Updates in Movement Disorders Hawai'i Association of Osteopathic Physicians and Surgeons

THE QUEEN'S HEALTH SYSTEMS

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The Queen's Medical Center, Neuroscience Institute
June 1, 2024

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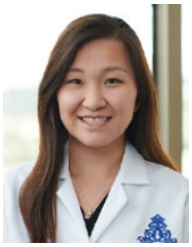
Speaker details

- Fay Gao – The Queen's Medical Center
  - Movement disorders neurologist at The Queen's Medical Center, Neuroscience Institute, and Program Director of Neuromodulation
  - Assistant clinical professor of medicine at the University of Hawai'i John A Burns School of Medicine



- I have no financial disclosures

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Overview of the talk

- Updates in Parkinson's disease: evaluation, pathogenesis, and treatment
- Research in Parkinson's disease in Hawai'i
- Updates in Essential tremor: treatment

Let's start with a question

- Do you personally know anybody who is affected with Parkinson's disease or have you ever treated any patients who had Parkinson's disease?

A. I know somebody who had Parkinson's disease personally
B. I have treated patients with Parkinson's disease
C. both A. and B.
D. neither A. nor B.

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Parkinson's Disease Overview: Pathology, Evaluation, and Management

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Case

- 72 year old woman comes to you complaining of right hand and chin tremor on rest, stiffness, and reduced dexterity for the past 3 years. She has more difficulty performing certain tasks such as using utensils, writing, and dressing. Her walking has also slowed down, but she has had no falls.
- She endorses constipation over the past 10 years and reduced sense of smell. Cognition has remained intact.
- Motor exam on videos

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Exam

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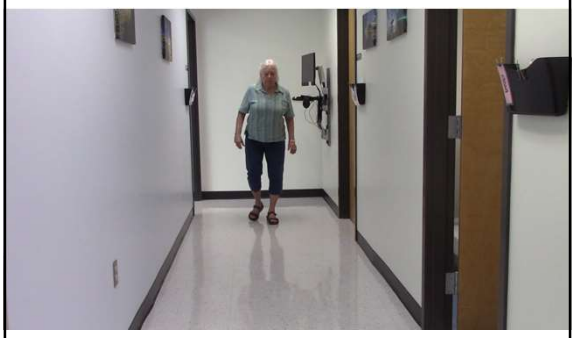
Exam



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Case

- Diagnosis: Parkinson's disease
- Poll: what would you do now?

  A. Start on carbidopa/levodopa
  B. Start on pramipexole
  C. Don't start any medications, enroll in exercise and diet regimen
  D. Not sure, refer to neurologist

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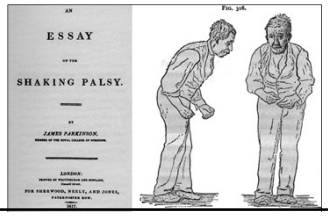
Parkinson's Disease

- Parkinson's disease is the second most common neurodegenerative disease
- First described by Dr. James Parkinson's in 1817
- Average age of onset 65; affects ~1% of population over 60, with 2:1 ratio of men : women
- Risk factors: exposure to certain environmental toxins, and family history (~10% attributable to mono or polygenic mutations)



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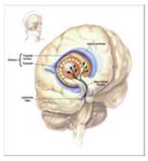
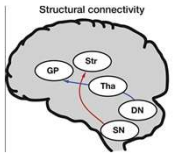
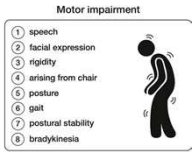
Pathology: Degeneration of Substantia Nigra: leading to reduced dopamine production







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Parkinson's Disease

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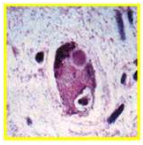
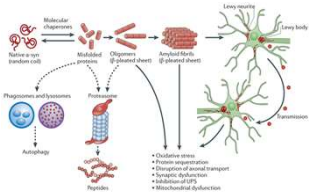
Lewy Body: Alpha synuclein (plus other protein)



- Under pathological conditions; alpha-synuclein misfolds and aggregates into insoluble oligomers
- Aggregated alpha-synuclein causes cell death
- Transmits to next neuron, and causes cascade of neurodegeneration



Staging of α-synuclein pathology by Braak et al.

But where does it start??

PARS syndrome: Parkinson's Associated Risk Syndrome

- Anosmia (Loss of smell)
- **Constipation**
- REM sleep behavior syndrome

Does Parkinson's disease actually start in the GI system?

Gut microbiome and Parkinson's disease

The microbiota-gut-brain axis, an interdependent series of communication loops between the enteric nervous system (ENS), the microbiota, the gut, and the brain, offers important insight into how changes in our gut affect distant organs like our brains.

- Gut microbiome composition change noted in PD patients
- Patients who underwent complete vagotomy (vs partial) or appendectomy had less incidence of PD
- Alpha-synuclein pathology detected in PNS: including Auerbach Plexus: retrograde transportation into dorsal nucleus of vagus

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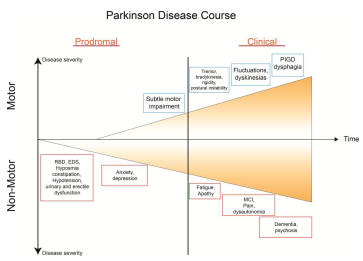
Eventually, degeneration spreads into nondopaminergic cells

- PD has widespread nondopaminergic pathology
  - Cholinergic neurons of the nucleus basalis of Mynert
  - Norepinephrinc neurons of the locus coerulus
  - Serotonin neurons in the midline raphe
  - Cerebral cortex, spinal cord, peripheral autonomic system
- PD manifests with variety of nonmotor symptoms, which are often more disabling than motor symptoms



J Jankovic J, Tan EK. "Parkinson's disease: etiopathogenesis and treatment" JNNP 2020:91:795-808.

Myth #1: There is no test to diagnose Parkinson's Disease

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Diagnosis

- Gold standard is pathological evidence of Lewy bodies (on autopsy)
- Diagnosis remains clinical, based on history and neurological examination, but there are now more ancillary tests to help support/exclude other differentials:
  - MRI, labs (exclude other disease)
  - DAT scan (dopamine transporter SPECT)
    - Evaluate integrity of pre-synaptic dopaminergic nigral-striatum system
    - Available at Queen's
    - Differentiate degenerative condition (PD, parkinsonism) vs non-degenerative condition (ET, tardive, vascular)
  - **Syn-One skin biopsy (new)**
    - Alpha synuclein seeding amplification assay
    - 3mm punch biopsies from skin x3
    - High sensitivity (96%) and specificity (99%)
  - **CSF biomarker (under investigation)**
    - Alpha-synuclein RT-quic in CSF

Treatment of Parkinson's Disease

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Myth #3:
There is nothing we can do about it. It gets worse and worse.

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Treatment Options and Strategies for Parkinson's Disease

- Ideally Cure/Reversal: thus far not available
- Neuroprotective: Prevent disease progression
  - No medicine/supplements thus far
  - Exercise
  - Diet: Mediterranean, MIND diet
- Compensatory
  - Rehabilitation to develop alternative neurocircuitry
- Education/Understanding of Disease Progression
  - Safety
  - Prevent Complications: fall, aspiration, deconditioning
  - Patient/Family to create realistic goals to have best QOL possible

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Role of Exercise

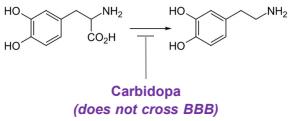
- Animal studies demonstrate neuroprotective mechanisms of exercise cortical excitation, changes in neurotrophic factors
- Regular exercise in mid-life significantly reduce the risk of developing PD later in life
- Shown to improve cognitive and motor scores in PD
- Able to decrease medications
- reduce dementia
- Reduce depression
- Improve sleep
- Improve constipation
- Improve QOL
- Prevent deconditioning
- Develop alternative circuit

- **Aerobic exercise should be prescribed as soon as the diagnosis is made**
  - Tailored towards patients' personal preference
  - PD specific options: PT with LSVT or PWR!, Rock Steady Boxing

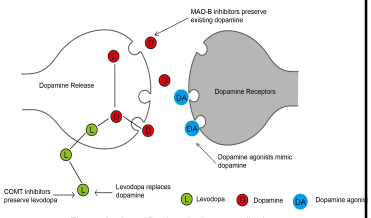
ROCK STEADY BOXING
FIGHTING BACK AGAINST PARKINSON'S

Symptomatic Medications

- When to start medication?
  - When there is a potential to improve QOL or there is a safety concern
- Which medication to choose?
  - Carbidopa/levodopa: mainstay
  - Dopamine agonists
  - MAO-B inhibitors



Carbidopa
(does not cross BBB)



The mechanism of Parkinson's disease medications

Symptomatic Medications

- Carbidopa/Levodopa:
  - Carbidopa (decarboxylase inhibitor) inhibits peripheral conversion of levodopa, reducing systemic side effects.
  - **10/100 mg is not weaker than 25/100 mg!**
  - C/L competes with protein for intestinal absorption
  - Side effects: nausea, hypotension; dyskinesias (late effect), cognitive impairment (late effect)
- Dopamine Agonists:
  - Ropinirole (Requip), pramipexole (Mirapex), rotigotine (Neupro), apomorphine (Apokyn)
  - Previously considered better initial choice due to less risk of dyskinesias, but more adverse effects: fatigue/sleep disorders, orthostatic hypotension, edema, impulse control disorders, dopamine dysregulation syndrome, cognitive impairment, hallucinations
- Selective MAO-B Inhibitors:
  - Rasagiline, selegiline, safinamide
  - Weaker effect but generally well tolerated

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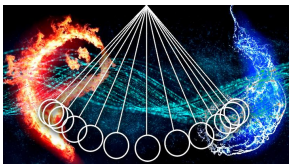
Pendulum Swing

Levodopa



Dopamine Agonist

Levodopa worked great ->
Liberal usage ->
Motor complications ->
Levodopa-Phobia ->
Dopamine Agonist ->
Problem with DA (Side effect, QOL) ->
Back to Levodopa: Minimally necessary dosage

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Case

- Our patient, the 72 year old woman with Parkinson's disease, had initial good response to carbidopa/levodopa 25/100mg, 1 tab TID.
- After 2 years, she had worsening freezing of gait and tremor.
- What do you do?

A. Switch to alternate medication
B. Add another medication
C. Increase the dose of levodopa
D. Refer for surgery

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Case

- She had an excellent response to raising dose to 2 tabs TID and had no more motor fluctuations.
- However, a year later, she returns to you complaining of recurrent off episodes of freezing and tremor, starting 1 hour before each dose.
- Motor exam on video

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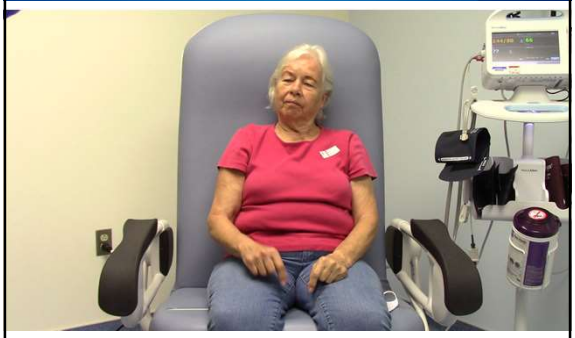
Exam



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Case

- You notice some dyskinesias on examination.
- What do you do?

A. Switch to alternate medication
B. Add another medication
C. Increase the dose of levodopa
D. Refer for surgery

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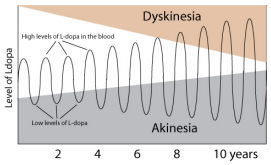
Treatment for Advanced PD

- 2 motor complications of advanced PD:
  - Dyskinesias, motor fluctuations
  - Arise from fluctuations in serum levodopa levels due to pharmacokinetics of intermittent oral administration



- Goal to achieve more steady pharmacokinetics:
  - Levodopa dosing adjustments
  - Long-acting levodopa formulations (Rytary)
  - Amantadine, long-acting Amantadine (Gocovri) for dyskinesias
  - MAO-B inhibitors: Rasagiline, Safinamide
  - Rescue: (Inbrija, Kynmobi)
  - COMT inhibitors: entacapone (Comtan), tolcapone (Tasmar), opicapone (Ongentys)
  - Adenosine receptor antagonist: istradefylline (Nourianz)
  - Alternative route of delivery: Parcopa, Rotigotine patch, Apokyn, Kynmobi
  - Deep brain stimulation, lesion surgery, MRgFUS
  - Duopa levodopa continuous intestinal gel infusion (via G-tube)

***FDA approved within past 5 years**

- NEW: subcutaneous levodopa pump (ND-0612, ABBV-951)

***pending FDA approvals**

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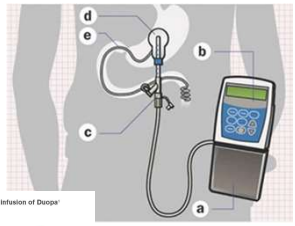
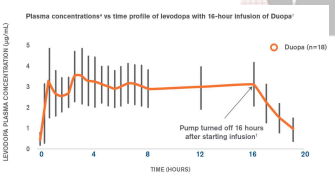
Continous duodenojejunal pump: DUOPA (carbidopa/L-dopa gel); approved 2015

- Benefits
  - Leads to near stable serum levodopa, reducing motor fluctuations
- Limitations
  - Does not improve dyskinesias
  - Involves surgical tube placement and risk of SBO and peritonitis





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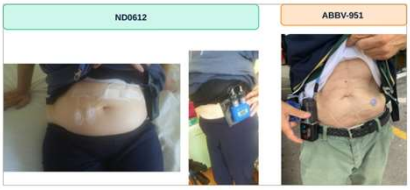
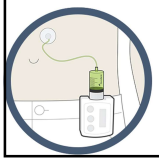
Subcutaneous levodopa pump

- Alternate to intestinal pump which does not require a surgical tube





ND-0612 – subcutaneous carbidopa/levodopa infusion

Under FDA review, expected response 2nd quarter of 2024

ABBV-951 – subcutaneous foscarbidopa/foslevodopa infusion

Rejected by FDA in 2023 due to concerns with pump, modifications submitted in 2024, under review

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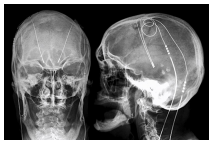
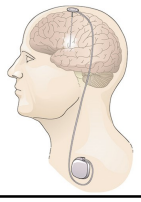
Deep Brain Stimulation

- Involves surgical placement of an electrode into a deep brain target (subthalamic nucleus or global pallidus internus), which is stimulated via a battery implanted into the chest wall
- Continuous electric stimulation results in improvement of motor symptoms, via changes in neuronal network firing, distinct from chemical pathways
  - Tremor, bradykinesia, rigidity
  - Motor fluctuations
  - Medication reduction
  - Dyskinesias and dystonia





- Approved indications:
  - Parkinson's disease (at least 3 years)
  - Essential tremor
  - Dystonia
- Off label:
  - Tardive dystonia
  - Secondary dystonia
  - Tourette syndrome
  - Orthostatic tremor
  - Holmes' tremor

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Deep Brain Stimulation

Advantages	Limitations
Uses non-pharmacologic treatment of PD symptoms, allowing for continuous motor control	Not curative or disease modifying; should not be offered to patients with unrealistic expectations
Allows for medication reduction, which often resolves dykinesias and reduces other adverse effects	May not improve gait, speech, or non-motor symptoms
Studies suggest that DBS may be more effective than medical therapy alone in patients who meet criteria	Worse outcome in patients with severe disease and functional impairment, such as those wheelchair-bound, or with dementia or psychosis
	Involves 2 operations with low but nonzero risk of surgical complications
	Lifelong hardware management, including battery replacements

- **Queen's Parkinson's and Movement Disorders Center offers Hawaii's first multidisciplinary program for DBS evaluation and implantation**

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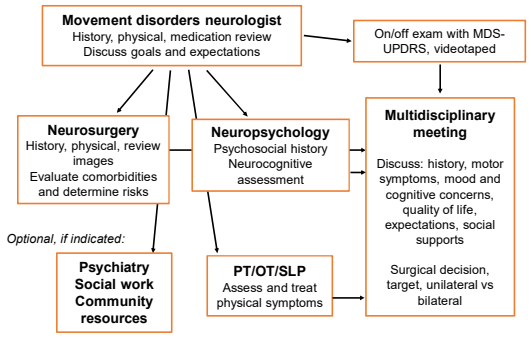
DBS candidacy evaluation multidisciplinary process



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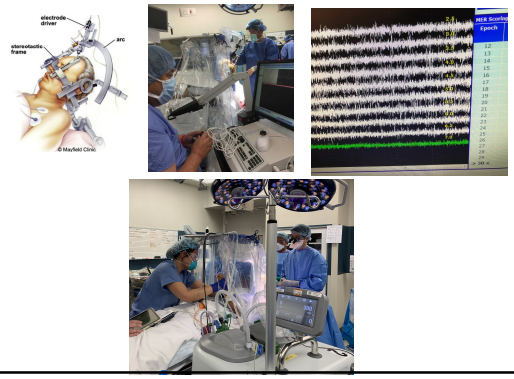
Intraoperative neurophysiologic mapping during awake DBS



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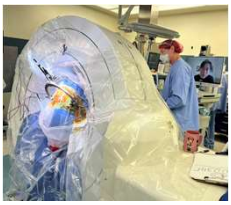
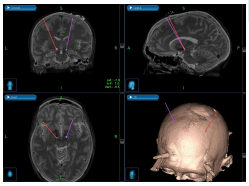
Intraoperative Portable 3D CT during awake or asleep DBS





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Case

- Our patient, now 75, is switched to Rytary. This helped to improve the off times, but her dyskinesias worsened and made her ADLs difficult.
- She was then referred for DBS evaluation, and all members of the multidisciplinary team agreed that she was an excellent candidate.
- She underwent implantation of bilateral STN leads.
- After programming, her motor exam is as follows.

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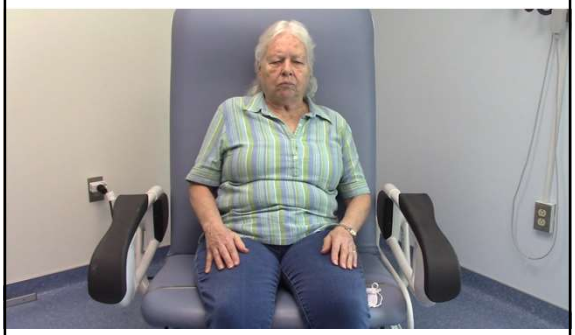
Before and After DBS



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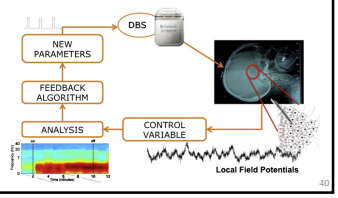
New and Coming Advances in DBS

- Exact mechanism of therapeutic effects is unknown, but leading hypothesis is that local and network wide effects of stimulating neurons lead to modulation of oscillatory activity. Specifically, the stimulation disrupt pathological oscillations of networks.
- Directional steering – allows for greater degree of flexibility in programming options
- Brain sensing – the electrode samples neurophysiologic information that informs the operator and helps them make the optimal programming choices
- Future – "adaptive DBS" A "closed loop" system that responds to patient's neurophysiologic information immediately, without use of an external operator



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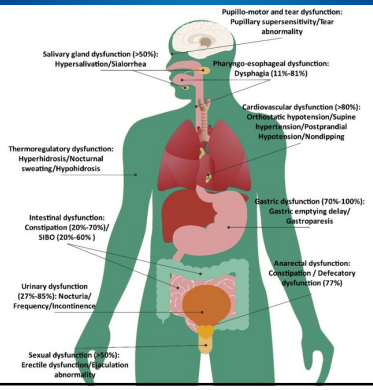
Treatment of Non-Motor Symptoms



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Treatment of Non-Motor Symptoms

- Depression
  - ?dopaminergic medications
  - SSRIs and SNRIs
- Fatigue
  - Multifactorial: low-dopamine state, depression, sleep disorder, polypharmacy
  - ?amantadine, SSRI
- Sleep disorders
  - REM sleep behavior disorder: melatonin, clonazepam
  - Restless legs syndrome: iron, dopamine agonist, gabapentin
  - Insomnia
- Cognitive impairment
  - Acetylcholinesterase inhibitors
- Psychosis: hallucinations, delusions
  - Acetylcholinesterase inhibitors
  - Atypical neuroleptics: quetiapine, clozapine
  - 5HT2A (serotonin) antagonist/inverse agonist: pimavanserin (Neuplazid)
- Autonomic dysfunction
  - Neurogenic orthostatic hypotension
    - Nonpharmacologic: salt/fluid, reduce/stop antihypertensives, compression stockings, HOB elevation
    - Sympathomimetics (midodrine, droxidopa), mineralocorticoids (fludricortisone), pyridostigmine
  - Constipation
    - Stool softeners, laxatives, GI motility-promoting agents (linaclotide)
  - Drooling (sialorrhea)
    - Atropine, glycopyrrolate, botulinumtoxin
  - Urinary urgency
    - Anticholinergics, mirabegron, botulinumtoxin injections

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Parkinson's disease care and research in the State of Hawai'i

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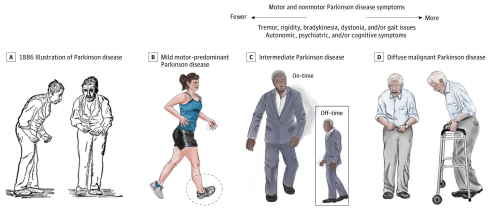
Changing Face of Parkinson's Disease

- **Growing Interest in Gender and Ethnic Diversity**



From: **Time for a New Image of Parkinson Disease**
JAMA Neurol. 2020;77(11):1345-1346.

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Prevalence of Parkinson's Disease in Hawaii

- **Hawaii's population: 1.43 million**
- **Ranks 8th/50 states in ratio of seniors**
- **Estimated 6,500-8,000 PD patients**
- **Projected to double in 2030**

~Based on

- 'Prevalence of Parkinson's disease across North America" by Parkinson Foundation (2018)
- US Census Bureau data
- Dr. Webster Ross (PHREI, VA, expert on PD epidemiology in Hawaii, and PI of Honolulu-Asia Aging Study)

- **Hawaii's Unique Challenges**
  - Lack of ethnic data
  - Geographical isolation
  - Queen's in the process of supporting a new grant for the state: SB2029 "The establishment of a Parkinson's data collective"

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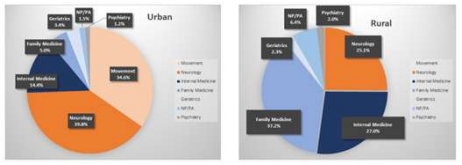
Disparity and Access

Clinical Parkinsonism & Related Disorders
Available online 22 April 2022, 100144
In Press, Journal Pre-proof

Difference in Rural and Urban Medicare Prescription Pattern for Parkinson's Disease in Hawai'i

Michiko K. Bruno [a, b, III], Gina Watanabe [b], Fay Gao [a, b], Todd Sirto [a, b], Kanoma Nakagawa [a, b], Connie Trinacty [c], Stacy Brown [a, b], Deborah A. Taira [c]

Figure 1: Prescriber Specialist Comparison of Urban vs Rural Standardized 30-day prescriptions



Difference between Urban vs Rural specialty p<0.001

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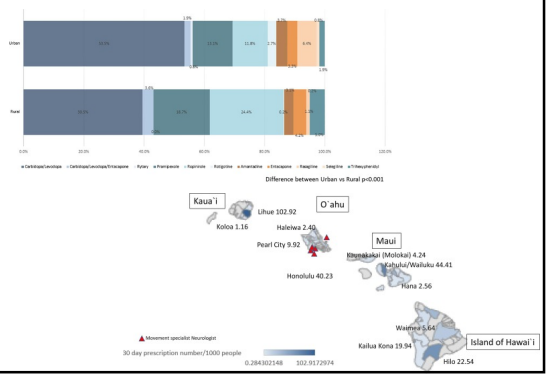
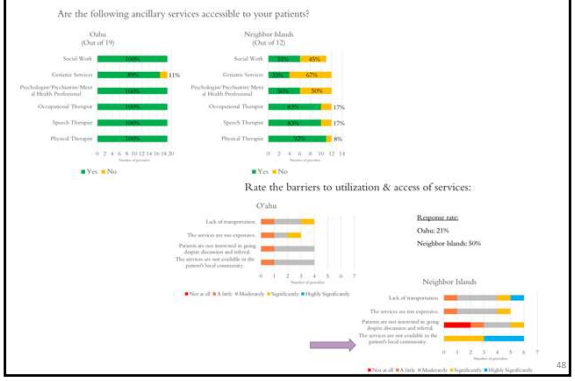


Summer 2022: Survey to understand the challenges and barriers faced by rural providers in Hawai'i



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Summer 2022: Survey to understand the challenges and barriers faced by rural providers in Hawai'i

I recommend the following resources to patients (check all that apply):

	Oahu Providers	Neighbor Islands Providers
N	19	12
Local support groups	18 (95%)	5 (42%)
Local exercise groups	14 (74%)	4 (33%)
Online resources for patient education	8 (42%)	3 (25%)
Michael J. Fox Foundation website	3 (16%)	2 (17%)
Davis Phinney Foundation website	1 (5%)	1 (8%)
National Parkinson's Disease Foundation	7 (37%)	3 (25%)
American Parkinson's Disease Association	6 (32%)	2 (17%)
Hawai'i Parkinson's Association website	8 (42%)	1 (8%)
Other	1 (5%)	0 (0%)
Community events	4 (21%)	3 (25%)

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Parkinson's and Movement Disorder Center

THE QUEEN'S MEDICAL CENTER

The Parkinson's and Movement Disorder Center at Queen's Neuroscience Institute is a multi-disciplinary program dedicated to comprehensive diagnosis and treatment for movement disorders.

Using a team-based approach, the Parkinson's and Movement Disorder Center offers a wide spectrum of treatments:

- **Complex medication adjustments**
- **Botulinum toxin injection therapy**
- **Deep brain stimulation (DBS) surgery**
- **Interjejunal continuous dopamine infusion (duopa) therapy**
- **Physical, occupational, and speech therapy**

Telehealth service is also available.

Our goal is to help patients achieve the best quality of life while living with Parkinson's diesease and other movement disorders.

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In July 2022, we received Hawaii's first "Comprehensive Care Center" designation by Parkinson's Foundation

Parkinson's Foundation Announces Major Global Care Network Expansion

Parkinson's Foundation

Ten new centers designated in the U.S.

NEW YORK & MIAMI (June 30, 2022) — The Parkinson's Foundation has announced the expansion of its Global Care Network in the U.S. with the addition of four Centers of Excellence and six Comprehensive Care Centers. The expansion aims to increase access to high-quality Parkinson's disease (PD) care nationwide and to recognize those Centers that are providing excellent care within a broad geographic region.

The Foundation's Comprehensive Care Center designation also recognizes medical centers that excel in utilizing a specialized, multidisciplinary team approach to: provide the highest level of evidence-based, patient-centered care; demonstrate leadership in professional training; and conduct impactful patient education and community outreach. Each of the six new centers reaches a new market, including the first-ever locations in the states of Michigan, Hawai'i, Louisiana, Connecticut and Arkansas. The newly designated Comprehensive Care Centers include:

- Spectrum Health (Grand Rapids, MI)
- Queens Medical Center (Honolulu, Hawaii)
- Ochsner Neuroscience Institute (New Orleans, LA)
- Hartford HealthCare (Hartford, CT)
- University of Tennessee Medical Center (Knoxville, TN)
- University of Arkansas Medical Sciences (Little Rock, AR)

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Efforts to improve research and access

THE QUEEN'S HEALTH SYSTEMS

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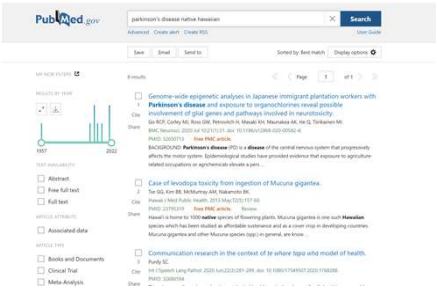
Pub Med Search ~ "Parkinson's disease" and "Native Hawaiians" results in……



NOTHING!!

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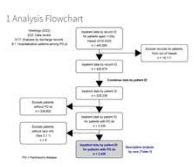
Michael. J. Fox Foundation 3-year grant

- Disparities in Care of Parkinson's Disease Patients Among Asian Americans, Native Hawaiian, and Pacific Islanders: A Retrospective Analysis of Hospitalization and Pilot Study for a Prospective Longitudinal Cohort.

Part 1: Retrospective analysis of PD hospitalizations in the state of Hawai'i.

Aim: To determine relative frequencies of PD in hospitalizations of AA and NHPI compared to Caucasians.



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PDGENEration and Global Parkinson's Genetics Program (GP2)

PDGENE (sponsored by the Parkinson's Foundation)
- Genetic testing and genetic counseling for 7 Parkinson's-related genes, including: GBA1, LRRK2, SNCA, VPS35, PINK1, and PARK7.
- A genetic data and sample repository for PD for future research.

GP2 (sponsored by the Michael J. Fox Foundation)
- Full genomic sequencing.
- Research to identify new genes related to PD.

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Parkinson's Foundation

Positive Result Example

- 44 year old male who developed right hand tremor at age 39, diagnosed with Parkinson's at age 41.
- Excellent response to carbidopa/levodopa, with near normal function when "on".
- However, quickly developed motor fluctuations with wearing off 2 hours after doses. Also developed severe dyskinesias at peak dose.
- Now taking carbidopa/levodopa 1.5 tabs every 2 hours when awake.
- Referred for DBS evaluation.
- Given very young age of onset, referred to PDGENE for testing.

Positive Result Example

Genetic test results: heterozygous pathogenic variant in LRRK2 gene
- Gene: LRRK2 NM_198578.4
- Inheritance: autosomal dominant for PD.
- Variant: c.6055G>A p.Gly2019Ser
- Phenotypically known for early onset, levodopa-responsive but prone to dyskinesias, excellent response to DBS

Patient met with genetic counselor to discuss significance of results.

He underwent DBS in early May 2024, pending programming.

Essential Tremor Overview

THE QUEEN'S HEALTH SYSTEMS

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Essential Tremor

- Essential tremor (ET) is a condition characterized by tremor of bilateral upper limbs on action.
  - May also involve tremor in other body parts: head, neck, voice
  - Often responsive to small amounts of alcohol
  - Family history in ~50% of cases
  - Affects ~2% of the population – 7-10 million people in U.S., the majority undiagnosed as many do not seek medical care
- The cause is unknown, and usually testing is normal.
- In some individuals, tremor causes significant difficulty performing day-to-day tasks, such as writing, eating, drinking, dressing, and working.

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Essential Tremor

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Essential Tremor

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Essential Tremor

- Tremor leads to a high burden of functional impairment, as well as social stigma often leading to embarrassment, avoidance of social events, and depression/anxiety.
- Despite the high frequency and severity of symptoms, many people do not seek care, or are told that there are no effective treatments.

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Essential Tremor

PHARMACOTHERAPY

Beta-blockers (propranolol),
Anti-seizure medications (primidone),
Anti-anxiety medications
Injectable Neurotoxin

WEARABLE DEVICES

Wearable neurostimulators (Cala Trio)
Weighted gloves
Assistive devices and instruments

PROCEDURAL INTERVENTION

Deep Brain Stimulation (DBS)
Focused Ultrasound (FUS)
Other Lesion Therapies (RF Thalamotomy, Stereotactic Radiosurgery/Gamma Knife)

- Medications give unsatisfactory response and/or cause undesirable side effects in up to 50% of people.

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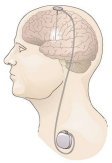
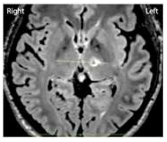
Procedural Interventions

- For severe, refractory tremor due to ET, a referral for surgical consultation is recommended.
- Historically, there are 2 surgical treatments for severe, refractory tremor.
  - Deep Brain Stimulation
  - Lesion therapy (traditionally achieved by either surgical lesion or incionsless Gammaknife)





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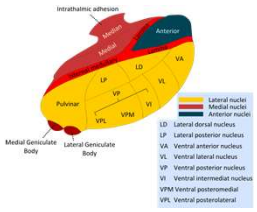
DBS for Essential Tremor

- DBS is an excellent and underutilized treatment for disabling ET refractory to medications
- Target: unilateral or bilateral VIM nucleus of thalamus
- Limitations:
  - Surgical treatment with ongoing hardware management
  - Bilateral VIM implantation can lead to ataxia or dysarthria
  - Dementia, prominent psychiatric symptoms, and elevated risk of morbidity may be contraindications



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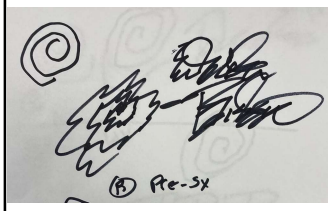
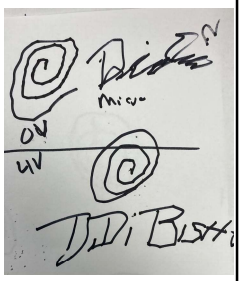
DBS for Essential Tremor





- Surgery is typically performed awake, without microelectrode recording; instead, using macroelectrode stimulation to test for symptom control

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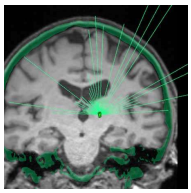
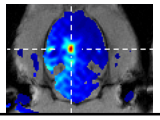
Focused Ultrasound (ExAblate)

- New since 2016
- MRI-guided Focused Ultrasound (FUS) is a novel treatment that achieves lesion therapy, **without a surgical incision**, using a combination of 2 technologies:
  - High Intensity Focused Ultrasound (HIFU), which uses sound waves from an external source (transducer) to heat up and destroy brain tissue
  - Magnetic Resonance Imaging (MRI), which guides the treatment in real time by identifying the patient's brain target and measuring the target temperature
- **The main objective is to create a lesion that leads to an immediate reduction in tremor, with minimal risk of complications**



Focused Ultrasound

- The procedure is performed in MRI suite while awake. The patient's head is secured via a frame to a "helmet" (called a transducer) which contains the ultrasound sources. An MRI is performed to target the brain.
- The physician uses a console to deliver a burst of ultrasound energy, which temporarily heats the target brain tissue. The physician team evaluates the degree of heating and tests the patient's tremor in real time, to determine the effects of the warming.
- The physician can modify the amount of energy, the location, and the shape of the target for precise control.
- The patient experiences immediate and sustained tremor reduction after the final dose of energy.



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How Focused Ultrasound Works

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Adverse Effects

- The whole procedure lasts 2-3 hours and is done awake with minimal sedation. After a brief period of monitoring, the patient can be discharged home.
- Most common side effects after treatment:
  - Headache, pain (51%)
  - Numbness, tingling (33%)
  - Gait imbalance (26%)
  - Most side effects gradually resolve within weeks after the procedure, but up to 20% may have sustained numbness and tingling in the same side

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Who is a candidate for Focused Ultrasound?

- Confirmed diagnosis of disabling tremor, refractory to medications, in **Essential Tremor** or **Tremor-dominant PD** (FDA-approved labels)
- 22 years old or older (ET) or 30 years or older (PD)
- Must be able to undergo MRI, tolerate some discomfort, and follow instructions for awake testing
- Pre-procedure, must undergo a CT head to measure skull density ratio, which ensures that ultrasound waves can pass through the individual's skull
  - Skull density ratio must be >0.40. Around 12% of population may not meet this requirement.
- Contraindications:
  - Inability to obtain MRI or lie still, abnormal skull density, pregnancy, certain brain tumors or prior strokes, unstable cardiac condition, bleeding or clotting disorder, alcohol abuse.

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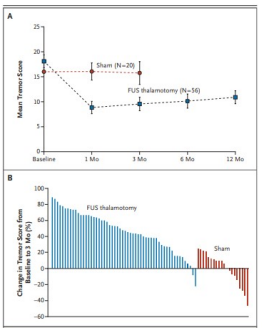
Clinical Trial Data

ORIGINAL ARTICLE

A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor

W. Jeffrey Elias, M.D., Nir Lipsman, M.D., Ph.D., William G. Ondo, M.D., Pejman Ghanouni, M.D., Ph.D., Young G. Kim, M.D., Ph.D., Wonhee Lee, M.D., Ph.D., Michael Schwartz, M.D., Kullervo Hynynen, Ph.D., Andres M. Lozano, M.D., Binit B. Shah, M.D., Diane Huss, D.P.T., N.C.S., Robert F. Dallapiazza, M.D., Ph.D.,



- Median improvement in hand tremor scale 47% in treatment group vs. 7% in sham group at 3 months.
- Patients reported significant improvement in their day to day function, with 62% reduction in functional disability.

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Queen's Exablate Opened on February 1, 2024

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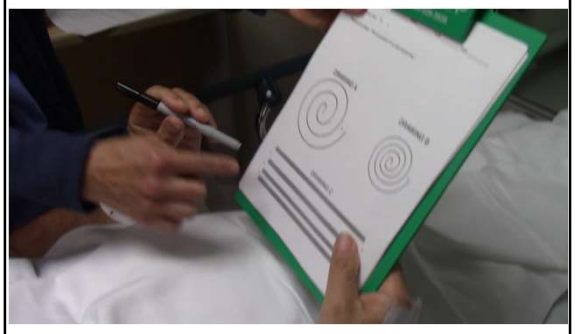
Tremor Before Procedure, February 1, 2024



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Focused Ultrasound Treatment, February 1, 2024

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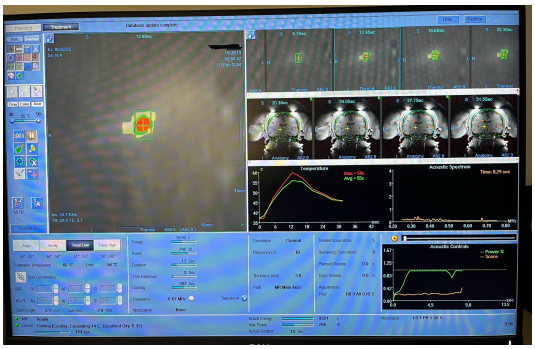
Focused Ultrasound Treatment, February 1, 2024



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Tremor After Procedure, February 1, 2024

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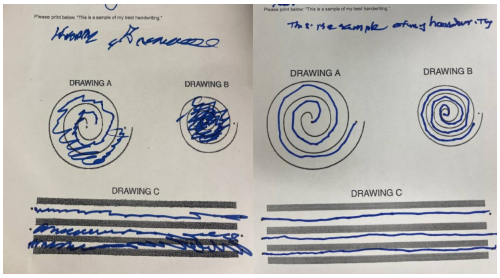
Before and After Procedure



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Conclusions

- Parkinson's Disease and Essential Tremor are the most common movement disorders and cause significant functional impairment and distress to a large aging population.
- Advances in pharmacological and neuromodulatory treatments offer significant reduction in symptom burden and allow patients living with movement disorders to optimize function.
- More research is needed to understand the biomolecular pathological mechanisms of Parkinson's disease, especially on the genetic level.
- The Parkinson's and Movement Disorder Center at Queen's Medical Center is dedicated to breaking through barriers of access for patients in the state of Hawai'i through excellent clinical care and research efforts.

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Mahalo!

THE QUEEN'S HEALTH SYSTEMS

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