Sunday General Session

**Differential Diagnosis and Management of Tremor**

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**Educational Objectives**  
By the end of this educational activity, participants should be better able to:  
1. Differentiate types of tremor seen in the primary care setting.  
2. Initiate therapy for various tremors diagnosed in the office.  
3. Discuss management of essential tremor and review various medication options.  
4. Discuss other options with patients when medications fail.

**Speaker Disclosure**  
Dr. Karkar has disclosed that he has no actual or potential conflict of interest in relation to this topic.
I. Definitions

- A tremor is a rhythmic, oscillatory fast movements of a limb or the head
- There are different types of tremors
- For each type of tremor, there are different causes or etiologies

II. Characterizing Tremors Into Types

- The first step in evaluating a patient with tremor is to characterize the tremor type. The second step is to determine the etiology
- The three major types of tremor are:
  - Action/postural
  - Resting
  - Intention

Learning Objectives

By the end of this educational activity, participants should be better able to:

- Differentiate types of tremor seen in the primary care setting.
- Initiate therapy for various tremors diagnosed in the office.
- Discuss management of essential tremor and review various medication options.
- Discuss other options with patients when medications fail.
IIa. Action/Postural

- Occurs in the context of performing action or maintaining a posture (for example, sustained extension) of a limb
- The tremor is usually bilaterally symmetric
- Also occurs during voluntary motion such as writing, eating. When severe, this type of tremor could be disabling
- There are different etiologies of action tremor, with the most common being essential tremor
  

IIb. Resting Tremor

- Occurs at rest (when the limb is relaxed and stationary) and stops with movement (unlike A/P tremor)
- Could occur while the person is sitting, standing or walking
- Typically is asymmetric, involving either an arm or leg
- Asymmetric resting tremor, in addition to bradykinesia and rigidity, is a major presenting symptom of Parkinson's disease

IIc. Intention Tremor

- This is also known as cerebellar tremor
- The tremor movement classically begins as the finger approaches a target (for example during finger-to-nose testing)
- It is often accompanied by other hallmarks of cerebellar disease such as ataxic gait, scanning speech, etc.

III. Essential Tremor

- Essential tremor is the most common cause of action tremor
- Prevalence estimates range from 0.4 to 6% and increase with advancing age (Louis et al., 2001)
- It is characterized by the presence of both action and postural tremors (always of the hands and sometimes also involving the head, lower limbs, voice, face/tongue or trunk)
- There is a family history in 30-50% of cases
- Although usually described as "benign", because the condition is limited to tremor, the tremor could be quite disabling (as it affects the hands while in active use) and is gradually progressive over time
- About 15-25% of patients with ET have a functionally significant impairment (Bain et al., 1994)

III. Diagnosis of Essential Tremor

- ET is a clinical diagnosis
- Differential diagnosis includes: Enhanced physiological tremor, Parkinson's disease, idiopathic dystonia, Wilson’s disease, among others
- The tremor is isolated in essential tremor, whereas other symptoms and signs co-exist with tremor in these other conditions
- Temporary amelioration with alcohol is a unique distinguishing factor of essential tremor

III. Physiological Tremor is in the Differential of Essential Tremor

- We all have rhythmic oscillatory movements of the hands, even if not apparent to the naked eye. This tremor is observed as an action/postural tremor
- Even when not obvious on exam, this could be detectable with electrophysiological techniques
- Stressful circumstances and certain medications and medical conditions may enhance this type of tremor and make it visible
- Physiological tremor is NOT progressive over time, in contrast to other “pathological” tremors
III. Proposed Diagnostic Criteria of Essential Tremor

- **Definite ET:**
  - Action tremor of moderate amplitude in at least one arm during at least four tasks
  - Tremor must interfere with at least one activity of daily living
  - Other causes of A/P tremor are eliminated
- **Probable ET:**
  - Action tremor of moderate amplitude in at least one arm during at least four tasks
  - Other causes of A/P tremor are eliminated

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**Case 1**
A 37 year old man presented with recent onset “tremulousness” of both hands that occurs in the context of activity (such as holding utensils to eat). The onset of the tremor appeared to coincide with starting a medication, valproic acid, to treat recently diagnosed epilepsy. On exam, the only finding was of a mild/moderate bilaterally symmetric action/postural tremor.

- What is the type of tremor?
- What is the etiology of the tremor?

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**Case 2**
A 56 year old woman presented for evaluation of tremors of the hands and of head “bobbing” that have progressed over the last 20 years to the point where she could no longer write legibly. There is a family history of similar tremors on her father’s side. She is concerned that her symptoms may be due to Parkinson’s disease. On exam, she has a moderate/severe action tremor of the bilateral arms (right slightly more pronounced), and evidence of a side-to-side tremoring of the head. There is no evidence of rigidity, resting tremor, or bradykinesia. She has a negative evaluation for hyperthyroidism and for Wilson’s disease.

- What is the type of tremor?
- What is the etiology of the tremor?

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**Case 3**
A 79 year old man presented to his primary care physician’s office with a six-month history of difficulty using his right hand. He described himself as becoming less “limber” on that side, and his family described intermittent shaking of the right hand. On exam, he had reduced facial expression, an intermittent tremor only of the right hand that stopped when he performed tasks with the hand; in addition, he had subtle bilateral fine tremoring of the extended arms. There was evidence of slower movements and mild rigidity of the right arm/leg. On gait testing, he had reduced right arm swinging associated with asymmetric tremor of the right hand. His gait was slightly slower than normal with a narrower base.

- What is the type of tremor? Does he have one or more than one type of tremor?
- What is the etiology of the tremor(s)?

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IV. Medical Treatment of Essential Tremor

- Goals of treatment are to reduce the amplitude of the tremor, improve function and/or reduce social embarrassment
- Treatment of mild tremor is not usually indicated
- Medical intractability of ET is relatively high (25-55% of patients have no response to medication) (Louis et al., NEJM, 2011)
- Most medications that have been found to be effective were the result of serendipitous discovery
- Propranolol and primidone are first-line therapies
  - Per AAN practice guideline [Jessee et al., 2002], there is a level A (established as effective) recommendation for the use of either medication to reduce limb tremor

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IV. First-Line Treatment: Propranolol

- Peripheral b-adrenergic receptors probably mediate most of the effects of b-adrenergic blocking agents (Jefferson et al., 1979)
- Propranolol has been found to be effective in reducing the severity of tremor in placebo-controlled studies (45-75% reduction) at a minimum dose of 80-120mg/day (for example, Tolsa et al., 1975).
- Relative contraindications of propranolol include asthma, congestive heart failure, diabetes, AV block
- Non-selective beta antagonists are more effective than b1 selective antagonists (Dietrichson et al., 1981)
IV. First-Line Treatment: Primidone

- Primidone is an antiepileptic medication which is metabolized to phenobarbital and phenylethylmalonamide.
- The parent compound mediates most of the effect against tremor (Findley et al., 1985).
- Although at least as effective as propranolol at 750mg/day, early tolerability is a limiting factor with primidone - nausea/vomiting and ataxia result in discontinuation in ~20% (Findley et al., J Neurol Neurosurg Psychiatry 1985).
- A typical starting dose is 50mg nightly and a very slow upward titration is recommended.

IV. Second-Line Therapies

- Topiramate: Some evidence of benefit, as an adjunctive agent, at a minimum effective dose of 50mg bid. Patient needs to be counseled about potential adverse effects.
- Gabapentin: In two of 3 trials GBR, at doses of 1200-3600mg, reduced tremor significantly (Onodo et al., 2000).
- Some benzodiazepines have been shown to be effective against tremor, however at the cost of sedation and potential dependence.
- Calcium channel blockers have had mixed results: Some (nimodipine) appear to help, whereas others (nifedipine) may worsen tremor (Louis et al., NEJM, 2001).
- Overall, there is a level B recommendation (probably effective) for the use of gabapentin, alprazolam, atenolol, sotalol, and topiramate (Dsiiewicz et al., 2005).

IV. Usual Approach in Clinic

- I start with Propranolol, aiming for 40-60mg bid, unless there is a contraindication. I subsequently transition the patient to extended release formulation.
- In case of no response to Propranolol (unusual), I next try Primidone at starting dose of 50mg bid.
- I often use Topiramate as an alternative adjunctive agent (starting with 50mg bid).

V. Non-medical Treatment of Essential Tremor

- Two surgical treatments have been shown to be effective for the treatment of medically refractory, disabling limb ET (level C recommendations):
  - Deep brain stimulation through an electrode implanted in the ventral intermediate nucleus of the thalamus (contralateral to the more disabled arm).
  - Surgical lesioning of VIN of the thalamus (thalamotomy).

V. Comparing Surgical Options

- When compared, the two methods were found to be equally effective at reducing tremor (Schuurman et al., NEJM, 2000). However, thalamic stimulation was associated with fewer adverse effects (level B recommendation).
- Potential risks of surgery: Speech and gait deficits, among other. Careful risk/benefit assessment prior to surgery.
- Other notes: Bilateral stimulation often needed to control head tremors.

V. Botulinum Toxin

- Botulinum toxin A may reduce hand tremor (level C recommendation).
- However, it is sometimes associated with hand weakness.
VI. Treatment of Other Tremors

- Resting tremor, in the context of parkinsonism, often is challenging to treat and, arguably, may not be necessary to treat:
  - Levodopa often improves bradykinesia and rigidity, but not tremor
  - If necessary to treat, anti-muscarinic agents, especially Trihexyphenidyl, are more likely to help than Levodopa

Treatment of Medication-Induced Tremors

- Important to identify reversible causes of parkinsonism, including neuroleptic agents (not only limited to old generation)
  - Resting tremor is a common manifestation of “extra-pyramidal” symptoms. Could appear identical to that of idiopathic Parkinson’s Disease.
- Dilemma of enhanced physiological tremor (EPT)
  - Not always feasible to discontinue the offending agent (for example, patient with difficult to control epilepsy who finally becomes controlled on Valproic Acid).
  - Although phenotypically similar to essential tremor, EPT does not respond as well to mainstream treatments.

Conclusions

- Action tremor is one of several types of tremor, and essential tremor is the most frequent cause
- The diagnosis of essential tremor necessitates excluding other etiologies of action tremor
- Goals of treatment are to reduce tremor amplitude, improve function and/or reduce social embarrassment
- Propranolol and primidone remain the first-line therapies
- For disabling, medically refractory tremor, chronic unilateral thalamic stimulation or thalamotomy are effective surgical options

Citations


Audience Response System Question

1. **Which is the more disabling type of tremor:**
   1. Resting tremor
   2. Action tremor

2. **The following are examples of pathological tremors except:**
   1. Un-enhanced physiological tremor
   2. Resting tremor
   3. Intention tremor
   4. Essential tremor
3. This type of tremor is typically seen in the setting of cerebellar disease:

1. Resting tremor
2. Essential tremor
3. Intention tremor
4. Physiological tremor

4. The following tremors are progressive except:

1. Essential tremor
2. Physiological tremor
3. Tremors associated with Parkinson's disease (rest, action)
4. Tremor associated with idiopathic dystonia

5. The goal of treatment for essential tremor is to:

1. Reduce the amplitude of the tremor
2. Reduce functional impairment
3. Reduce the patient's social embarrassment
4. 2 and 3
5. All of the above

6. The following medication(s) are first-line treatments for essential tremor:

1. Propranolol
2. Primidone
3. Gabapentin
4. 1 and 2
5. 2 and 3

7. Selective beta-1 adrenergic blockers are more effective than non-selective agents for the treatment of essential tremor:

1. True
2. False

8. A toxic reaction, including GI and neurological symptoms, is commonly encountered with early primidone therapy:

1. True
2. False
Audience Response System Question

9. Thalamic stimulation results in fewer adverse effects compared to thalamotomy:

1. True
2. False
The following medications were discussed in this presentation. The table below lists the generic and trade name(s) of these medications.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
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<tbody>
<tr>
<td>Alprazolam</td>
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<tr>
<td>Atenolol</td>
<td>Tenormin</td>
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<td>Gabapentin</td>
<td>Horizan, Neurontin</td>
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<td>Levodopa</td>
<td>None</td>
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<tr>
<td>Nifedipine</td>
<td>Adalat CC, Afeditab CR, Procardia</td>
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<tr>
<td>Nimodipine</td>
<td>Nymalize</td>
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<td>Primidone</td>
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<tr>
<td>Valproic Acid</td>
<td>Depakene</td>
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