

Quelling the Shakes: *PD and Essential Tremor*

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How do I diagnose PD?

Clinical diagnosis of Parkinson's disease (PD) requires two of the following criteria:

- 1) Bradykinesia (slowness of movement)
- 2) Rigidity (increased tone independent of speed and direction of movement)
- 3) Resting tremor

An alternate way to remember how to properly diagnose PD is the three S's: slow, stiff and shaky. Supportive features of PD include:

- flexed posture,
- shuffling gait (in early stages, gait may be near normal),
- reduced arm swing,
- postural instability,
- decreased facial expression (hypomimia),
- drooling,
- softer voice (hypophonia) and
- smaller handwriting (micrographia).



What is the basis for treatment in PD?

The primary biochemical abnormality in PD is loss of dopamine-producing neurons in the *substantia nigra*. Medical treatment is aimed primarily at providing exogenous levodopa (LD) that is converted into dopamine in the brain, stimulating the dopamine receptors themselves, or preventing breakdown of dopamine and/or LD.

Harold's case

- A 65 year old male with Parkinson's disease for five years reports that his medications don't seem as effective as before. He is on 100 mg levodopa and 25 mg carbidopa, three times daily.

Question 1: What do you think is going on? How would you treat him?

Answer 1: Upon further questioning, he says that his shaking worsens and he slows down 30 minutes to 60 minutes before his next dose. He describes classic features of wearing off. The 100 mg levodopa and 25 mg carbidopa dosage is increased to four times a day. This improves his symptoms, but after six months on this dose, he returns with the same initial complaints.

Question 2: What should you do now?

Answer 2: Options include adding 200 mg of entacapone, four times daily, or a dopamine agonist. A dopamine agonist is added. During the titration phase he develops nausea. The symptoms improve somewhat, but he continues to have nausea with the medication.

Question 3: What next?

Answer 3: Reduce the dose until the nausea has settled, and then slowly increase it. Other options include taking the medication with food or



What is essential tremor?

The tremor of essential tremor (ET) is a postural and/or action (kinetic) tremor. The patient may report difficulty eating soup with a spoon, drinking from a full cup, writing, using a screwdriver or threading a needle. Females more commonly have voice or head tremors than males.

ET is the most common cause of pathological tremor. It is approximately 10 times more common than PD and may affect individuals of any age. Prevalence increases with age and there is often a positive family history of tremor. Unlike PD, brain pathology is normal in ET.



How do I differentiate ET from PD?

There are no readily available diagnostic tests to differentiate the conditions; physicians must rely on their clinical judgment. ET does not produce a slow shuffling gait, nor does it affect speed of movement, though tremor may impair some movements. Response to alcohol is not specific for ET as various types of tremor may improve. Other questions to ask in assessing a patient with tremor include:

- neuroleptic use (including metoclopramide),
- all medications used, history of thyroid disease and
- family history of movement disorder.



How do I treat PD? What treatment and when?

There is no known cure for PD, nor does any treatment definitively slow its progression. Treatment is individualized and not every drug is effective for each person during all stages of the disease.

Table 1

Comparison of Parkinson's disease vs. essential tremor

Essential tremor	Parkinson's disease (PD)
Postural and kinetic tremor	Resting tremor
Upper limbs, head and voice are symmetric	Upper and lower limbs are asymmetric
May appear at any age; risk increases with age	Rare below age 40
Family history often positive	Family history can be positive or negative
Amplitude worsens over time	Tremor may be reduced or absent in advanced PD
No bradykinesia or rigidity	Bradykinesia, rigidity, reduced facial expression, softer voice, flexed posture, gait freezing and frequent falls

In early PD, I do not treat if the patient is functioning adequately to his/her satisfaction. Treatment options include:

- anticholinergics,
- selegiline,
- amantadine or
- dopamine agonists.

While anticholinergics are inexpensive, they are not very potent, they have multiple potential side-effects and should be avoided in the elderly. Selegiline is moderately expensive; while generally well tolerated, it is not very potent. Amantadine is less expensive than selegiline



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and has mild-to-moderate potency. Adverse effects include *livedo reticularis*, edema and hallucinations. Dopamine agonists are expensive and are of similarly moderate potency, with adverse effects including

- somnolence,
- confusion,
- lightheadedness,
- nausea/vomiting and
- hallucinations.

Both bromocriptine and pergolide are ergot derivatives and are rarely associated with pleural or retroperitoneal fibrosis. In addition, cardiac valvular abnormalities have been associated with pergolide and gambling problems are reported more frequently with pramipexole than other agonists.

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In patients over age 70 who require medical treatment, I often initiate either 100 mg levodopa and 25 mg carbidopa or 100 mg levodopa and 25 mg benserazide, three times per day. There is no good evidence to choose controlled release over standard formulation of levodopa/carbidopa. As anticholinergics and selegiline are not very potent, I will use amantadine, dopamine agonists and levodopa for moderate PD and dopamine agonists or levodopa for severe PD. Levodopa remains the gold standard of PD treatment. While adverse effects are similar to the dopamine agonists, levodopa is better tolerated.

What are motor fluctuations and how are they treated?

Wearing off is the predictable loss of efficacy before the next dose of medication (typically LD). Strategies include increasing dose frequency, increasing the dosage, addition of entacapone (a catechol-O-methyltransferase inhibitor which inhibits peripheral breakdown of LD), or addition of a dopamine agonist. Dyskinesias are choreiform movements that occur more commonly in younger patients and with higher doses of LD. In mild cases, patients are commonly unaware and not bothered by the movements. Treatment options include reducing LD dose, or adding amantadine. Initial treatment with dopamine agonists reduces the risk of developing dyskinesias. Prevention is the best therapy for dyskinesias, avoiding large doses of LD early in disease.

How do I treat ET?

The best evidence available is for the non-selective beta antagonist propranolol, both standard and long-acting (LA) formulations, or the anti-seizure drug primidone.

The dose range for propranolol is 60 mg/day to 320 mg/day; standard propranolol is typically given in three divided doses, while LA propranolol is administered once daily. LA propranolol has similar efficacy to standard propranolol, though patients generally prefer once-daily dosing. The beta-1 selective antagonists atenolol and metoprolol may each be used to treat ET, though the evidence is stronger for atenolol. Adverse effects of beta blockers include:

- lightheadedness,
- fatigue,
- bradycardia,
- impotence,
- worsening of underlying depression,
- nightmares,
- blunting the hypoglycemic response and
- exacerbating reactive airway disease.

Primidone is reported effective in doses of 50 mg/day to 1000 mg/day; however one study reported that 250 mg/day was no less effective than 750 mg/day. I initiate primidone at one-quarter of a 125 mg pill (*i.e.*, 31.25 mg) once a day, before bedtime, increasing by a similar amount every one week to two weeks until dosage has reached one full pill/day. If there is no improvement and the patient tolerates it, I add another one-quarter pill in the daytime and slowly increase dosage until at 125 mg twice a day. Adverse effects of primidone include:

- nausea/vomiting,
- drowsiness,
- fatigue,
- unsteadiness and
- ataxia.

Other medications showing evidence of benefit include topiramate and gabapentin. Of the benzodiazepines, the best evidence is for alprazolam at 0.125mg/day to three mg/day. I use benzodiazepines in patients with much worse tremor in a social setting and they may be used as needed. Adverse effects of benzodiazepines include:


- drowsiness,
- fatigue and
- potential for abuse.

If taken regularly, benzodiazepines should not be abruptly withdrawn. Alcohol is also effective

Take-home message

1. Parkinson's disease and essential tremor are each diagnosed clinically.
2. There is no cure for PD and no treatment to definitively slow the disease's progression. Treatment is individualized and the patient's expectations should be tempered (describing symptoms as improved rather than normal).
3. Levodopa remains the gold standard for treatment of PD.
4. ET is the most common cause of pathological tremor in men and is up to 10 times more prevalent than PD.
5. Beta-blockers and primidone are the mainstays of ET treatment.

for tremor control and may be used as needed in social settings.

Head tremor may respond to the medications listed above, but there are few studies on this. Head tremor tends to be more socially than functionally limiting. Botulinum toxin can reduce both head and voice tremor. The benefits of botulinum toxin in limb tremor are limited by dose-dependent hand weakness. 

References

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