THERAPEUTICS IN MOVEMENT DISORDERS COURSE, 2017

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The goal of this presentation is to present practical, therapeutic options to treat movement disorders. The emphasis will be on Parkinson disease, essential tremor, myoclonus, and ataxia. A few tips on atypical parkinsonian disorders will also be given. Dystonia and chorea will not be covered. *A special acknowledgement goes to Dr. Stephen Reich who created the original version of this syllabus.*

Parkinson Disease

Diagnosis of Parkinson Disease

- Up to 20% of patients diagnosed with PD have an alternative diagnosis at autopsy
- It is essential to reassess the diagnosis of PD at each visit as it can take three years or longer to make an alternative diagnosis (PSP, MSA, etc.)
- The clinical features most predictive of PD include:
    - Unilateral/asymmetrical onset
    - Classic rest tremor
    - Beneficial and sustained response to levodopa with the eventual development of fluctuations and dyskinesias
    - No history of exposure to DA blocking agents in the year before symptom onset
    - No atypical features such as:
        - Lack of response to levodopa
        - Early falls
        - Rapid progression
        - Early bulbar signs
        - Early dementia, hallucinations, delusions
        - Early/prominent dysautonomia
        - Signs not expected with PD: apraxia, ataxia, pyramidal, etc.
        - Slow vertical saccades/supranuclear vertical ophthalmoplegia
    - Be aware of the 2015 Movement Disorders Society Diagnostic Criteria for PD
        - 4 Step process
            - It it parkinsonism?
            - Are there any exclusion criteria for the diagnosis of PD?
            - Are there any red flags to cast doubt on the diagnosis of PD?
            - Are there supportive criteria for the diagnosis of PD?
- DaTscan should not be considered standard-of-care for the diagnosis of PD
    - Datscan is approved to differentiate PD from essential tremor, but this is rarely a clinical conundrum as they have very different phenotypes
    - DaTscan (off label) cannot distinguish PD from other causes of parkinsonism also associated with nigrostriatal degeneration (PSP, MSA, etc.)
    - DaTscan may be helpful (off label) when there is a question as to whether parkinsonism is drug-induced parkinsonism, vascular parkinsonism, or functional parkinsonism, but this has not been confirmed in studies
    - Despite DaTscan, the diagnosis for most patients with parkinsonism remains clinical

Initiating treatment for PD

- Features to consider when initiating treatment for PD
    - How are the symptoms impacting personal and professional functioning?
    - Age of the patient
    - Comorbid features (sleep)
    - Sensitivity to side effects
    - Cost

- Many neurologists are under the impression that levodopa should be "spared" as long as possible to avoid fluctuations
    - Levodopa vs an agonist as initial treatment is more likely to cause dyskinesias and fluctuations within 5 years of treatment yet, they are likely to be mild, not disabling, and several long-term studies have demonstrated that ultimately it does not seem to matter when levodopa was started (early vs late) in that the most disabling long-term problems in PD are usually not fluctuations
    - Benefits of agonists have to weighed against the greater clinical benefit of levodopa and increased side effects of an agonist
- Levodopa
    - No reason to delay treatment if the symptoms are problematic
    - Use 25/100 to ensure adequate carbidopa: start with half doses and add a half dose every week until reach 1 pill three times daily
    - The goal is not to make the patient normal – only to improve symptoms so there is better function
    - No advantage (long term) with extended release levodopa
    - No benefit (and increased risk of dyskinesias) initiating therapy with carbidopa/levodopa/entacapone
    - Advise patients when to take levodopa (about every 4 hours); ideally on an empty stomach one hour before meals (or 1.5 hours after)
    - Most patients do not need levodopa at bedtime
    - Patients at or above 70 are at low risk for motor fluctuations from levodopa and as such, consider levodopa as first line therapy
- Agonists
    - Fine to use in younger-middle age patients with mild symptoms
    - Less efficacious than levodopa
    - Advantage: once daily preparations
    - Use a therapeutic dose (esp. ropinirole)
    - Use with caution (if at all) in patients who already have daytime sleepiness or insomnia
    - Warn about impulse control disorders
- Other options for initial therapy
    - Amantadine
        - May help tremor and fatigue
        - Dose before 2pm to avoid insomnia
        - Can also cause rash and swelling of the feet
    - MAO-b inhibitor
        - No proven neuroprotective benefit
        - May also be beneficial for fatigue and later in the disease for freezing

Later in Parkinson Disease: Management of motor fluctuations

- The first motor fluctuation to typically appear is <u>end-of-dose wearing off</u>
- There are many options for treating wearing off but first, be sure that a mild degree of wearing off is really a problem for the patient. For some patients, a slight return of tremor shortly before a dose is due is not a problem and therefore no intervention is necessary.
- Options:
    - Decrease dosing interval of levodopa (increasing the dose increases the *magnitude* of the response but usually not the *duration*); although some patients can get by with a slightly lower dose of levodopa when the interval is reduced, it is best not to make both changes simultaneously
    - Add an agonist (see issues above), MAO-b inhibitor or COMT inhibitor
    - For several problematic off times daily, especially if they occur at unpredictable times, apomorphine can be considered
    - Newest option is Rytary which is a combination of immediate and extended release levodopa which has been demonstrated to reduce off time (see conversion table below if from package insert)
    - Levodopa intestinal gel. Smooths out motor fluctuations. Most complications are related to jejunostomy.
    - Liquid sinemet: total sinemet dose can be crushed and taken more frequently than pills
    - DBS can be considered

Awakening symptoms: dystonia and akinesia

- Options for treating early morning foot dystonia and/or akinesia
    - For the patient who routinely awakens at night to urinate is to take levodopa at that time, closer to wake-up time.
    - Take the AM dose of levodopa immediately upon awakening and wait before getting out of bed
    - Apomorphine upon awakening

Management of levodopa induced dyskinesias

- A few caveats about dyskinesias
    - They often bother others more than the patient
    - If not problematic, it is not necessary to treat them
    - Try to have patients determine if there is a pattern to their occurrence
    - Sometimes patients confuse tremor and dyskinesia; if there is any question about what the patient is experiencing, have the patient stay in the office for an extended period to observe what is occurring or bring a phone video
- Options for treating bothersome dyskinesias
    - Reduce the dose of levodopa and possibly the timing (lower dose, more frequently). The usual problem with this is by the time most patients are experiencing bothersome dyskinesias, they are very dependent on a fairly high dose of levodopa and a relatively short duration between doses and often do not tolerate a reduction. If this occurs, then one can increase the dose of an agonist to make up for the difference as they are much less likely to cause dyskinesias
    - Eliminate MAO-b or COMT inhibitors
    - Add amantadine. This is an under-recognized but well-proven treatment for dyskinesias and often has a dramatic effect which is long-lived. This may be mediated through its effect as an NMDA receptor antagonist.
    - Consider adding topiramate to the amantadine
    - Deep brain stimulation, especially of the GPi, although usually not performed solely for dyskinesias but instead, when they are taking place in the setting of motor fluctuations

When to consider deep brain stimulation for PD

- Disabling, medically refractory tremor AND/OR
- Problematic motor fluctuations despite optimal medical therapy
    - Must still have good quality ON time from levodopa
    - Cognitively and psychiatrically stable
- Levodopa intestinal gel is a possible alternative
- Some caveats about DBS
    - Be sure the patient has PD (vs parkinsonian syndrome)
    - Ideally should be performed in an experienced, multi-disciplinary center
    - Impart realistic expectations
    - In general, imbalance is not likely to improve unless exclusively confined to OFF times
    - Despite improvement in the original indication for DBS (e.g. reducing OFF time) the disease continues to progress and patients may “forget” the benefit
        - Benefit for original indication wanes with time but still demonstrated effectiveness at 10 years post-op
    - If suboptimal response consider:
        - diagnosis
        - lead placement
        - stimulation parameters
        - status of PD medications
        - co-morbid features (depression)

Falls in Parkinson disease

- Try to determine when/why falls happen
- Often seen in setting of executive dysfunction with impulsivity, decreased insight and impaired judgment
- Optimize motor fluctuations (minimize off time)
- Check for orthostatic hypotension
- Economize/eliminate medications (TCAs, benzodiazepines)
- Physical therapy for fall prevention/Tai Chi

- Home safety: bars in bathroom, remove throw rugs, banisters on stairs, lighting at night, etc.
- Educate patient: avoid carrying things while walking, hand on banister, etc.
- Walker (my preference is UStep but others with 4 wheels are fine); hiking poles; laser cane
- Knee pads
- Hiking poles

Management of selected non-motor features of PD (note, there is relatively little supportive evidence for treatment of the non-motor aspects of PD and virtually all recommendations are off label; see AAN practice parameter)

- Orthostatic hypotension (OH)
    - Be alert to presentations of OH other than traditional near-syncope
        - fatigue
        - cognitive impairment
        - falls
    - Look for OH
    - First try to eliminate any causal or contributing medications especially anti-hypertensives
    - Non-pharmacologic measures: increase water/salt intake; avoid standing quickly; avoid large meals and alcohol; avoid hot baths or showers; support hose (impossible for most patients with PD to use); keep the head of the bed propped up; recognize the earliest symptoms and sit or use an isometric exercise
    - Medications which can be considered
        - fludrocortisone
        - midodrine
        - droxidopa
        - Be sure to take the last dose early to avoid supine hypertension overnight
- Sialorrhea
    - Drooling is a common problem in PD. For most patients it is an annoyance but for some, particularly with advanced PD, it can be problematic. Pooling of saliva in the mouth can interfere with talking and poses a risk for aspiration. There are relatively few proven therapies for treatment of drooling.
    - Options: anticholinergics (intraorally vs systemic)
    - Local injection of botulinum toxin into salivary glands is what I have found most beneficial
- Sleep Disorders
    - Sleep disorders are nearly ubiquitous in PD and have a significant negative impact on QOL, including the spouse
        - Excessive daytime sleepiness
            - Inquire about sleep hygiene
            - Critical evaluation of medications (esp DA agonists)
            - Consider primary sleep disorder (OSA)
            - Common in advanced PD especially with dementia
            - Often difficult to treat
            - May use Modafanil or Methylphenidate
        - Insomnia
            - Remember, insomnia is a symptom, not a disease
            - Try to determine cause for insomnia
            - Important considerations:
                - PD symptoms interfering with initiating or maintaining sleep (tremor, difficult turning, cramps, etc.) which can be improved with adjustment of PD meds
                - Depression/insomnia
                - Nocturia
                - RLS
        - REM behavioral disturbance
            - Dream enactment
            - Very common in PD
            - May precede PD by years or decades
            - Need history from bed partner

- Can cause “falling” out of bed
- If infrequent and mild, not in need of treatment
- Move potentially injurious objects from around bed
- Options: low dose clonazepam (0.5mg) or melatonin (escalating to maximum of 12mg)

- Depression and anxiety in PD
  - Both are very common in PD and often inadequately recognized and treated
  - Both may fluctuate with motor fluctuations
    - Panic when off
    - Despondency when off
    - Hypomania when on
  - Treatment
    - Recognition/education
    - SSRIs, SNRIs
    - ECT if refractory or intolerant of meds
    - Low threshold for involving a psychiatrist (ideally one familiar with/interested in PD/geriatrics)
- Impulse control disorders and dopamine agonist withdrawal syndrome
  - Approximately 15% of patients with PD will develop an impulse control disorder (ICD)
  - The most common include gambling, shopping, sexual behavior, eating and hobbyism
  - They are often challenging to diagnose and are often done surreptiously
  - They are most closely associated with dopamine agonists and are dose related
  - Other potential risk factors include men, younger age, younger age of onset of PD; prior history of ICD including substance abuse and gambling and impulsive personality traits
  - Prior to initiating dopaminergic therapy, especially with a DA agonist, patient and their family should be warned about this potential side effect
  - It is important to screen for ICD at each visit
  - The treatment of choice for a ICD is gradual reduction/withdrawal of a DA agonist or the presumed offending drug (which can include levodopa and amantadine)
  - Recognize that withdrawal of a DA agonist can be problematic and this is known as the “dopamine agonist withdrawal syndrome” which includes anxiety and insomnia
- Dementia in PD
  - Dementia is common in PD, affecting at least 40% of patients over the course of the disease, with some studies reporting up to 80%.
  - Important to consider remediable causes and not just assume it is PD dementia
  - Education of the patient, caregiver and family
  - When PD is complicated by dementia, it adds a much greater burden to the caregiver.
  - Significant factor in predicting nursing home placement
  - First step in management is to eliminate as many drugs as possible
  - Cholinesterase inhibitors can be used. Recent evidence-based reviews demonstrate greatest evidence for rivastigmine with less convincing evidence for donepezil, galantamine and memantine
  - Impart realistic expectations if a cholinesterase inhibitor is used.
- Psychosis in PD
  - Common problem but uncommonly addressed
  - Patients/caregivers reluctant to bring up
  - Important to ask about, especially when PD is complicated by cognitive impairment
  - Includes
    - Delusions (infidelity, paranoia)
    - Hallucinations: visual (formed) , tactile or auditory hallucinations
    - Illusions
  - If infrequent with retained insight and not bothersome, not necessary to treat
  - If problematic
    - Eliminate as many meds as possible (I try to use just levodopa in advance PD, especially when there is dementia)
    - Options
      - Quetiapine (despite limited evidence, generally seen as first choice)

- Clozaril (risk of leukopenia but most effective and underutilized)
- Cholinesterase inhibitors
- Pimavanserin (5HT2A inverse agonist)

Atypical Parkinsonian Disorders

- Multiple system atrophy, corticobasal degeneration, and progressive supranuclear palsy pose therapeutic challenges
    - These disorders frequently do not have the same response to Parkinson disease medications given mechanistic differences
- In approximately 15-20% of patients with atypical parkinsonian disorders, there is improvement with levodopa
    - Some of these patients will require higher doses than standardly used in PD
- Response may also be seen with amantadine and agonists
- A general strategy is to treat the symptoms and signs with the medications described above for PD and modify based on the patient response
- Blood pressure monitoring is prudent in patients with orthostatic hypotension from multiple system atrophy
    - In some patients dopaminergic medications will exacerbate the hypotension

Essential tremor

- Diagnostically, it may be useful to distinguish between 'classic' essential tremor and 'atypical' essential tremor, which may be associated with other neurological signs
    - Some patients with atypical essential tremor will develop parkinsonism
    - Other patients will have mixed tremor, with both rest tremor and kinetic tremor
- Therapeutic considerations
        - Determine the effects of tremor on functioning
            - In patients with mixed tremor, it is typically the kinetic tremor
        - Be sure to ask about embarrassment since for some patients, that is the primary problem rather than functional impairment
        - Recommendations from recent AAN practice parameter
            - Primidone and propranolol (including LA) remain the treatments of choice
            - Start low and go slow, especially in the elderly
            - Impart realistic expectations. The tremor will not go away. Goal is improvement to be assessed by functioning
            - Primidone and propranolol are synergistic
            - Level B evidence: alprazolam; atenolol; gabapentin; topiramate
            - Level C evidence: see practice parameter
            - Despite the lack of level A or B evidence, DBS of the VIM thalamus should be considered in refractory cases
        - Commercial devices are now available that can cancel out the tremor, such as Liftware Steady^{TM}, which has sensor and motor-based technology
            - These devices are typically not reimbursed from insurance
            - They work best for classic essential tremor
            -

Myoclonus

- The etiologies of myoclonus are highly variable
    - First, determine which category of myoclonus is the most likely
        - Physiologic myoclonus such as sleep jerks or anxiety may not need to be treated
        - Epileptic myoclonus such be identified and treated with antiepileptics
        - Hereditary or essential myoclonus may respond to medications
        - Symptomatic myoclonus which is secondary to other disorders, may not need to be treated
- Localization of the myoclonus will lend best to determining which therapy will be most effective
    - Divisions are cortical/subcortical, brainstem, spinal, and peripheral
    - If myoclonus occurs at rest, this indicates a spinal or brainstem source

- Action-induced myoclonus is more likely cortical
- Spinal segmental myoclonus is focal and is occasionally stimulus sensitive
- Generalized myoclonus is usually subcortical or less frequently cortical

Localization	1st Line Treatment	2nd Line Treatment	3rd Line Treatment
Cortical or Subcortical	**Sodium valproate, piracetam, levetiracetam**	**Benzodiazepines, e.g. clonazepam**	**Zonisamide, topiramate, gabapentin, and lamotrigine**
Brainstem	**Benzodiazepines, e.g. clonazepam**	**Sodium valproate, piracetam, levetiracetam**	**Zonisamide, topiramate, gabapentin, and lamotrigine**
Spinal	**Benzodiazepines, e.g. clonazepam**	**Sodium valproate, piracetam, levetiracetam**	**Zonisamide, topiramate, gabapentin, and lamotrigine**
Peripheral	**Botulinum toxin (1st line for any focal myoclonus)**	**Gabapentin, pregabalin, carbamazepine, oxcarbazepine, topiramate**	**Benzodiazepines, e.g. clonazepam**

Ataxia

- Regardless of cause, ataxia is one of the more difficult movement disorders to treat
- However, some patients will respond and can stop falling
- My algorithm is to start with amantadine escalating to 200mg per day to a maximum of 400mg per day, with all of the caveats of side effects of higher doses of amantadine
- Buspirone 15-30mg bid is my second choice
- Varenicline has been shown to help in small case series of ataxic patients, prescription coverage may cover it without a need to appeal a denial
    - Studies suggest it may worsen tremor so this should be considered
    - Studies also suggest that it may be more effective in former smokers
- Riluzole is the last option at 100mg daily but it is quite expensive so should be reserved for last

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