Case Studies in Movement Disorders

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Disclosures

- Marissa Dean receives research support as the PI from the following clinical trial companies: MJFF for Parkinson's Research; Parkinson's Foundation; Sage Therapeutics
- Marissa Dean has served as a consultant for Neurocrine Biosciences
- Victor Sung has served as a consultant for Genentech and Teva.
- No off-label use of treatments will be discussed.

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Objectives

- Recognize and describe phenomenology in common and uncommon movement disorders
- Be able to create a differential diagnosis for involuntary movements through case discussions
- Create a workup and treatment plan for movement disorders through case presentations

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Acknowledgments

- Dr. Carolina Parker
- Patients and families for allowing the sharing of videos

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Case 1: Parkinson's disease?

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Case 1

- 59 yo RH man for second opinion of PD diagnosis
- 8 years ago – 'limping' with right leg
  - Progressively worsened over time; now with some stiffness in left leg
- 3 years ago – PCP noted right hand rest tremor
  - Associated with some difficulty with fine motor tasks
  - Slower overall – walking, ADLs
- 2 years ago – saw Neurologist and dx with PD
  - Started carbidopa/levodopa 25/100 mg 1 tab TID with improvement of symptoms

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Case 1

- Within past year:
  - Notices rest tremor in left hand
  - 1 fall in past 6 months
  - Describes festination of gait (walks fast with short strides)
  - No freezing
  - Still on same dose of carbidopa/levodopa, but symptoms progressing

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Case 1

- Additional symptoms
  - No anosmia
  - No dream enactment (lives alone)
  - + constipation (since starting quetiapine 1 year ago)

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Case 1

- Medical history
  - Schizophrenia – dx at 25 yo (34 years ago)
    - Symptoms at presentation included isolation, other negative symptoms, paranoia, delusions (no clear hallucinations)
    - Started olanzapine 28 years ago – caused jaw tremor
  - HTN, HLD, cataracts
- Relevant medications
  - carbidopa/levodopa 25/100 mg 1 tab TID (5a, 10a, 3p)
  - olanzapine 15 mg QHS
  - quetiapine 600 mg QHS
  - propranolol 20 mg BID ;
  - mirtazapine 30 mg QHS
- Prior medications
  - carbidopa/levodopa 25/100 mg 1.5 tab TID – caused him to feel 'manic'

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Case 1

- Family history
  - Schizophrenia – mother
  - No known neurological disease.
- Social history
  - Lives by himself
  - Assoc degree in computer science
  - Works full time at local grocery store
  - No etoh, tobacco, or illicit drugs

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Case 1 – exam

- Eye movements – normal
- Muscle tone
  - Rigidity – moderate in BUE, BLE (R>L)
- Reflexes
  - Grade 1 in arms, absent in legs, downgoing plantar response
- Sensation – normal

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Case 1 – video

Case 1 – group discussion

- What are the abnormal movements?
- Differential?
- Can you have PD ***and*** schizophrenia (SCZ)?

PD + SCZ = rare

- Limited to a handful of case reports since 1980s
- Opposing pathophysiology
  - PD – hypodopaminergic transmission in SN
  - SCZ – hyperdopaminergic transmission in mesolimbic pathway
- Opposing treatments
  - PD – dopamine receptor agonists
  - SCZ – dopamine receptor antagonists

Reference:
Kuusimaki et al, Mov Disord, 2021

Author	Patient profile
Friedman *et al.*[4]	32-year-old male with long-standing psychotic illness (autopsy confirmed diagnosis of IPD)
Lam[5]	58-year-old female with chronic schizophrenia (autopsy confirmed diagnosis of IPD)
Höflich *et al.*[23]	43-year-old female with schizophrenia
Orr *et al.*[3]	33-year-old female with schizophrenia
Urban *et al.*[6]	47-year-old female with schizophrenia
Winter *et al.*[1]	35-year-old male with schizophrenia
Habermeyer *et al.*[7]	64-year-old male with schizophrenia
Fujino *et al.*[8]	71-year-old male with chronic schizophrenia
de Jong *et al.*[10]	55-year-old male with schizophrenia
Gadit[21]	57-year-old male with schizophrenia
Amorim[24]	70-years-old male with schizophrenia
Stoner *et al.*[25]	52-year-old male with treatment-resistant schizophrenia

Reference:
Grover, Sahoo, and Goyal, Indian J Psychol Med, 2017.

Current views on SCZ pathophysiology

- More complex and heterogenous disorder
- DA dysregulation likely occurring in specific pathways + imbalance of excitatory/inhibitory pathways (glutamate/GABA)
- DA dysregulation not seen in all patients
- 25-30% of SCZ don't respond to D2 antagonists, but do respond to clozapine (higher affinity for D1)

Reference:
Kuusimaki et al, Mov Disord, 2021

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Large retrospective review in Finland

- Regional cohort of PD-treated patients (n=3045)
  - Prevalence of earlier SCZ dx – **0.46%** (0.1% in age/sex matched controls)
  - Prevalence of earlier schizophrenia spectrum disorder – **0.76%** (0.16% in age/sex matched controls)
- National cohort of PD (n=22,189)
  - Prevalence of earlier SCZ dx – **0.65%** (0.61% in age/sex matched controls)
  - Prevalence of earlier schizophrenia spectrum disorder – **1.5%** (1.31% in age/sex matched controls)

Reference:
Kuusimaki et al, Mov Disord, 2021

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So, SCZ may increase risk of PD?

- How?
  - Antipsychotic meds could predispose to hypodopaminergic state and nigral cell degeneration
  - Some patients may be normo-dopaminergic and without a dysregulated DA system

Reference:
Kuusimaki et al, Mov Disord, 2021

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Back to Case 1

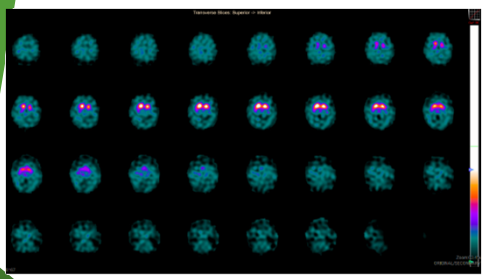
- So, SCZ + PD = possible?
- What can we do to help answer this question of PD?
  - Change olanzapine to alternate treatment
    - Lowered and became 'manic,' so back on current dose
  - DAT scan

Uncertain about PD?

- DAT scan for confirming clinical dx of PD[1]
  - Sensitivity 79-97%
    - Higher with longer disease duration and clinically established PD diagnosis
  - Specificity 97-98%
- DAT for uncertain parkinsonism[2]
  - Sensitivity and specificity 98%

References:
[1] Raul de la Fuente-Fernandez. *Neurology,* 2012.
2Suwijn et al, *EJNMMI Res.* 2015

Case 1 - DAT scan



Case 1 – DAT abnormal

- What meds/drugs can cause abnormal DAT?
  - Cocaine, amphetamines, ephedrines, fentanyl, ketamine, PCP
  - Modafinil, bupropion
- PD and SCZ meds don't significantly interfere with binding
- Are you convinced? Does our patient have PD? Anything else we can do?

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Uncertain about PD?

- Syn-One skin biopsy
  - NIH clinical trial results discussed as platform presentation at AAN 2023 (Synuclein-One Study)
  - 96 PD, 127 other synucleinopathies, 120 healthy
  - PPV 95.5% for all synucelinopathies; NPV 96.7%
  - 3 sites – neck, thigh, calf
  - Detects alpha synuclein in skin nerve fibers

Reference:
CND Life Sciences – cndlifesciences.com

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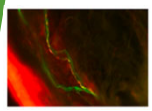
Case 1 – Syn-One skin biopsy

Phosphorylated Alpha-Synuclein (P-Syn)



Bx Site	P-Syn Deposition	Description
Posterior Cervical (Right)	Abnormal	One colocalized fiber seen across all stained sections.
Distal Thigh (Right)	Normal	No phosphorylated alpha-synuclein deposition observed in stained sections.
Distal Leg (Right)	Normal	No phosphorylated alpha-synuclein deposition observed in stained sections.

The green regions indicate PGP9.5 immunostained nerve fibers. The regions in red/orange are immunostained regions of phosphorylated alpha-synuclein within nerve fibers. This region displays evidence of phosphorylated alpha-synuclein deposition.

Conclusions

Synucleinopathy: There is pathologic evidence of phosphorylated alpha-synuclein deposition within cutaneous nerves. This finding is consistent with a diagnosis of an alpha-synucleinopathy. Clinical correlation is required to distinguish the type of synucleinopathy.

Small Fiber Neuropathy: There was reduced intraepidermal nerve fiber density. This can be seen in peripheral and central neurodegenerative disorders as well as small fiber neuropathy and polyneuropathies.

Amyloidosis: There is no pathologic evidence of amyloid deposition in cutaneous nerves. A normal Congo red stain does not exclude a diagnosis of amyloidosis.

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Case 1 – our patient

- Discussed DAT and skin biopsy results and confirmed diagnosis of PD *and* SCZ
- How to treat?
  - Our patient: low dose carbidopa/levodopa + olanzapine/quetiapine + propranolol (tremor)

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Author	Patient profile	Psychosis during treatment with anti-PD medications	Antipsychotic used for treatment of psychosis
Friedman *et al.*[4]	32-year-old male with long-standing psychotic illness (autopsy confirmed diagnosis of IPD)	Worsening of existing psychosis	Clozapine
Lam[5]	58-year-old female with chronic schizophrenia (autopsy confirmed diagnosis of IPD)	Worsening of existing psychosis	Clozapine
Hoflich *et al.*[24]	43-year-old female with schizophrenia	Worsening of existing psychosis	Clozapine + ECT
Orr *et al.*[7]	33-year-old female with schizophrenia	No relation with anti-PD drugs	Psychosis and IPD symptoms both responded to clozapine
Urban *et al.*[8]	47-year-old female with schizophrenia	No relation with anti-PD drugs	Increase in parkinsonian symptoms with FGA and SGA and good response to clozapine
Winter *et al.*[1]	33-year-old male with schizophrenia	No relation with anti-PD drugs	Clozapine
Habermeyer *et al.*[7]	64-year-old male with schizophrenia	Worsening of existing psychosis	Quetiapine
Fujino *et al.*[8]	71-year-old male with chronic schizophrenia	Worsening of existing psychosis	Aripiprazole improved both IPD and psychosis
de Jong *et al.*[16]	55-year-old male with schizophrenia	Worsening of existing psychosis	Clozapine
Gude[25]	57-year-old male with schizophrenia	Worsening of existing psychosis	Risperidone low dose (1.5 mg)
Amorim[26]	70-years-old male with schizophrenia	Parkinson plus syndrome at 68 years of age and had worsening of psychosis with syndopa	Risperidone 1 mg/day+depot paliperidone 75 mg monthly
Stoner *et al.*[23]	52-year-old male with treatment-resistant schizophrenia	No relation with anti-PD drugs	Quetiapine

IPD – Idiopathic Parkinson's disease; PD –Parkinson's disease; SGA – Second-generation antipsychotic; FGA – First-generation antipsychotics; ECT – Electroconvulsive therapy

Reference:
Grover, Sahoo, and Goyal; Indian J Psychol Med, 2017.

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Case 1 – take home points

- Although rare, PD and schizophrenia can co-occur
  - Drug-induced parkinsonism is much more common
- Consider DAT or Syn-One skin biopsy for diagnosis
- Treatment is challenging and will likely include clozapine and/or quetiapine

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Case 2: Parkinson's disease?

Case 2

- 48 yo LH CM presents to establish care for PD after moving
  - 4 years ago
    - Wife noticed a softer speech later in the day
    - While at a work conference, noticed his left leg was weak, felt off-balance, and seemed more fatigued than usual
    - A week later, noticed left arm 'drawing up' during exercise
    - Saw a Neurologist – had normal MRI brain, told was due to stress and to relax

Case 2

- 2 years ago
  - Fatigue worsened; started on amitriptyline at night, which improved fatigue and sleep overall
  - Started having issues with handwriting
  - Saw new Neurologist – told it was stress-related
  - Then, started to drag left foot and had large jerks in left arm
  - Got another opinion – diagnosed with PD

Case 2

- Symptoms now:
  - Occasional tremor in left hand with handwriting and extending arm
  - Stiffness/pain in left arm; some difficulty with fine motor tasks
  - Still sometimes drags left leg; no falls or imbalance
  - +hypophonia
  - No anosmia or dream enactment
  - +constipation, managed with diet
- Prior meds:
  - Carbidopa/levodopa 25/100 mg 4 tabs TID – no significant benefit; worsened pain in left arm
  - Baclofen – didn't help pain in left arm

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Case 2

- Medical history – OSA on CPAP (adherent)
- Medications – amitriptyline 50 mg QHS
- Family history –
  - Bilateral hand tremor – father
  - Parkinsons - brother (dx 24 yo), 2 paternal uncles (dx 18 yo and 30 yo), 2 paternal aunts, paternal great grandmother
- Social history – Prior employment with US Airforce; now doing consulting. No alcohol, tobacco, or illicit drug use.

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Case 2 – exam

- Eye movements – normal
- Muscle tone – mild rigidity in left upper and lower extremity
- Reflexes – grade 2 throughout with down going plantar response bilaterally
- Sensation – normal

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Case 2 – video

Case 2 – group discussion

- What are the abnormal movements?
- Does he have PD?
- Differential?

Approach to differential

- Young-onset parkinsonism (21-50 yo)
- +dystonia
- Strong family hx of YOPD in AD pattern

Possible AD genetic etiologies

- Monogenic Parkinson's disease
  - SNCA (young or late onset PD, +cog changes, +psych, +ataxia/myoclonus)
  - LRRK2, GBA – usually adult-onset
- Neurodegen with brain iron accumulation (NBIA)
  - Neuroferritinopathy (FTL) - +dystonia, +cog, +psych
- Fahr's disease - +dystonia, +chorea/tremor/ataxia

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Possible AD genetic etiologies

- Dopa-responsive dystonia (GCH1) – onset in childhood/20s, +diurnal fluctuation, +levodopa response
- Rapid onset dystonia-parkinsonism (ATP1A3) – abrupt onset with limited progression, +dystonia
- SCAs (several) - +parkinsonism, +ataxia/chorea

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Workup

- MRI brain w/out contrast – normal
- CT head w/out contrast - normal
- Genetic testing:
  - ***ATP1A3 pathogenic variant***
  - *Same mutation confirmed in 2 paternal uncles and brother*
  - *Paternal grandmother (asymptomatic) donated brain to science – also had mutation*

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ATP1A3-related neurologic disorders

- RODP
- Alternating hemiplegia of childhood
- Cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS syndrome)

Reference: Brashear et al, *Gene Reviews*, 2018.

RODP

- Abrupt onset over minutes to 30 days
- Triggers include medical/emotional stress, childbirth, etoh binging
- Face>arm>leg
- Prominent bulbar findings
- Absent/minimal response to levodopa
- Dystonia can precede abrupt RODP phenotype
- Second event has been described in some

Reference: Brashear et al, *Gene Reviews*, 2018.

Case 2 – treatment

- Botulinum toxin with PM&R in left arm and leg – beneficial
- Trihexyphenidyl – provides some benefit
- At 51 yo, had rapid onset of speech/swallowing changes over 24 hours that plateaued
  - Unchanged since that time
- Minimal progression of motor symptoms over last 8 years

Case 2 – take home points

- Consider genetic etiologies with young-onset parkinsonism + dystonia
- PD GENEration – free genetic testing for adults diagnosed with PD
  - *GBA, LRRK2, PRKN, SNCA, PINK1, PARK7* and *VPS35 genes*
  - https://www.parkinson.org/advancing-research/our-research/pdgeneration

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Case 3: focus on a new treatment

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Case 3

- 53yo left handed F initially presented 5 years ago with L hand rest tremor
- Followed in clinic for migraine, tremor was noted on exam and just observed
- Tremor then became impairing at work (postal worker) and having dexterity problems
- On exam, L sided bradykinesia, mild rigidity, and rest tremor
- Diagnosed with PD at age 49

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Case 3

- Additional history
- She occasionally has diplopia with the movements and others have noted that her eyes may have jerky movements as well
- There is no abnormality of speech or swallowing
- Other than some word-finding difficulties at times, no other cognitive symptoms
- Has some depression/anxiety but no other significant psychiatric symptoms

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Case 3

- Started on rasagiline 1mg daily with some benefit (4 years ago)
- Tremor worsening, so Requip XL added 2 years ago, titrated to 6mg daily, developed intolerable sedation/nausea at 8mg
- Tried Sinemet 25/100, developed severe nausea at BID and stopped
- Added Cala Trio 1 year ago

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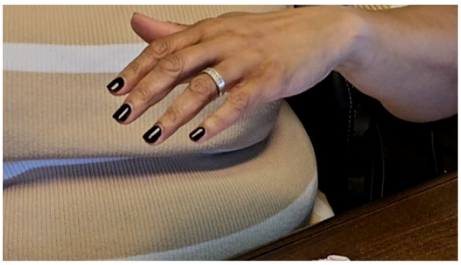
Case 3 – pre-treatment



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Case 3 – post-treatment

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Case 3 – Cala Trio / kIQ

- Transcutaneous Afferent Patterned Stimulation (TAPS) therapy
- Stimulation applied at median and radial nerves then modulates VIM output
- 42% reduction in tremor amplitude in ET patients
  - Improvement in ADL's vs. sham
  - Improvement in TETRAS scores vs. sham
- 64% reduction in tremor amplitude in PD patients

Pahwa R et al, *Neuromodulation* 2019
Brillman S et al, *Tremor Other Hyperkin Mov* 2023

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Cala Trio / kIQ

- 40 minutes of stimulation twice daily
- Average duration of benefit is 90 minutes after each stimulation session
- Replacement bands required roughly 1-2x/year
- Gained Medicare coverage June 2024
- Submit letter of medical necessity/order form
- Perform Bain/Findley and submit with request

Reference: Thomas M, Jankovic J. *CNS Drugs.* 2004;18:437-452

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Cala kIQ

Please note if the patient should use the alternative postural wing beating hold.

LETTER OF MEDICAL NECESSITY

Diagnosis ICD-10 Code (required):
☐ **G25.000 Essential tremor** ☐ **Other** _____
☐ Confirmation: Patient does not have any of these contraindications:
- An implanted electrical medical device, such as a pacemaker, defibrillator, heart monitor, insulin pump, bladder stimulator, or deep brain stimulator
- Suspected or diagnosed epilepsy or other seizure disorder
- Pregnancy

☐ Confirmation: Patient tremor is not caused by:
- Medication-induced tremor
- Thyroid issues (e.g., hyperthyroidism)
- Metabolic disorders (e.g., B-12 deficiency)

Unique Patient Characteristics (check all that apply)
☐ Negative impacts to quality of life
☐ Forced to change jobs/retire/end employment
☐ Depression
☐ Anxiety/Stress
☐ Medications causing side effects
☐ Tremor responds to alcohol
☐ Not a candidate for deep brain stimulation or focused ultrasound
☐ Additional comments (attach if needed) _____

Clinical Findings (check all that apply)
☐ Family History of tremor
☐ Uncontrolled shaking
☐ Tremors on action or intention
☐ Difficulty holding items
☐ Frequently spills/drops items
☐ Difficulty eating normally
☐ Difficulty with dressing/daily hygiene needs
☐ Difficulty writing legibly/signature
☐ Difficulty using cell phone/computers

Reasons Cala TAPS Therapy is Required (check all that apply)
☐ Ability to improve daily function for independent self-care
☐ Patient has failed to improve with usage of traditional treatment options
☐ Shared Decision patient wants to try non-pharmacological therapy, non-invasive treatment

Previous Pharmacological Treatments (check all that apply)
☐ Primidone
☐ Propranolol
☐ Other _____
☐ Contraindicated to pharmacology

PRESCRIBER AUTHORIZATION

This document serves as a Standard Written Order, Prescription, and Letter of Medical Necessity for Cala TAPS Therapy for this patient. As this patient's physician, I attest that the clinical findings on this document accurately reflect the health information. I certify that the Cala TAPS Therapy

Bain & Findley

For each item circle the number which describes how easy or difficult it is for you to perform the activity.

Item number	Item Description	Score
1	Cut food with a knife and fork	1 2 3 4
2	Use a spoon to drink soup	1 2 3 4
3	Hold a cup of tea	1 2 3 4
4	Pour milk from a bottle or carton	1 2 3 4
5	Wash and dry dishes	1 2 3 4
6	Brush your teeth	1 2 3 4
7	Use a handkerchief to blow your nose	1 2 3 4
8	Use a bath	1 2 3 4
9	Use the lavatory	1 2 3 4
10	Wash your face and hands	1 2 3 4
11	Tie up your shoelaces	1 2 3 4
12	Do up buttons	1 2 3 4
13	Fix up a zip	1 2 3 4
14	Write a letter	1 2 3 4
15	Put a letter in an envelope	1 2 3 4
16	Hold and read a newspapers	1 2 3 4
17	Use a telephone	1 2 3 4
18	Make yourself understood on the telephone	1 2 3 4
19	Watch televisions	1 2 3 4
20	Pick up your change in a shop	1 2 3 4
21	Insert an electric plug into a socket	1 2 3 4
23	Unlock your front door with the key	1 2 3 4
23	Walk up and down stairs	1 2 3 4
24	Get up out of an armchair	1 2 3 4
25	Carry a full shopping bag	1 2 3 4

KEY:

Score	Score Description
1	Able to do the activity without difficulty
2	Able to do the activity with a little effort
3	Able to do the activity with a lot of effort
4	Cannot do the activity by yourself

IT Bain PG Findley LJ. Atkinson P, et al. Assessing tremor severity. *Journal of Neurology, Neurosurgery& Psychiatry*. 1993;56(8):866-73.

Cala kIQ – My experience

- Great new non-invasive treatment option
- Has INCREASED my referrals for DBS (if they fail Cala device)
- Education on proper use is key – requires titration and consistent use up front
- Not all patients respond
- For very large amplitude tremor, will not be as effective as DBS

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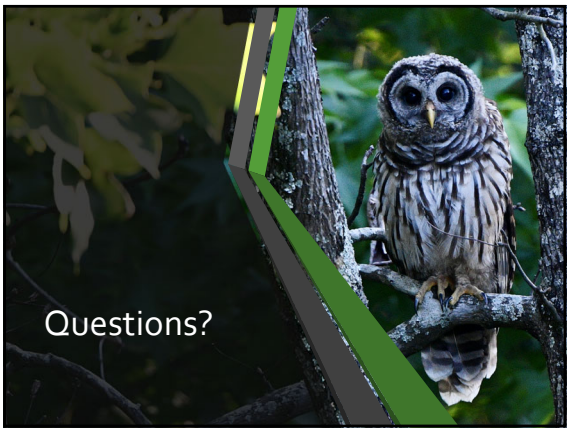
Questions?