# PART II: THERAPEUTICS FOR MOTOR AND NON-MOTOR SYMPTOMS

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1) **Motor Symptoms –** The International Parkinson and Movement Disorder Society (MDS) has published guidelines for the treatment of motor symptoms in PD that was most recently updated online in 2015. The AAN has also published practice parameters on neuroprotective strategies and alternative therapies and on the management of motor complications. All references are listed at the end of this syllabus.

   a) Disease-modifying therapy – There are currently no established disease-modifying therapies for PD, but a number of potential treatments are under investigation, including supplements, prescription medications approved for other indications, and exercise therapy.

   b) Symptomatic treatment –

      i) Initial symptomatic therapy – First-line initial symptomatic therapies (class A evidence) include levodopa (most effective), dopamine agonists, and monoamine oxide B (MAO-B) inhibitors. Second-line initial symptomatic therapies (class B evidence) include amantadine and anticholinergic medications, but these drugs are weaker and often poorly tolerated. Initiating therapy with a dopamine agonist rather than levodopa may delay the onset of motor complications, but is less effective and increases the risk of neuropsychiatric complications such as impulse control disorders and psychosis. Long-term outcomes appear to be the same with early levodopa versus levodopa-sparing strategies, suggesting that disease progression (rather than initial medication choice) may be the primary risk factor for motor complications.

      ii) Prevention of motor complications – Initial use of entacapone (carbidopa/levodopa/entacapone) or controlled-release carbidopa/levodopa does not reduce the risk of motor complications.

      iii) Treatment of motor complications – *For wearing off*, evidence-based treatments include catechol-O-methyltransferase (COMT) inhibitors (entacapone is most commonly used; tolcapone is used infrequently due to the risk of hepatotoxicity and need for blood monitoring); MAO-B inhibitors (rasagiline; selegiline is also used but lacks evidence-based data); and the recently approved carbodopa and levodopa extended-release capsules (see below). Reducing the interval between levodopa doses is another common approach. Traditional carbidopa/levodopa controlled-release (CR) tablets have not been shown to reduce wearing off. *For dyskinesias*, evidence-based treatments include adjustment of dopaminergic medications; amantadine (not always tolerated due to side effects); and clozapine (rarely used due to the potential for severe neutropenia and need for blood monitoring). Advanced therapies such as deep brain stimulation (DBS) and carbidopa/levodopa intestinal gel are also effective treatments for motor complications.

      iv) Newer therapies

         (1) Combined immediate- and controlled-release levodopa capsules (Rytary™) – In January 2015, this new oral formulation of carbidopa/levodopa was approved, which in clinical trials reduced "off" time compared with immediate-release levodopa. The capsules are typically swallowed, but for people with dysphagia they can be opened and poured into applesauce. The doses are not bioequivalent to other forms of levodopa, and the conversion table in the package insert is only a suggested starting point that frequently requires adjustment.

         (2) Carbidopa/levodopa intestinal gel (Duopa™) – In January 2015, the FDA approved this advanced therapy whereby levodopa is delivered via PEG/J tube using an infusion pump that runs for 16 hours/day. This represents an alternative to DBS for patients with advanced PD, particularly those with contraindications to DBS such as mild to moderate cognitive impairment. Limitations include the need to refrigerate the carbidopa/levodopa cartridges, carry around the (17 oz) pump

throughout the day, and have a caregiver to help with pump management. Benefits include the reduction of motor complications and potential simplification of the oral medication regimen.

(3) Brio™ Neurostimulation System (St. Jude Medical™) – In June 2015, this became the second FDA-approved implantable DBS system for use in PD. Compared with the Medtronic Activa® DBS Therapy System, the new Brio System is slightly smaller and has rechargeable batteries.

v) Treatments under investigation

(1) Medical marijuana – There is no evidence-based data to support the use of synthetic or plant-based cannabinoids in PD. An AAN evidence-based review showed that oral cannabis extract is probably *ineffective* for levodopa-induced dyskinesias in PD. Providers should be aware of the high placebo rate (up to 70%), potential cytochrome P-450 interactions, and numerous potential side-effects, including cognitive impairment, psychosis, and imbalance that can lead to falls.

(2) MRI-guided high-intensity focused ultrasound (MRgFUS) thalamotomy or pallidotomy for PD – Potential alternative to DBS (or surgical lesioning) that involves no radiation, anesthesia, or indwelling hardware. FDA-approved in July 2016 for symptomatic treatment of essential tremor (unilateral thalamotomy). Not yet approved for use in PD.

(3) Transcranial magnetic stimulation (TMS) – This non-invasive office procedure is FDA-approved for use in depression, and has been used off-label for PD. A recent review and meta-analysis suggested that TMS may improve PD motor symptoms, but further study is needed.

(4) Inhaled levodopa – Phase III trial results were released in February 2017, showing benefit for treatment of "off" periods in PD. Motor scores 30 minutes after treatment were significantly improved vs. placebo, but a igh placebo response was also seen. An NDA is being filed in 2017.

(5) Extended-release amantadine (Nurelin™) – An NDA was submitted in October 2016 for amantadine extended-release capsules as an orphan drug for treatment of levodopa-induced dyskinesias. Immediate-release amantadine is frequently used off-label for this indication. Both formulations of amantadine are limited by side-effects, including edema and anticholinergic effects.

(6) Safinamide (Xadago®) – This is a novel, reversible MAO-B inhibitor that also acts as a use-dependent voltage-gated sodium channel blocker, and a modulator of calcium channels and glutamate release. It is being evaluated as adjuctive therapy for wearing off in PD. It was approved for use in Europe in early 2015. An NDA was re-submitted to the FDA in late 2016.

(7) Opicapone (Ongentys®) – A novel, once-daily COMT inhibitor, which in phase III trials was superior to placebo and non-inferior to entacapone in reducing "off" time. It was approved for use in Europe in June 2016, but an NDA has not yet been submitted to the FDA.

(8) Other treatments for motor complications – These are in varying stages of development. They include novel levodopa delivery systems, subcutaneous apomorphine infusions (currently available outside of the US); and adenosine A2A receptor antagonists.

2) **Non-motor Symptoms (NMS) –** The AAN published a practice parameter in 2006 that evaluated evidence-based treatments for depression, psychosis, and cognitive impairment in PD, and another in 2010 that examined treatments for other NMS. In 2011, the International Parkinson and Movement Disorder Society (MDS) published a broad, evidence-based review of the management of NMS in PD that was updated in 2012 in an online version. All references are listed at the bottom of this syllabus.

a) Evidence-based treatments for NMS

i) Depression – *Amitriptyline may be considered in non-demented patients (AAN, Level C). Pramipexole is efficacious (MDS); likely also nortriptyline and desipramine (MDS). Insufficient evidence for amitriptyline, SSRIs, nefazodone, atomoxetine, pergolide, Ω-3 fatty acids, or repetitive transcranial magnetic stimulation (MDS).* Tricyclic antidepressants are often avoided due to the risk of side-effects such as cognitive impairment, psychosis, urinary retention, and arrhythmias.

ii) Cognitive impairment / dementia – *Donepezil or rivastigmine should be considered (AAN, level B). Rivastigmine is efficacious (MDS). Insufficient evidence for donepezil, galantamine, or memantine (MDS)*. Note that cholinesterase inhibitors have limited benefit, and may worsen motor function in PD.

**iii)** Hallucinations & psychosis – *Clozapine (should be considered - AAN, level B; clozapine is efficacious, MDS). Quetiapine may be considered (AAN, level C), but olanzapine should not (AAN, level B).* Clozapine requires frequent blood monitoring due to the risk of severe neutropenia, and is not commonly used. Recommended doses of quetiapine do not worsen motor symptoms, but efficacy data is limited, and both short- and long-term side-effects are common. Pimavanserin is a new option (see below). All other available neuroleptics worsen motor symptoms, and should be avoided.

iv) Sialorrhea – *Botulinum toxin A and B (AAN - should be considered, level B; MDS - efficacious). Glycopyrrolate (anticholinergic that does not cross the blood brain barrier) - is possibly useful, but has only been tested for <1 week, and the safety profile is unclear (MDS).*

v) Constipation – *Polyethylene Glycol (Macrogol) – (AAN - may be considered, level C; MDS-possibly useful).*

b) Newer therapies for NMS

i) Droxidopa (Northera™) – In February 2014, this medication received FDA approval for the short-term management of symptomatic neurogenic orthostatic hypotension in PD and several other disorders, making it only the second drug approved for this indication. It should be noted that the drug is very expensive and sustained benefit for >2 weeks has not been demonstrated.

ii) Pimavanserin (Nuplazid™), a selective serotonin (5-$HT_{2A}$) receptor inverse agonist, was FDA approved in April 2016 as a first-in-class drug for PD psychosis. In clinical trials, it was well-tolerated and did not cause sedation or worsen PD motor symptoms. Like other antipsychotics, it has a black box warning about increased mortality when used in elderly patients with dementia-related psychosis.

c) Many non-motor symptoms have no evidence-based therapies and are treated empirically – Some of these symptoms (e.g., anxiety/panic attacks, paresthesias, some types of pain) may represent "non-motor offs" and respond to dopaminergic therapy. Some treatments for NMS have strong empirical evidence of benefit despite the absence of randomized clinical trials (e.g., treatment of REM sleep behavior disorder with clonazepam). Some NMS are managed as they are in the general population, despite a paucity of data for specific use in PD (e.g., bladder symptoms, erectile dysfunction, insomnia, excessive daytime sleepiness). Other NMS such as apathy, fatigue, hyposmia, and hypogeusia may be refractory to therapy.

d) Non-motor Complications of Dopaminergic Therapy – For dopamine agonist-related impulse control disorders (ICDs), there is *insufficient evidence for the use of amantadine in pathological gambling (MDS), and no evidence-based treatments for other ICDs such as compulsive eating, compulsive buying/shopping, or hypersexuality (MDS).* There are no evidence-based treatments for dopamine agonist withdrawal syndrome (DAWS; a stereotyped drug withdrawal syndrome that resembles cocaine withdrawal and does not respond to levodopa), dopamine dysregulation syndrome (DDS; compulsive dopaminergic medication overuse), or punding (repetitive purposeless behaviors such as assembling/taking apart objects).

## Suggested References

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**Other Suggested References:**

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