Current Approaches to Parkinson's Disease

WEBCONFERENCE WORKBOOK

AN EDUCATIONAL SERVICE OF cmecorner.com

JOINTLY SPONSORED BY AKH INC. AND MCM EDUCATION.
BEFORE THE PROGRAM, PLEASE COMPLETE THE PRE-PROGRAM SURVEY ONLINE AT:  
www.CMEcorner.com/12PDWC/PRE

If you are unable to complete the survey online, please print and complete this page before the program begins.

Multiple participants: If your site has multiple participants, please be sure each person separately accesses the link or individually completes the printed survey.

Please mail any printed surveys to: MCM Education, 54 Friends Lane, Suite 125, Newtown, PA 18940; or FAX to: 267-364-0570.

Please indicate your profession:  
_ Physician _ Physician assistant _ Nurse practitioner _ Nurse _ Other (please specify)_________

Please indicate your speciality:  
_ General neurology _ Movement disorders _ Geriatrics _ Other (please specify)_________

Date of Webconference:_____________________________

Pre-Program Survey

Please select the response that most closely matches your opinion:

For questions 1-3 please refer to the following case:
A 36-year-old male patient comes to you with complaint of a constant “shakiness” (rest tremor) in his left hand, fatigue, an unsteady feeling when standing, and cramping in his legs. He has hypertension, which has been poorly managed and has led to minor renal insufficiency.

1. Which two symptoms described by the patient are considered cardinal Parkinson’s disease features?
   A. Rest tremor and fatigue
   B. Rest tremor and cramps
   C. Rest tremor and postural instability
   D. Postural instability and cramps
   E. Fatigue and postural instability

2. Results from his DaTscan will provide you with enough information to make the final diagnosis of PD in this patient.
   Strongly Agree
   6       5      4     3     2        1
   Strongly Disagree

3. Based on his history, which agent would you be least likely to prescribe to this patient?
   A. Amantadine
   B. Anticholinergic
   C. Dopamine agonist
   D. Levodopa
   E. MAO-B inhibitor

4. A patient with PD, taking levodopa, benztropine, pramipexole, and rasagiline, starts suffering from psychotic symptoms. After ruling out other medical causes, which PD medication should be the first you modify or discontinue?
   A. Levodopa
   B. Benztropine
   C. Pramipexole
   D. Rasagiline

PLEASE DO NOT COMPLETE THE NEXT PAGE UNTIL AFTER THE PROGRAM.
AFTER THE PROGRAM, PLEASE COMPLETE THE POST-PROGRAM SURVEY ONLINE AT: www.CMEcorner.com/12PDWC/TEST.

If you are unable to complete the survey online, please print and complete this page after the program.

Multiple participants: If your site has multiple participants, please be sure each person separately accesses the link or individually completes the printed survey.

Please mail any printed surveys to: MCM Education, 54 Friends Lane, Suite 125, Newtown, PA 18940; or FAX to: 267-364-0570.

Please indicate your profession:  
_ Physician  _ Physician assistant  _ Nurse practitioner  _ Nurse  _ Other (please specify)_________

Please indicate your speciality:  
_ General neurology  _ Movement disorders  _ Geriatrics  _ Other (please specify)_________

Date of Webconference: _______________________

---

Post-Program Survey

Please select the response that most closely matches your opinion:

For questions 1-3 please refer to the following case:

A 36-year-old male patient comes to you with complaint of a constant “shakiness” (rest tremor) in his left hand, fatigue, an unsteady feeling when standing, and cramping in his legs. He has hypertension, which has been poorly managed and has led to minor renal insufficiency.

1. Which two symptoms described by the patient are considered cardinal Parkinson’s disease features?
   A. Rest tremor and fatigue  
   B. Rest tremor and cramps  
   C. Rest tremor and postural instability

2. Results from his DaTscan will provide you with enough information to make the final diagnosis of PD in this patient.
   Strongly Agree  
   6  5  4  3  2  1  Strongly Disagree

3. Based on his history, which agent would you be least likely to prescribe to this patient?
   A. Amantadine  
   B. Anticholinergic  
   C. Dopamine agonist  
   D. Levodopa  
   E. MAO-B inhibitor

4. A patient with PD, taking levodopa, benztropine, pramipexole, and rasagiline, starts suffering from psychotic symptoms. After ruling out other medical causes, which PD medication should be the first you modify or discontinue?
   A. Levodopa  
   B. Benztropine  
   C. Pramipexole  
   D. Rasagiline

5. Based on your participation in this program, please list 1 change you intend to make to your PD care practices.

_____________________________________________________________________________________________________

Thank you.
Current Approaches to Parkinson’s Disease
Release date: June 11, 2012

Login
- Log in into the webconference via the link provided in the reminder email.
- It is recommended that participants log in 10-15 minutes prior to the webconference start time.

Ask a Question
- Pose a question for the post-presentation Q&A session at any time during the presentation.
- Just type your question into the “Ask a Question” text area in the bottom of your console or click on the Q&A widget, then click the submit button.

Slides
- The slides will advance automatically throughout the presentation.

Technical Problems
- If you are experiencing problems with the presentation, please press the F5 button on your keyboard to refresh your console, or close and re-launch the presentation.
- You can also visit the Webconference Help Guide, by clicking on the “Help” widget below the slide window.

Important: System Setup & Compatibility Check
- Test the computer that you plan to use and make sure you have the minimum technical requirements to attend this webconference. Allow sufficient time prior to the webconference for this test.

Program Description

An estimated 1 million adults in the United States have Parkinson’s disease (PD). Neurologists and other clinicians specializing in movement disorders play a vital role in improving outcomes for patients with PD. However, much uncertainty about optimal treatment approaches and variability in clinical practice remains.

Wide variability in clinical practice presents an opportunity for clinicians to improve competency in providing the highest quality of care according to treatment guidelines and the latest clinical evidence. Clinicians managing patients with PD need to be familiar with current evidence regarding new therapies and strategic approaches available for the treatment of the different stages of PD. The goal of this continuing medical education activity is to improve competency and build additional skills among neurologists and other clinicians regarding best practices in the diagnosis and treatment of PD, ultimately improving outcomes for patients with PD.

Jointly sponsored by AKH Inc. and MCM Education.

Supported by an educational grant from Teva Neuroscience, Inc., a subsidiary of Teva Pharmaceutical Industries Ltd.

©2012, MCM Education. All rights reserved. This publication is designed for use with a webconference program. None of the contents may be reproduced in any form without prior written permission from the publisher. The opinions expressed in this publication and webconference are those of the speakers and do not necessarily reflect the opinions or recommendations of their affiliated institutions, the publisher, AKH Inc., or Teva Neuroscience, Inc. Any medications or other diagnostic or treatment procedures discussed by the program speakers should not be utilized by clinicians without evaluation of their patients’ conditions and possible contraindications or risks or without a review of any applicable manufacturer’s product information and comparison with the recommendations of other authorities.
HUBERT H. FERNANDEZ, MD, FAAN
Professor of Medicine (Neurology) • Cleveland Clinic Lerner College of Medicine
Head, Section of Movement Disorders • Center for Neurological Restoration
Cleveland Clinic, Neurological Institute • Cleveland, OH

Dr. Fernandez is Head of the Program for Movement Disorders in the Center for Neurological Restoration at Cleveland Clinic in Cleveland, OH. He received both his BS degree in biology and his MD degree in the Philippines. He completed his internship in internal medicine at University of Pennsylvania/Pennsylvania Hospital in Philadelphia, PA; his residency in neurology at Boston University Medical Center in Boston, MA; and his fellowship in movement disorders at Brown University/Memorial Hospital in Pawtucket, RI.

Dr. Fernandez is an internationally recognized expert in movement disorders who has been voted one of the Best Doctors in America by his peers. After completing his medical training in 1999, he joined the faculty of Brown University School of Medicine as Assistant Professor in the Department of Clinical Neurosciences and served as Associate Director of the Movement Disorders Unit at Memorial Hospital and Neurological Director of its Functional Neurosurgical Program. In 2003, Dr Fernandez relocated to the University of Florida, where he eventually became Director of the Clinical Research Unit for Neurological and Psychiatric Disorders, Vice Chair of Academic Affairs, and Professor of Neurology prior to joining Cleveland Clinic. An active and productive researcher, he has initiated or participated in over 50 clinical trials. He has authored numerous articles, abstracts, books and book chapters, and has served on the editorial board of Movement Disorders and is currently an editorial board member of the American Journal of Clinical Neurology, European Neurological Journal, and Clinical Neuropharmacology.

Dr. Fernandez is also an active member of the Parkinson Study Group (PSG), Dystonia Study Group (DSG), and Huntington Study Group (HSG), American Academy of Neurology (AAN) and its Movement Disorders Section, Movement Disorders Society (MDS), Florida Society of Neurology (FSN) and the World Neurology Foundation (WNFo). He is a fellow of the AAN, and a member of the American Neurological Association (ANA). He is currently elected as a councilor for the AAN Movement Disorders Section, executive committee member of the PSG and DSG; and is also an executive board member of the WNFo. He has served as president of the FSN, and is the current co-medical editor of the MDS website.

CHERYL H. WATERS, MD, FRCPC
Albert B. and Judith L. Glickman Professor • Division of Movement Disorders
Columbia University • New York, NY

Dr. Waters is the Albert B. and Judith L. Glickman Professor of Clinical Neurology at Columbia University College of Physicians & Surgeons in New York, NY. She is also Chief of Clinical Practice and Services in the Division of Movement Disorders at Columbia University. She holds a Bachelor’s degree and a Master’s degree in pharmacology from the University of Toronto, where she studied dopamine receptor function with Philip Seeman. She completed medical school at University of Toronto. She completed her internship at University of Chicago and residencies in Internal Medicine and Neurology at the University of Toronto. In addition, she completed a Neurology and Clinical Pharmacology Research Fellowship at the Addiction Research Foundation and Playfair Neuroscience Unit in Toronto.

She is a Fellow of the Royal College of Physicians (FRCP) in Canada and a Fellow of the American College of Physicians (FACP), as well as a member of the ANA and the Movement Disorders Section of the AAN. She has been involved in research on the genetics of Parkinson’s disease and has been an investigator in numerous studies involving a variety of new medical and surgical treatments for Parkinson’s disease. She has authored numerous articles and book chapters on Parkinson’s disease and is also an author of the book Diagnosis and Management of Parkinson’s Disease, now in its 6th edition.
Disclosures
It is the policy of AKH Inc. to ensure independence, balance, objectivity, scientific rigor, and integrity in all of its continuing education activities. The faculty must disclose to the participants any significant relationships with commercial interests whose products or devices may be mentioned in the activity or with the commercial supporter of this continuing education activity. Identified conflict of interest is resolved by AKH prior to accreditation of the activity. AKH and MCM Education planners and reviewers have no relevant financial relationships to disclose.

Dr. Fernandez discloses that he has received research support from Abbott Laboratories, Inc.; ACADIA Pharmaceuticals Inc.; Biotie Therapies; EMD Serono, Inc.; IPSEN; Merz Pharma; Novartis Pharmaceuticals; Schering-Plough Corporation, and Synosia Therapeutics (Acquired by Biotie Therapies in 2011); Teva Pharmaceuticals; honoraria from Allergan, Inc.; IPSEN; Merz Pharma; Teva Neuroscience, Inc., a subsidiary of Teva Pharmaceutical Industries Ltd.; US WorldMeds; and is a consultant/steering committee member with Abbott Laboratories, Inc., EMD Serono, IPSEN; Merz Pharma; and United BioSource Corporation.

Dr. Waters discloses that she has received honoraria from Teva Pharmaceuticals, and has received research funding from Abbott Laboratories, Inc., Schering-Plough Corporation, and Synosia Therapeutics (Acquired by Biotie Therapies in 2011).

This educational activity may contain discussion of published and/or investigational uses of pharmaceutical agents. Some uses of these agents may not have been approved by the FDA. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

Credit Statements
Physicians: This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of AKH Inc. and MCM Education. AKH Inc. is accredited by the ACCME to provide continuing medical education for physicians.

AKH Inc. designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses: AKH Inc. is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s COA.

AKH Inc. designates this educational activity for 1 contact hour (0.1 CEU). Accreditation applies solely to educational activities and does not imply approval or endorsement of any commercial product by the ANCC-COA.

The release date of this activity is June 11, 2012

Participants must successfully complete the post-test with a grade of 70% or higher and submit an evaluation to receive credit.

Target Audience
This program has been developed for movement disorder specialists, neurologists, neurological nurses, gerontologists, advanced practice nurses, nurse practitioners, and other health care professionals involved or interested in PD diagnosis and management.
Learning Objectives
Upon completion of this educational activity, the participant should be able to:

1. Identify early features of Parkinson’s disease (PD) to expedite diagnosis of PD.
2. Develop customized treatment plans for PD patients based on unique phases and clinical manifestations of PD.
3. Discuss the clinical differences between MAO-B inhibitors and other classes of pharmaceutical agents that may impact therapeutic decisions for individual patients.
4. Review ongoing trials for PD and their potential to improve motor function, mental health, and cognition in patients with PD.

Abbreviations
The following abbreviations are mentioned in this workbook.

3-OMD  3-O-methyl-dopa
AAN    American Academy of Neurology
COMT   catechol-o-methyltransferase
DA     dopamine agonist
DaTscan dopamine transporters scan
DBS    deep brain stimulation
GABA   gamma-aminobutyric acid
GI     gastrointestinal
HAM-D  Hamilton Depression Scale
ICD    impulse control disorder
MADRS  Montgomery–Åsberg Depression Rating Scale
MAO-B  monoamine oxidase B
PD     Parkinson’s disease
SAD-PD Study of Antidepressants in Parkinson’s Disease
SSRI   selective serotonin reuptake inhibitor
UPDRS  Unified Parkinson’s Disease Rating Scale
## Generic/Brand Glossary

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand/Alternative Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>Symmetrel</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Elavil, Endep, Vanatrip</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>Apokyn</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Parlodel, Cycloset</td>
</tr>
<tr>
<td>Carbidopa</td>
<td>Parcopa, Stalevo</td>
</tr>
<tr>
<td>Carbidopa/Levodopa</td>
<td>Sinemet, Sinemet CR</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Celexa</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Klonopin</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Clozaril, FazaClo</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Norpramin, Pertofrane</td>
</tr>
<tr>
<td>Domperidone</td>
<td>Motilium, Motillium, Motinorm, Costi</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Aricept</td>
</tr>
<tr>
<td>Entacapone</td>
<td>Comtan, Stalevo (also contains carbidopa &amp; levodopa)</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>Florinef</td>
</tr>
<tr>
<td>Isradipine</td>
<td>Dynacirc</td>
</tr>
<tr>
<td>Levodopa</td>
<td>Parcopa, Sinemet, Sinemet CR, Stalevo</td>
</tr>
<tr>
<td>Memantine</td>
<td>Namenda</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Ritalin, Concerta, Metadate, Methylin</td>
</tr>
<tr>
<td>Midodrine</td>
<td>Amatine, ProAmatine, Gutron</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Pamelor, Aventyl</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Paxil, Paxil CR, Pexeva</td>
</tr>
<tr>
<td>Pergolide</td>
<td>Permax, Pergotoliderived</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>MiraLAX, Dulcolax</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>Mirapex, Mirapexin, Sifrol</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>Mestinon</td>
</tr>
<tr>
<td>Rasagiline</td>
<td>Azilect</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Exelon</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>Requip, Requip XL</td>
</tr>
<tr>
<td>Selegilene</td>
<td>Deprenyl, Eldepryl, Zelapar</td>
</tr>
<tr>
<td>Sildenafil citrate</td>
<td>Viagra</td>
</tr>
<tr>
<td>Tolcapone</td>
<td>Tasmar</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Effexor</td>
</tr>
</tbody>
</table>
**Parkinson's Disease (PD) Epidemiology**

- Uncommon before age 50 years
- Annual incidence (all ages): 8.6 to 19.0/100,000
- Incidence increases dramatically with age: approximately 100/100,000 over age 70 years
- Prevalence in individuals older than 65 years: approximately 1%
- More common in men


**With Time, The Pathology of PD Spreads Throughout the Brain**

**Braak’s staging of Parkinson’s disease pathology**

co, coeruleus-subcoeruleus complex; dm, dorsal motor nucleus of the glossopharyngeal and vagal nerves; fc, first-order sensory association areas, premotor areas, as well as primary sensory and motor fields; hc, high-order sensory association areas and prefrontal fields; mc, anteromedial temporal mesocortex; sn, substantia nigra

Motor Features of PD

Cardinal features
• Rest tremor
• Rigidity
• Bradykinesia
• Postural instability

Other motor features
• Masked face
• Shuffling gait
• Freezing
• Micrographia
• Dystonia
• Cramps

Non-Motor Features of PD

• Autonomic
  – Constipation
  – Hyperhidrosis
  – Urinary dysfunction
  – Sexual dysfunction
  – Sialorrhea

• Psychiatric disorders
  – Depression/Anxiety
  – Apathy
  – Fatigue

• Sleep disorders
  – Insomnia
  – REM behavior disorder

• Cognitive
  – Dementia
  – Psychosis

Differential Diagnosis of PD

Idiopathic Parkinson's Disease
Essential Tremor
Progressive Supranuclear Palsy
Multi-System Atrophy
Secondary Parkinson Plus
Other
Alzheimer's Disease
Lewy Body Disease
Corticobasal Degeneration
Vascular
Drugs
Toxins
Encephalitis
Other

Clinical Features that May Suggest a Diagnosis Other than PD

- Poor response to adequate dosages of levodopa
- Early onset of postural instability
- Axial more than appendicular rigidity
- Early dementia
- Supranuclear gaze palsy
- Profound autonomic dysfunction
- Significant limb dystonia prior to levodopa exposure


Dopamine Transport Imaging (DaTscan™)

- Normal Abnormal
  - Neurodegenerative parkinsonism (ALL);
  - Essential tremor;
  - Drug-induced parkinsonism;
  - Vascular parkinsonism;
  - Psychogenic;

Dopamine transport imaging differentiates between parkinsonian disorders with and without dopamine deficiency

Treatment Goals

- Slowing disease progression
- Controlling symptoms
- Preserving quality of life
**Agents Recently or Currently Being Tested for Disease-Modifying Properties**

**No**
- Coenzyme Q10
- Pramipexole

**Results Pending**
- Creatine
- Inosine
- Isradipine
- Exercise

**Maybe**
- Rasagiline


©Massachusetts Medical Society. Used with permission.

**Can Exercise Slow PD Progression?**

Exercise Therapy Is Effective in Improving Activities of Daily Living


**Sites of Action of PD Drugs**

Adapted from www.wemove.org
Considerations in the Initial Management of PD

- Control of disability
- Favorable side-effect profile
- Optimal long-term strategy
- Cost

Case Example 1

- A 37-year-old male presents to your office with tremor of right hand for 4 to 5 years.
- He also has decreased manual dexterity on right and right foot cramping.
- He has a family history that is positive for essential tremor.
- His past medical history is unremarkable.

Case Example 1 (Cont'd)

- Examination reveals increased tone bilaterally, right greater than left; a rest tremor on the right; and bradykinesia in some tasks on the right.
- Right arm swing is depressed while walking.
- MRI normal, DaTscan-decreased uptake in the corpus striatum, especially on the left side.

How would you treat this patient?
Levodopa Clearly Beneficial as a Treatment of PD

Change in total unified PD rating scale by dose of levodopa


© Massachusetts Medical Society. Used with permission.

Levodopa Associated With Risk of Motor Complications

- Dyskinesia
  - Peak dose
  - End of dose
- Motor fluctuations
  - End-of-dose wearing off
  - Unpredictable "on-off"
  - "Yo-yo-ing"

Time from Initiation of Therapy (years)


Occurrence of Dyskinesia: Initial Dopamine Agonist Therapy


Impulse Control Disorder (ICD) in PD

Results from a multi-center study of 3000 patients

- ICDs were identified in 13.6% of PD patients overall:
  - 17.1% of patients taking a dopamine agonist (DA) alone
  - 6.9% of patients on levodopa, and not taking a DA
- Types of ICDs
  - 5.7% compulsive buying
  - 5.0% problem/pathologic gambling
  - 4.3% binge eating disorder
  - 3.5% compulsive sexual behavior


MAO-B Inhibitors for Early PD

- Indications: monotherapy in early PD; add on to levodopa
- Available dosage: 1 mg tablet daily
- Benefits: mild symptomatic improvement; well tolerated
- Side effects: minimal; potential drug interactions

Symptomatic treatment effect of rasagiline on total UPDRS at 6 months

MAO-B Inhibitors for Early PD

- Indications: monotherapy in early PD; add on to levodopa
- Available dosage: 1 mg tablet daily
- Benefits: mild symptomatic improvement; well tolerated
- Side effects: minimal; potential drug interactions

Symptomatic treatment effect of rasagiline on total UPDRS at 6 months


UPDRS: Unified Parkinson’s Disease Rating Scale

Treatment-Emergent Adverse Events With Rasagiline Monotherapy*

AAN Practice Guidelines for Treatment of Early PD

- When symptomatic therapy is required:
  - MAO-B inhibitors may be used.
  - Either dopamine agonists or levodopa may be used when dopaminergic therapy is required.
    - Levodopa provides better immediate symptomatic relief.
    - Agonists have lower risk of motor complications, particularly dyskinesias.
    - Agonists may carry a higher side effect profile.


Advanced Parkinson’s Disease

Issues in Advanced PD

- Reduced quality of life
- Functional impairment
- Higher risk of depression and cognitive impairment
- Higher risk for comorbidities
- Increased medical expenses
- Caregiver burden and risk of early nursing home placement

Problems in Advanced PD

- Motor
- Neuropsychiatric
- Autonomic

Motor Problems

- Fluctuations
- Dyskinesias
- Freezing of gait
- Falls

Causes of Falls

- Postural instability
- Freezing
- Dyskinesia
- Hypotension
- Other neurological problems
- Environmental
Schematic of Possible Changes in Clinical Effect in Patients as PD Progresses

Definition of Terms

- "On" state – relatively good overall function and mobility corresponding to the medication working
- "Off" state – relatively poor overall function and mobility corresponding to the medication not working
- Dyskinesias – involuntary, nontremor movements
- Troublesome dyskinesias – may be painful, impair balance, or are excessive to the point of causing impairment in coordination or general function

Treatment of Dyskinesia

Peak dose or end of dose

Treatment options include:
- Amantadine
- Clozapine (rarely used)
- Experimental therapy
- Deep Brain Stimulation (DBS)
Amantadine

- **Mechanism:** NMDA receptor antagonist, dopamine releasing agent
- **Indications:** Early PD, dyskinesias, fatigue
- **Benefits:** Mild symptomatic benefit, effective for dyskinesias
- **Side effects:** Leg swelling, livedo reticularis, neuropsychiatric, interacts with anticholinergics

<table>
<thead>
<tr>
<th></th>
<th>Amantadine*</th>
<th>Placebo*</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dyskinesia</td>
<td>22.0 (13.2)</td>
<td>29.0 (12.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Maximal dyskinesia</td>
<td>5.2 (2.6)</td>
<td>6.3 (2.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>UPDRS IVa dyskinesia</td>
<td>3.2 (1.6)</td>
<td>4.3 (1.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>UPDRS III motor off</td>
<td>38.4 (14.8)</td>
<td>41.7 (13.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>UPDRS III motor on</td>
<td>22.3 (12.1)</td>
<td>23.4 (9.0)</td>
<td>0.44 NS</td>
</tr>
</tbody>
</table>


Case Example 2

- A 65-year-old female with PD for 4 years is taking carbidopa/levodopa 25/100 QID.
- She is experiencing regular and predictable wearing off of the effect, 1½ hours prior to each dose.
- With this wearing off she gets painful foot dystonia and shortness of breath, as well as a return of her PD symptoms.

How would you manage this patient?
Wearing Off

- Definition: Re-emergence of features of Parkinson’s disease at end of dose
- May be motor or non-motor

Examples of Other “Off” Symptoms

- Slowness of thinking
- Irritability
- Fatigue
- Drenching sweats
- Constipation
- Urinary urgency
- Abdominal bloating
- Pain

Case Example 2:
Wearing Off Treatment Options

- Extended-release levodopa
- More frequent dosing of levodopa
- COMT inhibitors: entacapone or tolcapone
- Dopamine agonists
- MAO-B inhibitors
- Anticholinergics
- Botulinum toxin injection
Agents Commonly Used in the Management of PD

- Levodopa
- COMT Inhibitors
  - Tolcapone
  - Entacapone
- MAO-B Inhibitors
  - Selegiline
  - Zydis selegiline
  - Rasagiline
- Dopamine Agonists
  - Pramipexole
  - Ropinirole
  - Bromocriptine
  - Apomorphine
  - Rotigotine
- Other
  - Amantadine
  - Anticholinergics

Non-Motor Features of PD

- Autonomic
  - Constipation
  - Hyperhidrosis
  - Urinary dysfunction
  - Sexual dysfunction
  - Sialorrhea
- Psychiatric disorders
  - Depression/anxiety
  - Apathy
  - Fatigue
- Sleep disorders
  - Insomnia
  - REM behavior disorder
- Cognitive
  - Dementia
  - Psychosis

Incidence of Non-Motor Symptoms of PD

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANS dysfunction*</td>
<td>90%</td>
</tr>
<tr>
<td>ANS dysfunction</td>
<td>80%</td>
</tr>
<tr>
<td>Dementia</td>
<td>78%</td>
</tr>
<tr>
<td>Sleep disorders *</td>
<td>66%</td>
</tr>
<tr>
<td>Urogenital dysfunction</td>
<td>57-83%</td>
</tr>
<tr>
<td>Gastrointestinal symptoms *</td>
<td>50-95%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>50%</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>50%</td>
</tr>
<tr>
<td>Depression *</td>
<td>40-50%</td>
</tr>
<tr>
<td>Pain</td>
<td>40-50%</td>
</tr>
<tr>
<td>Impulse control disorders</td>
<td>7.14%</td>
</tr>
</tbody>
</table>

*Identified as possible pre-motor symptoms

### AAN Recommendations for Treatment of Non-motor Symptoms of PD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Recommendation</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>Donepezil† should be considered</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Rivastigmine should be considered</td>
<td>B</td>
</tr>
<tr>
<td>Depression</td>
<td>Amitriptyline may be considered</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Insufficient evidence for other treatments</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Methylphenidate† may be considered</td>
<td>C</td>
</tr>
<tr>
<td>Erectile Dysfunction</td>
<td>Sildenafil citrate (50 mg) may be efficacious</td>
<td>C</td>
</tr>
<tr>
<td>Constipation</td>
<td>Polyethylene glycol may be considered</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Insufficient evidence to support/refute the use of botulinum toxin</td>
<td>U</td>
</tr>
</tbody>
</table>

*Evidence level was based on the AAN's classification scheme
†: Off-label use

---

### AAN Recommendations for Treatment of Non-motor Symptoms of PD (cont’d)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Recommendation</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostatic Hypotension</td>
<td>Insufficient evidence to support/refute treatment in PD</td>
<td>U</td>
</tr>
<tr>
<td>Urinary Incontinence</td>
<td>Insufficient evidence to support/refute treatment in PD</td>
<td>U</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Insufficient evidence to support/refute the treatment of anxiety with levodopa</td>
<td>U</td>
</tr>
<tr>
<td>REM Behavior Disorder (RBD)</td>
<td>Insufficient evidence to support/refute the treatment of RBD</td>
<td>U</td>
</tr>
<tr>
<td></td>
<td>Clonazepam† and melatonin are often used in the general population</td>
<td>U</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Insufficient evidence to support/refute the benefit of levodopa/emetropina on objective sleep parameters that are not affected by motor status</td>
<td>U</td>
</tr>
<tr>
<td></td>
<td>Insufficient evidence to support/refute the benefit of melatonin on the treatment of poor sleep quality</td>
<td>U</td>
</tr>
</tbody>
</table>

---

**Neuropsychiatric**

- Cognitive impairment and dementia
- Psychosis
- Compulsive disorders
- Depression
- Apathy
- Anxiety
Case Example 3

- A 75-year-old male retired physician comes to your office with PD and hallucinations.
- He is seeing deceased relatives in his house and accusing his wife of having an affair.
- His medications for PD include carbidopa/levodopa 25/100 QID.
- He continues to suffer from slowness and some disability.

How would you manage this patient?

Management of Psychotic Symptoms

- Rule out causes of mental status changes
  - Infection
  - Electrolyte imbalance
  - Medications
- Modify PD regimen
  - Reduce PD medications to minimum tolerable, yet effective dose
  - Discontinue, if necessary
- Evaluate risk/benefit of atypical antipsychotic

<table>
<thead>
<tr>
<th>Priority of modification</th>
<th>Anticholinergics</th>
<th>Amantadine</th>
<th>MAO-B inhibitors</th>
<th>Dopamine agonists</th>
<th>COMT inhibitors</th>
<th>Levodopa/carbidopa</th>
</tr>
</thead>
</table>
| Therapy for Cognitive Impairment in PD

- Cholinesterase inhibitors
- Memantine?
- Avoid anticholinergics
- Atypical neuroleptics
- Caregiver support

Case Example 3 (Cont'd)

- He is likely to have mild underlying dementia.
- He cannot lower his levodopa because he is quite impaired from the PD.
- His wife should get counseling.
- He should be treated with a cholinesterase inhibitor and an atypical antipsychotic (quetiapine and clozapine ONLY).

Depression

- Severe depression is unusual.
- Suicide is unusual.
- Weight loss, fatigue, insomnia can be due to PD or depression.
- Difficult to differentiate.

Treatment of Depression in PD

- Very few studies have been conducted.
- Most antidepressants work, but very few randomized clinical trials exist.
- Caution with the side effects of antidepressants (low blood pressure, dry mouth, confusion and sedation with the tricyclics, and increased tremor and impotence with the SSRIs).
Summary of PD Depression Double-Blind Studies

Citalopram or desipramine vs placebo\(^1\)

- Citalopram and desipramine both more effective than placebo, but significant short-term effect (at 14 days) only with desipramine

Nortriptyline or paroxetine CR vs placebo\(^2\)

- Nortriptyline was superior to placebo; paroxetine was not

---


---

SAD-PD: Efficacy

SAD-PD: Study of Antidepressants in PD

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Effect</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine vs Placebo</td>
<td>-6.2</td>
<td>(-9.7, -2.7)</td>
<td>.0007</td>
</tr>
<tr>
<td>Venlafaxine vs Placebo</td>
<td>-4.2</td>
<td>(-7.8, -0.6)</td>
<td>.02</td>
</tr>
</tbody>
</table>


---

Sleep Disorders

- Insomnia and sleep fragmentation
- Nightmares, hallucinations
- REM behavior disorder
- Sleep apnea
- Excess daytime sleepiness and sleep attacks
- Frequent urination
- PD immobility
**Autonomic Dysfunction**

- Constipation
- Urinary problems
- Sexual problems
- Orthostatic hypotension
- Sweating
- Pain
- Dysphagia
- Seborrhea

**Orthostatic Hypotension**

- Eliminate blood pressure medications.
- Try to stop PD medications (ie, dopamine agonists):
  - Fludrocortisone
  - Midodrine
  - Pyridostigmine
  - Domperidone (outside of US)

**Gastrointestinal (GI) Problems**

- Drooling
- Dysphagia
- Weight loss
- Gastroparesis
- Constipation
Other Autonomic Problems

Gastrointestinal (GI)
- Treat constipation
- No good treatments for gastroparesis

Genitourinary (GU)
- Urinary anticholinergics may cause confusion and hallucinations
- Alpha adrenergic blocking agents may cause hypotension

When to Consider DBS

<table>
<thead>
<tr>
<th>Early</th>
<th>Mild</th>
<th>Moderate</th>
<th>Advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild symptoms, no disability</td>
<td>Symptoms with some disability</td>
<td>Worsening symptoms</td>
</tr>
<tr>
<td></td>
<td>Does not yet need treatment</td>
<td>May need treatment but not yet levodopa</td>
<td>Need for levodopa ± adjunctive therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Beginning of complications from disease and treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increasing disability despite therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Complications of disease and treatment</td>
</tr>
</tbody>
</table>

TIME TO CONSIDER DBS

- Symptoms with some disability
- May need treatment but not yet levodopa
- Worsening symptoms
- Need for levodopa ± adjunctive therapy
- Beginning of complications from disease and treatment
- Increasing disability despite therapy
- Complications of disease and treatment

Best Medical Therapy (BMT) vs DBS

<table>
<thead>
<tr>
<th>Time</th>
<th>BMT change from baseline to 6 mos (n=134)</th>
<th>DBS change from baseline to 6 mos (n=121)</th>
<th>Mean difference between BMT vs DBS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>On without troublesome dyskinesia</td>
<td>0.1</td>
<td>4.6</td>
<td>-4.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>On with troublesome dyskinesia</td>
<td>-0.3</td>
<td>-2.6</td>
<td>2.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Off</td>
<td>0.1</td>
<td>-2.4</td>
<td>2.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Asleep</td>
<td>0.3</td>
<td>0.4</td>
<td>-0.1</td>
<td>.66</td>
</tr>
</tbody>
</table>

Adverse Events from DBS

40% of patients in study receiving DBS had a serious adverse event, including:

Up to 3 months following DBS
- Fall ($P = .02$)
- Pain ($P = .04$)
- Confusional state ($P < .001$)
- Speech disorder ($P = .004$)
- Headache ($P < .001$)

4-6 months following DBS
- Dystonia ($P = .02$)
- Fall ($P = .03$)


Future Directions in PD Treatment

• Treat or restore function in advanced disease.
• Treat dyskinesia.
• Prevent development of motor complications.
• Treat “nondopaminergic” features.
• Neuroprotective treatments?
Current Approaches to Parkinson’s Disease
CME/CE Post-Test

NOTE: Use this sheet only if you do not have internet access. Otherwise, go to www.CMEcorner.com/12PDWC/TEST.

Release date: June 11, 2012

Please circle the letter of the best answer to the following questions.

1. Which of the following pairs of PD non-motor features have the greatest reported incidence?
   A. ANS dysfunction/olfactory dysfunction
   B. Depression/olfactory dysfunction
   C. Depression/pain
   D. ANS dysfunction/depression

2. ______ has/have proven disease-modifying properties.
   A. Creatine
   B. Isradipine
   C. Pramipexole
   D. All of the above
   E. None of the above

3. After 5 years of levodopa use, approximately ____ of PD patients will have therapy-associated motor complications.
   A. 10%
   B. 20%
   C. 40%
   D. 60%

4. In comparing levodopa and dopamine agonists (DAs) for symptomatic use in PD, which of the following is true?
   A. DAs provide better immediate symptomatic relief.
   B. DAs have lower risk of motor complications, particularly dyskinesias.
   C. Levodopa may carry a higher side effect profile.
   D. Levodopa causes more impulse control disorders (ICDs) than the use of DAs.

5. In advanced PD, the shortest duration of response to levodopa can be:
   A. <2 hours
   B. 2-3 hours
   C. 4-6 hours

6. The incidence of levodopa-induced dyskinesias decreases with older age of onset of PD.
   A. True
   B. False

7. Which of the following atypical antipsychotics is appropriate to use in patients with PD?
   A. Risperidone
   B. Ziprasidone
   C. Clozapine

8. Even 4-6 months after deep brain stimulation (DBS), research shows that the risk for _____ still remains statistically significant.
   A. confusional state
   B. falls
   C. pain
   D. speech disorder

9. Based on the SAD-PD study, which of the following statements about treating depression in PD patients is true?
   A. Venlafaxine was found to be effective; paroxetine was not found to be effective.
   B. Paroxetine was found to be effective; venlafaxine was not found to be effective.
   C. Both venlafaxine and paroxetine were effective for depression PD patients.
   D. Neither venlafaxine nor paroxetine was effective for depression PD patients.

10. DaTscan results will be abnormal if patient has__________.
    A. drug-induced parkinsonism
    B. neurodegenerative parkinsonism
    C. psychogenic parkinsonism
    D. vascular parkinsonism
CONTINUING EDUCATION PROGRAM EVALUATION  
Current Approaches to Parkinson’s Disease  
Release Date: June 11, 2012  

Please complete this program evaluation online at:  www.CMEcorner.com/12PDWC/TEST 
Print and complete this evaluation only if you are NOT able to complete the online post-test and evaluation.

REQUIRED FOR CREDIT.  PLEASE PRINT CLEARLY.

<table>
<thead>
<tr>
<th>First Name: __________________________</th>
<th>Last Name: __________________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am a: _ Physician _ Physician assistant _ Nurse practitioner _ Nurse _ Other (please specify) __________________</td>
<td></td>
</tr>
<tr>
<td>My Primary Specialty is: _ General neurology _ Movement disorders _ Geriatrics _ Other (please specify) __________________</td>
<td></td>
</tr>
<tr>
<td>Practice Setting: _ Private practice _ Academic institution _ Community hospital _ Other (please specify) __________________</td>
<td></td>
</tr>
</tbody>
</table>

As a result of my participation in this activity, I am better able to:  

<table>
<thead>
<tr>
<th>As a result of my participation in this activity, I am better able to</th>
<th>Strongly Agree 4</th>
<th>Agree 3</th>
<th>Disagree 2</th>
<th>Strongly Disagree 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Identify early features of Parkinson’s disease (PD) to expedite diagnosis of PD.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Develop customized treatment plans for PD patients based on unique phases and clinical manifestations of PD.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Discuss the clinical differences between MAO-B inhibitors and other classes of pharmaceutical agents that may impact therapeutic decisions for individual patients.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Review ongoing trials for PD and their potential to improve motor function, mental health, and cognition in patients with PD.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. The content was effective in meeting my expectations.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. My personal objectives were achieved.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. The program was scientifically rigorous and clinically relevant.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Dr. Waters was knowledgeable and effectively presented the content.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Dr. Fernandez was knowledgeable and effectively presented the content.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10. Based on information presented in the program I will change my practice. □ Yes □ No  
   If “Yes,” what will those changes be? ________________________________________________  

11. The program was objective and free of commercial bias. □ Yes □ No  
   If “No,” please explain: _____________________________________________________________  

NEEDS ASSESSMENT: What issue(s) related to the topics discussed in this program would you like addressed in future CME/CE activities?  

ADDITIONAL COMMENTS:  

THANK YOU.  
(PLEASE ALSO COMPLETE POST-TEST.)
References


