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EXPERT ROUNDTABLE SUPPLEMENT

MANAGING PARKINSON'S DISEASE WITH CONTINUOUS DOPAMINERGIC STIMULATION

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ABSTRACT

The pathophysiology of Parkinson's disease is marked by the loss of dopaminergic neurons, which leads to striatal dopaminergic deficiency. This causes resting tremor, hypokinesia, rigidity, bradykinesia, and loss of postural reflexes. Most current treatments for Parkinson's disease aim to restore striatal dopamine signaling by increasing the supply of dopamine with oral levodopa (L-dopa), stimulating dopamine receptors directly using dopamine agonists, or inhibiting the reuptake of endogenous dopamine. L-dopa is standard therapy for patients with Parkinson's disease. However, with continued treatment and disease progression, the response to oral dopaminergic drugs becomes unstable and motor fluctuations emerge, including off periods and dyskinesia. Direct duodenal-administered infusible L-dopa/carbidopa is effective for the management of refractory motor fluctuations in some patient populations. However, enteral infusions cannot mimic the function of the normal dopaminergic brain, and around-the-clock constant-rate administration carries the risk of causing refractory off periods associated with severe immobility and hyperpyrexia. Subthalamic nucleus (STN) deep brain stimulation (DBS) is also a promising treatment. DBS passes a high-frequency electrical current into the target area, mimicking the effect of lesioning the stimulated area. However, this treatment requires invasive surgery and is appropriate for a limited segment of the patient population.

This supplement provides a rationale for the use of continuous dopaminergic receptor stimulation and offers guidelines on the individualization of treatment decisions, with special focus on continuous L-dopa infusion and STN DBS. Erik Wolters, MD, PhD, offers an introduction to the impact of continuous L-dopa infusion. Andrew J. Lees, MD, FRCP, provides an overview of the physiologic response to L-dopa and reviews clinical pharmacologic studies of intravenous and intraduodenal L-dopa. Jens Volkmann, MD, discusses selection criteria for STN DBS and duodenal L-dopa/carbidopa infusion. Teus van Laar, MD, PhD, and Ad Hovestadt, MD, discuss the first data from a Dutch cohort study of duodenal L-dopa/carbidopa.

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This activity has been peer reviewed and approved by Eric Hollander, MD, Chair and Professor of Psychiatry at the Mount Sinai School of Medicine. Review Date: March 6, 2008.

Statement of Need and Purpose

Parkinson's disease is a neurodegenerative disorder affecting ~1% of the United States population >65 years of age. It is characterized by progressive degeneration of specific neuronal populations, notably the dopaminergic neurons in the substantia nigra pars compacta. Therapeutic strategies focus on reducing the severity of symptoms using dopaminergic medications. Levodopa (L-dopa) is the most efficacious drug used to treat Parkinson's disease symptoms. However, the response to L-dopa changes over time, and its long-term use is associated with disabling motor complications. There are several strategies to manage long-term complications of L-dopa therapy, including manipulation of L-dopa dosing (or alternate formulations) and use of antiparkinsonian agents. Motor complications such as unpredictable on/off fluctuations and dyskinesia seem to result from chronic, non-physiologic pulsatile stimulation of dopamine receptors from standard L-dopa/carbidopa formulations. It has been hypothesized that more continuous dopaminergic stimulation may decrease the risk of developing disabling complications. To limit motor complications and worsened course of illness, educational programs that synthesize the major research on treatment strategies are needed.

Target Audience

This activity is designed to meet the educational needs of neurologists.

Learning Objectives

- Discuss the role of continuous dopaminergic stimulation in preventing or reducing the motor complications associated with levodopa (L-dopa) therapy.
- Describe treatment strategies to improve functional outcomes in patients experiencing motor fluctuations with L-dopa therapy.

Faculty Disclosures

Erik Wolters, MD, PhD, is professor in the Department of Neurology at VU University Medical Center in Amsterdam, the Netherlands. Dr. Wolters reports no financial, academic, or other interest in any organization that may pose a conflict of interest.

Andrew J. Lees, MD, FRCP, is professor of neurology and director of the Reta Lila Weston Institute of Neurological Studies at the Institute of Neurology, University College London. Dr. Lees reports no financial, academic, or other interest in any organization that may pose a conflict of interest. His article includes discussion of unapproved uses of investigational pharmacologic agents.

Jens Volkmann, MD, is associate professor in the Department of Neurology at Christian-Albrechts-University in Kiel, Germany. Dr. Volkmann is a consultant for Medtronic, and has received honoraria or consulting fees from Medtronic and Solvay. His article includes discussion of experimental or unapproved uses of duodenal levodopa/carbidopa.

Teus van Laar, MD, PhD, is associate professor in the Department of Neurology, University Medical Center Groningen in the Netherlands. Dr. van Laar has received honoraria from Solvay.

Ad Hovestadt, MD, is a neurologist in the Department of Neurology at Meander Medical Center Amersfoort in the Netherlands. Dr. Hovestadt has received honoraria from Solvay.

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Peer Reviewers

Eric Hollander, MD, reports no financial, academic, or other support that may pose a conflict of interest.

Jack Chen, PharmD, reports no financial, academic, or other interest in any organization that may pose a conflict of interest.

Mark Lew, MD, is a consultant for Boehringer-Ingelheim, GlaxoSmithKline, Ipsen, Novartis, Prestwick, Solstice, Schwarz Pharma, Teva Neuroscience, Valeant, and Vernalis; is on the speaker's bureaus of Allergan, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Solstice, Teva Neuroscience, UCB Pharma, and Valeant; and has received research support from Boehringer-Ingelheim, Eisai, Ipsen, Kyowa, Mentor, the National Institutes of Health, Novartis, Schwarz Pharma, Schering Plough, Solstice, Solvay, Teva Neuroscience, and UCB Pharma.

Lauren Seeberger, MD, is a consultant for Allergan and Teva Neuroscience, and has served on the advisory board of Teva Neuroscience.

Mark Stacy, MD, is a consultant for Medtronic.

To Receive Credit for this Activity

Read this supplement, reflect on the information presented, and complete the CME posttest and evaluation on pages 15 and 16. To obtain credit, you should score 70% or better. Early submission of this posttest is encouraged. Please submit this posttest by April 1, 2010 to be eligible for credit.

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