PD ExpertBriefing:

Fatigue, Sleep Disorders and Parkinson's Disease

Presented By:

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Butler Hospital
Department of Neurology
Alpert Medical School of Brown University

Will begin:
Tuesday, June 1, 2010
at 1:00 PM ET
Welcoming Remarks

Robin Elliott
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Parkinson’s Disease Foundation
Fatigue, Sleep Disorders and Parkinson's Disease

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Disclosures

• Drugs will be discussed with regard to unapproved uses
• Dr. Friedman has accepted money for lectures, consulting or research from: Glaxosmithkline; Ingelheim-Boehringer; Teva; Epivax; Cephalon; EMD Serono; Acadia Pharmaceuticals; Biogenidec
Parkinson's disease is defined by its motor features but includes non-motor signs and symptoms as well.
Non-Motor Features of Parkinson’s Disease

• Somatic
  – Autonomic (BP; GI; GU; cardiac)
    • Respiratory; rhinorrhea?
    • Sweating
  – Sensory (pain, impaired smell)
  – Skin (seborrheic dermatitis)

• Behavioral
“The clinical factors that showed the highest predictive values for worse health related quality of life were non-motor symptoms such as depression, sleep disorders and fatigue.”

Qin Z. et al. 2009
It is best categorized as a NEUROBEHAVIORAL Disorder
Its most devastating consequences are behavioral.
“For this is the great error of our day in the treatment of the human body, that physicians separate the soul from the body.”

Plato
## Behavioral

<table>
<thead>
<tr>
<th>Intrinsic</th>
<th>Iatrogenic</th>
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<tbody>
<tr>
<td>Depression</td>
<td>Hallucinosis</td>
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<tr>
<td>Apathy</td>
<td>Delirium</td>
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<td>Dementia</td>
<td>Psychosis</td>
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<td>Anxiety &amp; Inner tremor</td>
<td>Hypersexuality</td>
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<td>Fatigue</td>
<td>Mood Fluctuations</td>
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<td>Sleep</td>
<td>Impulse dyscontrol</td>
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<td>Personality</td>
<td>Sleep disorders</td>
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<td>Akathisia</td>
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*Behavioral symptoms can be categorized into intrinsic and iatrogenic.*
“I am a 74 year old man. I have had PD 3 years. I can live with PD (not great, but livable). But the fatigue is unbearable. As all my life I was full of superman energy, now I’m only good for about an hour or so at a time, and between the lightheaded and the fatigue I’m wasted. I take 1 ½ pills of C/L TID. I take 200 mg provigil and a bunch of pills like NADH. I exercise as best I can and follow eating rules. I’ve been told to go see a shrink and start on anti-depressants. I don’t think I am depressed. I’m retired. No wife or things to stress me out. I’ve been told fatigue is one of the three major problems of having PD. Most of the time I’ am horizontal. I was told you gave a talk on this problem.....”
Fatigue Definitions

Fatigue is a subjective experience meaning:

a. lassitude, overtiredness, lacking in energy
b. “Weariness from bodily or mental exertion”
Fatigue

Different types of fatigue

– Mental
– Hypovigilance-boredom
– Hypervigilance-excessive attention
– Emotional
– Cognitive
– Physical
Fatigue is Common

- It is a diagnostic symptom of anxiety and depression.
- It overlaps with apathy.
- Chronic fatigue is reported as “major problem” by 25% of consecutive patients in a primary care clinic. 75% reported having it > one year.
Fatigue is common in neurological disorders (and does not correlate with severity)

- Fatigue affects better recovered GBS patients more!
- Post stroke
- Post polio
- Myasthenia gravis
- Chronic headache
- Multiple sclerosis
- Chronic pain
Parkinson Fatigue Scale

1. My life is restricted by fatigue
2. I get tired more quickly than other people I know
3. Fatigue is one of my three worst sx
4. I have to rest during the day
5. I feel completely exhausted
6. Fatigue makes me reluctant to socialize
7. Because of fatigue it takes me longer to get things done
8. I have a feeling of “heaviness”
9. If I wasn’t so tired I could do more things
10. Everything I do is an effort
11. I lack energy for much of the time
12. I feel totally drained
13. Fatigue makes it difficult for me to cope with everyday activities
14. I feel tired even when I haven’t done anything
15. Because of fatigue I do less in my day than I would like
16. I get so tired I want to lie down wherever I am

Brown et al 2005
Fatigue is common in PD

- Van Hilten: 65 non-demented PD reported “excessive” fatigue in 31. No correlation to time of day. (1993)
- Van Hilten: “Frequent” daytime fatigue affected 43% of non-depressed, non-demented PD patients.
  - Half had fatigue before PD
  - 15% reported fatigue as worst PD symptom
  - 54% reported fatigue as equal to their other PD sx.
Fatigue is common in PD

• Consecutive, non demented PD:
  – 1/3 reported fatigue as **worst** symptom
  – 58% scored fatigue >4/7 as one of three worst symptoms
  – Correlated with depression
  – Mean score of FSS=4.6 (vs 4.8 by MS patients)

Friedman
Fatigue is common in PD

50% of PD patients suffered from fatigue in Norwegian study of NON demented, NON depressed PD patients (all PD patients in Rogaland identified, 91% participated=98 subjects).

Herlofson 2003

Swedish study of 948 subjects, fatigue was 6th most common symptom at presentation and 3rd (women) or 5th (men) at sampling, affecting 66% (women) and 65% (men)

Scott 2000
Fatigue is Common in PD

70 patients living near Duke University
- 40% reported fatigue
- Correlated with self assessed “poor health”
- 59% of “poor health” patients reported fatigue
- Fatigue increased during one year follow up
Fatigue is Common in PD

• Shulman: fatigue affected 40% of “selected,” non-demented PD; half rated fatigue as one of 3 most disabling sx; fatigue correlated with anxiety, not depression or motor dysfunction

• Abe: 26 selected subjects vs headache patients; no differences in fatigue or depression
Fatigue is Common in PD

1/3 of PD patients enrolling in ELLDOPA endorsed fatigue as a significant symptom (mild, untreated, significantly biased population) at entry.

Shiffito & PSG (2006)

Of 118 consecutive PD patients in Sweden 48% were fatigued (FACIT-F); 83% were worse during “off”; 32% had fatigue as a pre-motor sx;

Hagell et al JNNP 2008
A physiological study of fatigue in PD

Fact:
PD patients use more energy per activity (eg breathing) than normal controls

Hypothesis:
Fatigued PD patients were less efficient (used more energy) per unit task than non-fatigued PD patients.
Summary of Results (1)

• There is no difference in the patients’ severity of disease by either the Hoehn-Yahr or UPDRS

• Patients with fatigue perceive that their health is worse than patients without fatigue (SF-36 question)

• Patients with fatigue report less frequent participation in vigorous physical activity by both the “sweat” question and strenuous activity
  – Overall physical activity is similar between the groups
Summary of Results (2)

- Patients with fatigue take longer to complete the Up and Go test and walk a shorter distance on the 6 minute walk test.
  - This could reflect lower fitness and physical activity levels
    - Someone who exercises more is likely to do better than someone who does not exercise
  - Patients who did less well could have more severe disease
    - This is unlikely due to similar ratings on other rating scales
Natural history of fatigue in PD

• Only two studies published:
  – Fatigue scores worsened over 9 years
  – **All** severely fatigued patients at baseline remained fatigued 9 years later
  – Only 2/13 who were severely fatigued at follow up had not been fatigued earlier

• Fatigue starts early, does not resolve, does not respond to treatment.

Friedman
Long term outcome in PD

• 8 year prospective study of all PD patients in Rogaland, Norway; 35.7% fatigued at baseline
• 42.9% at 4 years
• 55.7% at 8 years
  – 56% had sustained fatigue; 44% were intermittent
  – Fatigue associated with motor severity, depression, EDS, PIGD variant

Alves et al 2005
Fatigue Treatment

ELLDOPA trial

Small but statistically significant response to L-Dopa (no data on amantadine; no “anecdotal” evidence); patients not selected to have fatigue;
Elldopa Conclusions

• Fatigue is frequent at any stage of PD.

• Progression of disease in early PD is not tightly associated with changes in fatigue.

• Dopaminergic therapy slows worsening of fatigue in early PD.

• Better understanding of the pathogenesis of fatigue is necessary to develop appropriate therapeutic intervention.
Treating fatigue in PD

Okun et al

• Testosterone replacement: 15 subjects in each arm of DBPCT:
  • No change in multidimensional fatigue inventory

• Two trials of modafinil, without success
Treating fatigue in PD

Daniel et al: 15 subjects treated open label with dopamine agonists for three months compared to 15 healthy, age matched controls. Epworth sleepiness scores increased on agonists but no change in the multidimensional fatigue inventory or the fatigue index for a motor task.

Mendonca et al treated 36 subjects, DBPCT, and found Methylphenidate 10 mg tid effective.

Movement Disorder 2007
“Sx of depression and anxiety are the main predictors of fatigue in PD. Furthermore, fatigue is associated with lack of motivation, parkinsonism and pain.”

Hagell and Brundin 2008
Pathophysiology of fatigue in PD

Increased energy expenditure?

Ia. Resting energy expenditure higher in PD than healthy age matched controls

Ib. Fatigue not generally associated with motor impairment

II. Oxygen cost of breathing increased in PD

III. NO differences found on tests of energy utilization between fatigued and non-fatigued PD patients

IV. Expectation-performance mismatch
Future directions for PD-fatigue research

I. Pathophysiology: defining different mechanisms
   A. Separating primary and secondary fatigue
   B. Brain metabolic studies
   C. Endocrine studies (hypothalamus-pit; testosterone)
   D. Further physiological and neuropsych studies (eg better understanding of amotivation)

II. Treatment
   A. Stimulants; exercise programs; counseling +/- exercise; antidepressants
Sleep

- Insomnia
- Poorly maintained sleep
- Early morning awakening
- Sleep apnea
- Restless legs
- Sleep talking
- Inverted sleep cycle
- Vivid dreams
- REM sleep behavior disorder
Sleep Problems

• Insomnia
• Sleep maintenance
• Early awakening
• Sleep apnea
• Restless legs
• Akathisia
• Inverted sleep cycles

• Vivid dreams
• Sleep talking
• REM sleep disorder
• Other medical problems
Insomnia

- Getting comfortable
- Pain
- “off”
- Tremor
- Daytime naps
- Excessively early bedtime
- Anxiety/depression
Sleep Maintenance

• Nocturia and difficulty falling back to sleep
• Wearing off of sleep meds
• Tremor
• Inability to fall asleep
• Sweat attacks
Early Morning Awakening

- Depression
- Daytime naps
- Early bedtime
- Anxiety
Inverted Sleep Cycle

• Increasing naps during the day leading to reduced need to sleep at night: vicious cycle
REM Sleep Behavior Disorder

- Recognized only in late 1980’s
- REM sleep = Rapid Eye Movement sleep: dream sleep
  - Mammals are paralyzed during dream sleep
  - Why this is good
  - RBD patients not paralyzed during some dreams
Questions and Answers
Closing Remarks

Robin Elliott
Executive Director
Parkinson’s Disease Foundation
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**Tuesday, June 8, 2010**

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