Parkinson disease: A summary of recent evidence-based medicine reviews

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ABSTRACT

Parkinson disease (PD) is a complex movement disorder in which the symptomatology, severity and progression vary substantially among patients. Therefore, there is a need to individualize patient therapy. Factors that should be considered when individualizing therapy include published guidelines, practice parameters, and Evidence Based Medicine (EBM) reviews, as well as clinical experience and judgment, patient specific factors and preferences, consensus and expert opinions, and health economic constraints. This article discusses EBM findings regarding treatment of the motor symptoms and the non-motor symptoms associated with PD.

KEYWORDS

Parkinson disease, neurology, treatment, Evidence Based Medicine (EBM)

Parkinson disease (PD) is a complex movement disorder characterized pathologically by progressive degeneration not only of the nigrostriatal dopaminergic neurons but also extra-nigral neurons.[1] Clinically, functional disability arises from the motor and non-motor symptoms. Many of the motor-related symptoms are directly observable when the patient is in clinic; while other symptoms or features require direct questioning and follow-up to detect and ascertain (Table 1). In particular, the onset of symptoms that do not (generally) respond to dopaminergic therapy, such as dementia, dysphagia, falling, gait imbalance, and symptomatic orthostatic hypotension, are milestones of impending disability and increased need for caregiver assistance.

It is well recognized that symptomatology, severity, and progression will vary substantially among patients with PD, thus serving as the basis for individualizing patient therapy.[1] Changes in an individual's response to therapy, emergence of drug-related adverse effects, emergence of motor complications, development of levodopa-unresponsive symptoms, and onset of PD-related non-motor symptoms should be anticipated and will add to the complexity of patient management.

Table 1. Parkinson Disease: Signs and symptoms

Motor

- For clinically probable PD, the patient exhibits at least two of the following: resting tremor,[A] rigidity,[B] or bradykinesia.[A] Asymmetry of onset[C] and severity[A,B] of these features is typical.

Other features:

- Postural instability[A,B] (difficulty with maintaining balance; more common in advanced PD).
- Slow or clumsy manual dexterity[A,B]
- Difficulty arising from a seated position[A,B]
- Diminished arm swing during ambulation[A]
- Dysarthria[A] or hypophonia[A]
- Dysphagia[C]
- Falls[C]
- Festinating gait[A]
- Flexed posture[A]
- Freezing[A]
- Hypomimia[A]
- Micrographia[A]

Autonomic and Sensory

- Bladder disturbances[C] ("failure to store:"e.g., detrusor hyperreflexia or "failure to empty:" e.g., detrusor-sphincter dyssynergia)
- Constipation[C]
- Diaphoresis[A]
- Fatigue[C]
- Olfactory disturbance[C]
- Orthostatic hypotension[B,C]
- Pain[C]
- Paresthesias[C]
- Paroxysmal cutaneous flushing[A]
- Seborrhea[A]
- Sexual dysfunction[C]
- Sialorrhea[A]

Behavioral and Psychiatric

- Anxiety[C]
- Apathy[C]
- Bradyphrenia[A]
- Confusional states[A,C]
- Dementia[A,B,C]
- Depression[B,C]
- Hallucinosis/psychosis[B,C] (typically drug-induced)
- Sleep disorders[B,C] (e.g., excessive daytime sleepiness, insomnia, obstructive sleep apnea, rapid eye movement sleep behavior disorder).

[A]*Directly observable*
[B]*Detectable on assessment and examination*
[C]*Requires history and interview. Follow-up with appropriate clinical specialist and additional tests may be required.*

In clinical practice and decision making, published guidelines, practice parameters, and Evidence Based Medicine (EBM) reviews[2-8] offer one component of data that should be utilized in conjunction with clinical experience and judgment, patient specific factors and preferences, consensus and expert opinions, and health economic constraints. It is important for guidelines and EBM reviews to be updated regularly in order to remain current and useful for clinicians in the field. The two most recent updates of EBM in the field of PD will be summarized in this article.[2,3]

One of the caveats of interpreting EBM is that the heavy reliance on results of randomized controlled studies can result in "evidence bias;" whereby the standard of practice clinical merit of certain treatments might be inadequately captured due to factors such as research methodology or research priorities. One example is deep brain stimulation in which, until recently, there was a lack of comparator-controlled data (e.g., sham surgery or active comparator) resulting in a mismatch between the evidence (which was considered insufficient) and clinical practice (which supported efficacy). Another example is in the area of non-motor symptoms of PD in which several areas have not been adequately researched including anxiety, apathy, constipation, fatigue, insomnia, orthostatic hypotension, sexual dysfunction, sweating, and urinary incontinence. This results in an evidence gap or insufficiency of evidence for standard of care therapies.

The most recent ***Movement Disorders Society*** (MDS) EBM review addresses the motor[2] and non-motor[3] features of PD. This article will summarize the key findings of the motor symptom treatment update (published as a 39-page document) and the non-motor symptoms treatment update (a 38-page document). In addition, this author's comments are provided to address whether the EBM conclusions appear consistent with standard of care clinical practice.

UPDATE ON MOTOR SYMPTOM TREATMENTS

The most recent MDS motor symptom EBM update is a follow up to previous MDS EBM reviews published in 2002and 2005.[2,9,10] The EBM includes randomized, controlled trial (defined as level 1) data of pharmacological, surgical, and nonpharmacological interventions for the motor symptoms of PD published up to December 2010. In all, 68 new studies were identified

and qualified for review. Products not available or not indicated for PD in the United States (US) are also included. However, the EBM data on pergolide will not be discussed in this article (since the product is no longer on the market).

PHARMACOLOGIC TREATMENTS

Prevention or delay of PD progression:

Amantadine, Anticholinergics, COMT inhibitors, Dopamine agonists, Levodopa formulations, MAO-B inhibitors: insufficient evidence either for or against efficacy.

Author comment: The conclusions of the EBM review appear consistent with general clinical practice. No treatment is indicated for preventing or delaying the progression of PD.

Symptomatic monotherapy:

- *Amantadine:* maintains status as likely efficacious
- *Anticholinergics:* maintains status as likely efficacious
- *Dopamine agonists:*
    - Apomorphine: insufficient evidence either for or against efficacy.
    - Bromocriptine, lisuride: maintains status as likely efficacious
    - Cabergoline, piribedil, pramipexole extended release, ropinirole, rotigotine: updated to efficacious
    - Dihydroergocryptine, pramipexole: maintains status as efficacious
    - Ropinirole prolonged release: updated to likely efficacious
- *Levodopa formulations*:
    - Standard, controlled-release: maintains status as efficacious
    - Rapid-onset oral (***refers to melevodopa which is investigational***), duodenal infusion (***not marketed in the US***): insufficient evidence either for or against efficacy.
- *MAO-B inhibitors:*
    - Selegiline ODT: insufficient evidence either for or against efficacy.
    - Rasagiline, selegiline: maintains status as efficacious

Author comment: The conclusions of the EBM review appear consistent with general clinical practice. The choice of agent will be influenced by clinician experience, type of motor symptom, severity, comorbidities, expected side effects, patient preferences, cost issues, and desired outcomes. For example, anticholinergic monotherapy is generally used to target control of PD tremor; however, if bradykinesia or rigidity is also present, monotherapy with other agents is preferred. If patients have evidence of cognitive impairment, amantadine, anticholinergics, and dopamine agonists are avoided. If motor symptoms are severe, levodopa is preferred.

Symptomatic adjunctive therapy (to levodopa):

- *Amantadine:* maintains status as likely efficacious
- *Anticholinergics:* maintains status as likely efficacious
- *Catechol-O-methyltransferase (COMT) inhibitors:*
    - Adjunctive entacapone in patients with existing motor complications: maintains status as efficacious
    - Adjunctive entacapone in patients without baseline motor complications: non-efficacious
    - Tolcapone: maintains status as efficacious (***reserve for patients who have failed other therapies; requires monitoring of liver enyzmes***)
- *Dopamine agonists:*
    - Dihydroergocryptine, pramipexole extended release: insufficient evidence either for or against efficacy.
    - Lisuride: maintains status as likely efficacious
    - Apomorphine, bromocriptine, cabergoline, piribedil, pramipexole: maintains status as efficacious
    - Ropinirole, ropinirole prolonged release, rotigotine: updated to efficacious
- *Monoamine Oxidase (MAO-B) inhibitors:*
    - Selegiline, selegiline ODT: insufficient evidence either for or against efficacy.
    - Rasagiline: updated to efficacious
- *Zonisamide* ***(not marketed in the US for PD)***: new designation as efficacious

Author comment: The conclusions of the EBM review appear consistent with general clinical practice. However, subsequent new data indicates that adjunctive pramipexole extended release is efficacious.[11] Although zonisamide is available in the US, it is not frequently utilized (off-label) for PD motor symptoms.

Prevention or delay of motor fluctuations and/or dyskinesias:

- *Amantadine:* insufficient evidence either for or against efficacy
- *Anticholinergics:* insufficient evidence either for or against efficacy
- *COMT inhibitors:*
  - Entacapone: Non-efficacious
  - Tolcapone: insufficient evidence either for or against efficacy.
- *Dopamine agonists:*
  - Apomorphine, dihydroergocryptine, lisuride, piribedil, pramipexole extended release, rotigotine: insufficient evidence either for or against efficacy
  - Bromocriptine: maintains status as likely efficacious
  - Ropinirole: maintains status as efficacious
  - Cabergoline, pramipexole, ropinirole prolonged release: updated to efficacious
- *Levodopa formulations*.
  - Rapid-onset oral, duodenal infusion (***not marketed in the US***): insufficient evidence either for or against efficacy.
  - Standard, controlled-release: maintains status as non-efficacious
- *MAO-B inhibitors:*
  - Rasagiline, selegiline, selegiline ODT: insufficient evidence either for or against efficacy in prevention of motor fluctuations
  - Selegiline: non-efficacious for prevention of dyskinesias

Author comment: The conclusions of the EBM review appear consistent with general clinical practice. However, subsequent new data indicates that adjunctive pramipexole extended release is efficacious.

Treatment of dyskinesias:

- *Amantadine:* maintains status as efficacious
- *Clozapine:* updated as efficacious (***clinical usefulness limited by risk of agranulocytosis***)

Author comment: The conclusions of the evidence-based review appear consistent with general clinical practice.

Treatment of motor fluctuations:

- *Amantadine:* insufficient evidence either for or against efficacy
- *Anticholinergics:* insufficient evidence either for or against efficacy
- *COMT inhibitors:*
  - Entacapone and tolcapone: maintains status as efficacious (***reserve tolcapone for patients who have failed other therapies; requires monitoring of liver enzymes***)
- *Dopamine agonists:*
  - Dihydroergocryptine, lisuride, piribedil, pramipexole extended release: insufficient evidence either for or against efficacy
  - Bromocriptine, cabergoline: maintains status as likely efficacious
  - Apomorphine, pramipexole, ropinirole: maintains status as efficacious for motor fluctuations
  - Ropinirole prolonged release, rotigotine: updated to efficacious for motor fluctuations
- *Levodopa formulations*:
  - Controlled-release, rapid-onset oral: insufficient evidence either for or against efficacy.
  - Standard: maintains status as efficacious for motor fluctuations
  - Duodenal infusion (***not marketed in the US***): updated to likely efficacious
- *MAO-B inhibitors:*
  - Selegiline, selegiline ODT: insufficient evidence either for or against efficacy
  - Rasagiline: updated to efficacious for motor fluctuations

Author comment: The conclusions of the EBM review appear consistent with general clinical practice. However, subsequent new data indicates that adjunctive pramipexole extended release is efficacious for treatment of motor fluctuations.[11]

SURGICAL TREATMENTS

Prevention/delay of disease progression, symptomatic monotherapy, and prevention/delay of motor complications:

Insufficient evidence either for or against efficacy.

Symptomatic adjunct to levodopa

- *Human fetal cell transplantation:* non-efficacious
- *Subthalamotomy:* insufficient evidence either for or against efficacy.
- *Thalamic stimulation, unilateral thalamotomy:* updated to likely efficacious (***for drug-resistant tremor***)

- *Bilateral subthalamic nucleus (STN) stimulation, unilateral pallidotomy:* maintained status as efficacious
- *Bilateral pallidal (GPi) stimulation:* updated to efficacious

Author comment: The conclusions of the EBM review appear consistent with general clinical practice. Thalamic stimulation is favored for targeting drug-resistant tremor. Bilateral STN and GPi stimulation are generally reserved for selected patients with significant motor complications despite optimized pharmacotherapy.

Treatment of motor complications

- *Human fetal cell transplantation:* non-efficacious
- *Subthalamotomy, thalamic stimulation, unilateral thalamotomy:* insufficient evidence either for or against efficacy.
- *Bilateral STN stimulation, bilateral GPi stimulation, unilateral pallidotomy:* updated to efficacious

Author comment: The conclusions of the EBM review appear consistent with general clinical practice. Bilateral STN and GPi stimulation are the favored surgical approaches reserved for selected patients with significant motor complications despite optimized pharmacotherapy.

NON-PHARMACOLOGICAL TREATMENTS

Prevention of disease progression, symptomatic monotherapy, prevention of motor complications, and treatment of motor complications

Insufficient evidence either for or against efficacy regarding non-pharmacological treatments.

Symptomatic adjunct to levodopa

- *Acupuncture:* insufficient evidence either for or against efficacy
- *Physical therapy:* updated to likely efficacious

Author comment: The conclusions of the EBM review appear consistent with general clinical practice.

UPDATE ON NON-MOTOR SYMPTOM TREATMENTS

In their various combinations, non-motor symptoms of PD often become the chief therapeutic challenge in PD (especially in advanced stages). Despite the high prevalence and associated disability of non-motor symptoms, many of these symptoms do not yet have treatments supported by good quality evidence. The recent MDS EBM review on non-motor symptom treatments includes randomized, controlled trial (defined as level 1) reports of pharmacological and non-pharmacological interventions published between January 2002 to December 2010.[3] In all, 54 new studies were identified and qualified for efficacy review and several other studies covered safety issues. The following is an abbreviated summary of highlights.

Constipation: Macrogol (i.e., isosmotic polyethylene glycol solution) rated as likely efficacious.

Author comment: The conclusions of the evidence-based review appear consistent with general clinical practice. Standard of care also includes maintaining adequate hydration (if permitted), physical activity, stool softeners and minimization of drug-induced constipation.

Dementia: Rivastigmine rated as efficacious. There was insufficient evidence to make adequate efficacy conclusions for donepezil, galantamine, or memantine.

Author comment: The conclusions of the evidence-based review appear consistent with general clinical practice; although donepezil and galantamine are also commonly used. Standard of care also includes minimization of drug-related cognitive impairment.

Depression: Pramipexole rated as efficacious; desipramine and nortriptyline rated likely efficacious. There was insufficient evidence to make adequate efficacy conclusions for amitriptyline, atomoxetine, citalopram, fluoxetine, moclobemide, nefazodone, paroxetine, omega-3 fatty acids, selegiline, electroconvulsive therapy, and repetitive transcranial magnetic stimulation.

Author comment: In clinical practice, pramipexole is not frequently utilized for the sole purpose of treating PD depression. Despite the insufficiency of evidence, selective serotonin reuptake inhibitors are commonly utilized. The tricyclic antidepressants are less commonly utilized for PD depression due to tolerability issues associated with anticholinergic and CNS related side effects.

Excessive daytime sleepiness: Modafinil had insufficient evidence to make an efficacy conclusion.

Author comment: Excessive daytime sleepiness in PD remains a challenge to treat and can be exacerbated by many factors. Minimization of drug-related daytime sedation, treatment of depression, and management of poor sleep hygiene are examples of standard of care approaches.

Fatigue: Methylphenidate and modafinil have insufficient evidence to make adequate efficacy conclusions.

Author comment: PD associated fatigue remains difficult to treat and can be exacerbated by many factors. Optimization of motor symptoms, minimization of drug-related sedation, treatment of depression, orthostatic hypotension, and poor sleep hygiene are examples of standard of care approaches.

Insomnia: Eszopiclone, levodopa/carbidopa controlled release, and melatonin had insufficient evidence to make efficacy conclusions.

Author comment: PD associated insomnia can be exacerbated by many factors. Optimization of nocturnal motor symptoms, minimization of drug-related daytime sedation, treatment of depression, management of poor sleep hygiene, and identification and treatment of co-morbid nighttime conditions (e.g., restless legs syndrome, sleep apnea) are examples of standard of care approaches. Despite the insufficiency of evidence, non-benzodiazepine sedative hypnotics (as well as tricyclic antidepressants and trazodone) are commonly utilized. Benzodiazepines should be avoided due to CNS-related side effects and greater fall risk.

Medication-related impulse control disorders (e.g., pathological gambling): Amantadine had insufficient evidence to make an efficacy conclusion.

Author comment: Impulse control disorders occur more frequently as a side effect of dopamine agonists compared to other PD treatments. The initial standard of care treatment consists of reducing the dose or eliminating the suspected offending drug.

Orthostatic hypotension: There are insufficient evidence to make efficacy conclusions for dihydroergotamine, domeperidone (***not marketed in the US***), droxidopa, etilefrine (***not marketed in the US***), fludrocortisone, indomethacin, midodrine, and yohimbine.

Author comment: Despite the insufficiency of evidence, fludrocortisone and midodrine are commonly utilized. Since the publication of the EBM, droxidopa has been FDA approved for neurogenic orthostatic hypotension (which can be associated with PD). Standard of care includes non-pharmacologic measures (e.g., increased salt intake, abdominal binders) and minimization of drug-related orthostasis.

Psychosis: Clozapine rated as efficacious (***clinical usefulness limited by risk of agranulocytosis***). For quetiapine, there was insufficient evidence to make an efficacy conclusion. Olanzapine rated unlikely efficacious and also has an unacceptable risk of motor deterioration.

Author comment: The conclusions of the evidence-based review appear consistent with general clinical practice; clozapine use is limited by risk of agranulocytosis and need for specialized monitoring. Despite insufficiency of evidence, quetiapine is commonly utilized.

Sexual dysfunction / Erectile dysfunction: For sildenafil, there was insufficient evidence to make an efficacy conclusion.

Author comment: Despite insufficiency of evidence, the phosphodiesterase type-5 inhibitors are commonly utilized. Standard of care also includes minimization of drug-related sexual dysfunction.

Sialorrhea: Botulinum toxin types A and B (rimabotulinum toxin B) as well as oral glycopyrrolate are rated as efficacious (although glycopyrrolate is limited by insufficient evidence for treatment beyond 1 week). For ipratropium bromide spray, there was insufficient evidence to make an efficacy conclusion.

Author comment: The conclusions of the evidence-based review appear consistent with general clinical practice. Note: the botulinum toxin formulations included in the EBM studies were abobotulinum toxin A, onabotulinum toxin A, and rimabotulinumtoxin B. Studies with incobotulinum toxin A were not included.

Urinary Frequency, Urgency, and/or Urge Incontinence: There are insufficient evidence to make efficacy conclusions for desmopressin, flavoxate, oxybutynin, prazosin, propiverine (***not marketed in the US***), and tolteradine.

Author comment: Despite the insufficiency of evidence, bladder anticholinergics are commonly utilized for overactive bladder in PD. The alpha-adrenergic blockers are useful for overflow incontinence due to benign prostatic hypertrophy. Note: intradetrusor onabotulinum toxin A injection treatment was recently FDA approved for neurogenic detrusor overactivity (which is associated with PD).

SUMMARY

The therapy goals for PD are to improve outcomes in domains of motor and non-motor symptoms, activities of daily living, and quality of life while minimizing acute and long-term adverse effects. Toward this end, familiarity with EBM guidelines in PD is a component that will enable the pharmacist clinician to better participate in therapy decisions, management of drug efficacy and adverse effects, and education of patients, caregivers, and peers.

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How to cite this editor-reviewed article
Chen JJ. Parkinson disease: A summary of recent evidence-based medicine reviews. Ment Health Clin [Internet]. 2012;2(2):25-31. Available from: http://dx.doi.org/10.9740/mhc.n113743