choices
  - Deficits influence motivational level—can be confused with bradykinesia
    - Overlaps with apathy
  - Self-initiation of (complex) tasks (cleaning, walking)
    - ‘Freezing’ or getting overwhelmed when faced with complex task
    - Need for ‘intellectual scaffolding’

Yogeve-Seligman et al. 2008
Attentional Disturbances

• Attention comprises a number of processes related to how one becomes receptive to stimuli and processes incoming salient stimuli (internal or external)
• Context dependent
• Several types
  – Focused/selective, sustained, divided, alternating

PD
• ---Ability to divide attention is important in everyday life
• Affects gait/balance
Bradyphrenia (Slowed Mental Processing)

- Ability to process and respond to information

- Affects
  - Speech (latency)
  - Other processes
    - Problem-solving
    - Comprehension of information
Memory Disturbances

- Problems with recall—Remembering information that has already been learned
  - Deficits in search strategies

- Ability to benefit from cues (Recognition Memory)

- May need repetition to learn new information
Language Dysfunction

- Word-finding deficits
- Naming and mis-naming deficits later
- Decreased comprehension, especially with complex ideas
- Less spontaneous speech
- Simplified speech
Visual-spatial Dysfunction

- Trouble perceiving, processing, discriminating and acting on visual information in the environment

- Affects
  - Navigation in the home
  - Estimation of distances when reaching
  - Visual perceptions/misperceptions (illusions)
PD-Dementia: Clinical Features

- Bradyphrenia
  - Memory retrieval deficits
    - Poor recall with good recognition (versus ‘rapid forgetting’ of AD)
    - Later deficient encoding
    - Milder remote memory
  - Executive dysfunction
    - Impairments on complex attentional, strategic, or processing tasks
    - Evident when patients have to spontaneously or independently initiate and maintain information
    - Diminished spontaneity

- No or limited aphasia, agnosia, apraxia, even late in course
  - Slowed/inefficient word production
  - Less pronounced and later naming deficits
  - Grossly intact comprehension
‘Red Flags’ of Cognitive Dysfunction

- Fatigue
- Depression
- Apathy
- Bradyphrenia
- Gait changes
- Medication non-compliance
- Psychosis/Hallucinosis

Yogevo-Seligmann 2008; Amboni, 2008
Treatment of Cognitive Dysfunction
Education: Recognition & Diagnosis

- Prompts evaluation for alternative causes
- Clarifies the problem(s)
- Provides basis for interventions
  - Appreciation of relationships between motor and non-motor issues
  - Education/Support to patients and caregivers
  - Adaptive strategies
  - Non-pharmacological treatments
  - Medication treatments
Treatment of Other Conditions

- Exclude Delirium
- Depression
- Anxiety
- Sleep Disturbances
- Psychosis
- Caregiver Strain
Cognitive Training

- Addresses executive functions
  - Maintenance and inhibition of attention
  - Flexibility in thinking
  - Planning

- Requires specific training
  - Short-term cognitive executive functioning training program
  - Most programs offer generic approach

Sammer G et al., J Neurol Sci, 2006
Pharmacological Targets of Treatment

- Discrete neuropsychological deficits
  - Executive dysfunction
  - Memory
- Neuroprotection
- Alzheimer /LB pathology
- Antidepressant/psychiatric pathology
- Discrete neurotransmitter dysfunction
  - Cholinesterase inhibitors
  - Noradrenergic reuptake inhibitors
  - Glutamatergic antagonists
Cholinesterase inhibitors

<table>
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<tr>
<th></th>
<th>Reversible</th>
<th>Noncompetitive</th>
<th>Acetylcholinesterase</th>
<th>Butyrocholinesterase</th>
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<tr>
<td>Tacrine</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Donepezil</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Rivastigmine</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Galantamine</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-; modulates nicotinic chol receptors</td>
</tr>
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</table>

FDA Indications
- Alzheimer’s disease
- Rivastigmine for Parkinson’s disease
NMDA Antagonists

- Amantadine (Symmetrel)
  - Tricyclic amine, NMDA-receptor antagonist
  - Improves long-term potentiation in hippocampal neurons
  - Blocks glutamate transmission (?Neuroprotective)
  - Used for treatment of early PD and for fluctuations
  - Postponement of cognitive impairment and dementia by 4 years (Inzelberg et al, 2006)
Association Between Amantadine and the Onset of Dementia in Parkinson’s Disease

Rivka Inzelberg, MD,1,2* Ubaldo Bonuccelli, MD,3 Edna Schechtman, PhD,4 Ala Miniowich, MD,5 Rosa Strugatsky, MD,1 Roberto Ceravolo, MD,3 Chiara Logi, MD,3 Carlo Rossi, MD,3 Colin Klein, MD,5 and J. Martin Rabey, MD5
Memantine for Treatment of PD-D

• Memantine
  – Noncompetitive NMDA antagonist
  – Blocks NMDA glutamate receptors
  – Noncompetitive 5HT3 antagonist
  – Noncompetitive nicotinic acetylcholine receptors
  – D2 Receptor agonist

• RPC trials of Memantine in PDD and DLB
  – Aarsland 2009, Marsh 2009, European trial
  – 24-week placebo-controlled trial, dose range 5-20 mg/day
  – No statistically significant side effects
  – Improved Clinical Global Impression Scores
  – Improvement on tests of attention, memory, fluency
  – Improved IADLs
Pharmacological Treatment of Executive Dysfunction

- **Modafanil** (**Provigil**)
  - Indicated for Daytime sleepiness, narcolepsy
  - Promotes wakefulness
  - Mechanism of action unclear, involves hypocretin, histamine, epinephrine, gamma-aminobutyric acid, and glutamate
  - Improved cognition and slowed response latency in ADHD adults (Turner DC 2004)
  - Treatment trials in PD for fatigue

- **NE modulation of attention**
  - Methylphenidate (MPH): inhibits catecholamine reuptake
    - Mixed results: Improved attention (Auriel et al, 2006), Improved choice reaction time with MPH alone (Camicoli et al. 2006)
  - Naphtoxazine (**NA α-1 agonist**)
    - Partial reversal of attentional deficits (Bedard MA et al., 1998)
Treatment of Executive Dysfunction

• Atomoxetine
  – Indicated for treatment of attention deficit disorder
  – NE Reuptake inhibitor
  – ? Procholinergic effects (Tzavara ET, 2006)
  – Improved inhibitory capacity (Stroop) in Adult ADHD
  – May help ED in PD (Marsh et al. 2009)
Cognitive Dysfunction in PD

- Prominent and disabling feature of PD
- Heterogeneous profile
- Prominent executive dysfunction
- Earlier stage deficits may not be evident on formal cognitive testing
- Involves multiple transmitter systems, neural networks
  - Dopaminergic and non-dopaminergic pathology
- Need for clinical trials addressing the spectrum of cognitive dysfunction
Cognitive Dysfunction

- Prominent and disabling feature of PD

- Heterogeneous profile with both selective and global impairments that impact daily functioning

- Prominent executive dysfunction

- Earlier stage deficits may not be evident on formal cognitive testing

- Involvement of multiple neurotransmitter systems
  - Dopaminergic deficit contributes to clinical features
  - Non-dopaminergic systems and Lewy Bodies also important

- Need for further investigations of potential treatments
Future Directions

• Dissection of the clinical heterogeneity of cognitive dysfunction via longitudinal follow-up, treatment response, genetic, and imaging studies

• Use of imaging and other biomarkers or phenotypes to evaluate or predict progression to dementia

• Facilitation of drug development
  – Targeted cognitive or neuropathological treatments
  – Inclusion of cognitive outcomes in studies evaluating treatments for motor and psychiatric deficits or neuroprotection