MOVEMENT DISORDERS UPDATE- WHATS NEW IN MEDICINE

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LEARNING OBJECTIVES

Review common movement disorders and typical presentations to raise awareness for an early diagnosis

Practical management in primary care settings and knowing when to refer to neurology

Update on new treatment and management options for movement disorders

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DISCLOSURES

No relevant financial disclosures

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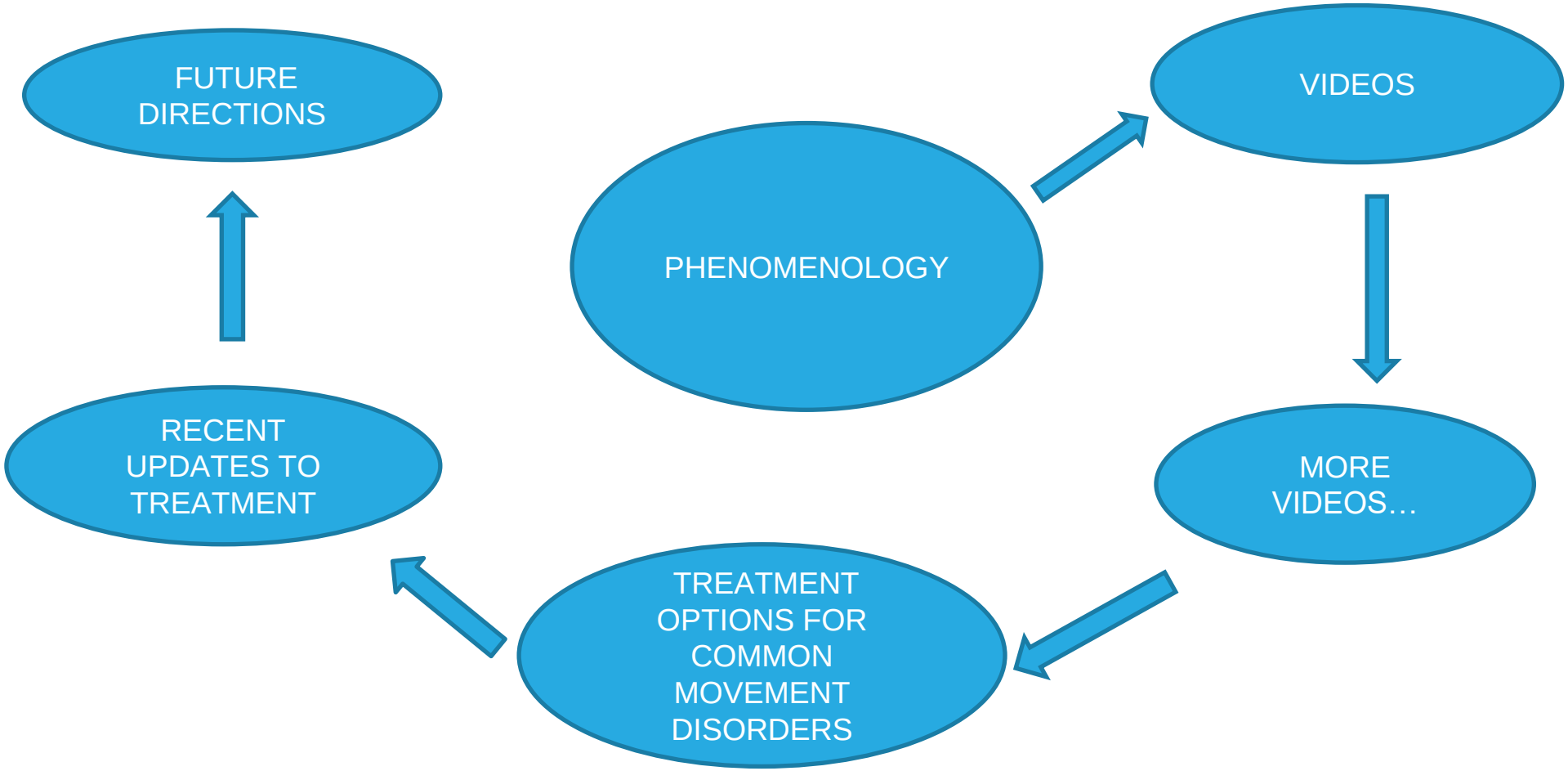
MOVEMENT DISORDERS UPDATE



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PHENOMENOLOGY-ITS ALL IN THE NAME

HYPER KINETIC: Excessive movements
Akathesia
Chorea/ Choreoathetosis
Ballism
Dystonia
Myoclonus
Tics
Tremors
Stereotypes
Peripherally induced movements:
Hemifacial spasm
? Ataxia

INVOLUNTARY/
UNVOLUNTARY MOVEMENTS

HYPOKINETIC: Paucity of movements
Bradykinesia/ Akinesia
Apraxia
Psychomotor slowing
Freezing of gait
Blocking tics
Catatonia

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BASIC PREMISE BEHIND MOVEMENTS……
CENTER SURROUND CONCEPT

Figure AB-18: Basal Ganglia

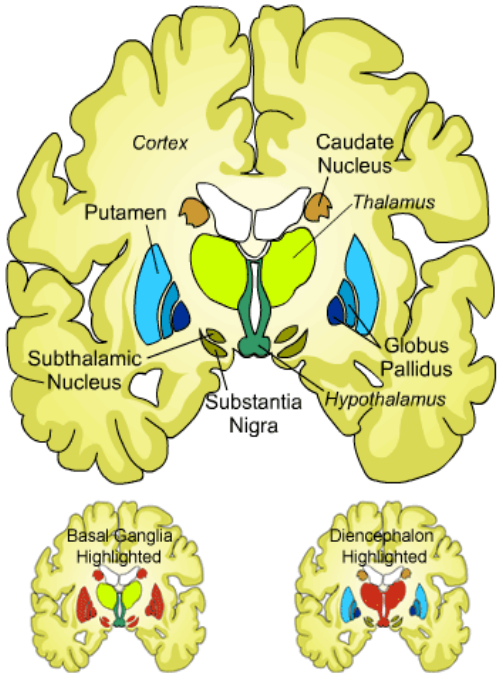
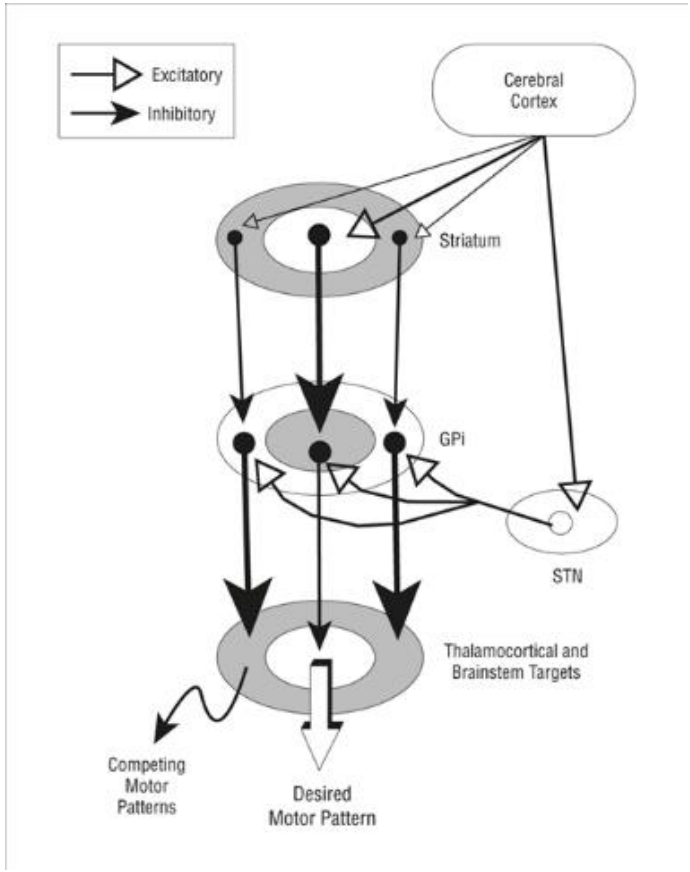
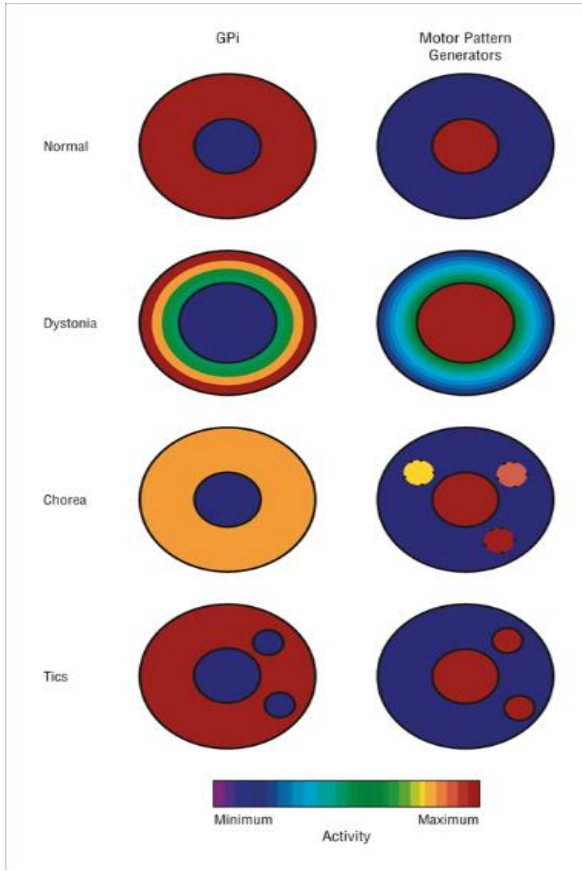


Diagram colors are consistent with Figure AB-19.





http://jamanetwork.com/journals/jamaneurology/fullarticle/784785

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BASIC PRINCIPLES IN DIAGNOSIS

- Identifying the movement is half the battle
- Several movement disorders have overlapping phenomenology (parkinsons with chorea/dyskinesia and dystonia, essential tremor with cervical dystonia, choreoathetosis with hyperglycemia or CVA
- Some involuntary movements are suppressible (chorea, parkinsonian tremor)
- Abrupt onset of a movement disorder often suggests a functional movement disorder except for Rapid Onset dystonia parkinsonism
- One cue to the presence of a functional movement disorder is entrainability and distractibility
- Response to medication can sometimes cue the diagnosis (levodopa response in Parkinson's, dopa responsive dystonias)

COMMON HYPERKINETIC MOVEMENTS

TREMOR: Rhythmic oscillatory movement produced by alternating or simultaneous contraction of agonist & antagonist

- Rest tremor
- Posture
- Action

VIDEO LINK:

DYSTONIA: Sustained repetitive, twisting movements associated with co contraction of agonists-antagonist

Cervical dystonia
Writers cramp

VIDEO LINK:

CHOREA: Involuntary, irregular, purposeless, non rhythmic rapid and abrupt movements
Associated Parakinesias….
Non predictable and hard to suppress

VIDEO LINK:

MYOCLONUS : Sudden, brief, shock like jerky involuntary movements: positive and negative myoclonus

VIDEO LINK:

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HYPERKINETIC MOVEMENTS….

TICS: abnormal Unvoluntary movements that are suppressible and can be jerky, regular or even myoclonic appearing,
With Tourettes can be a combination of motor and vocal tics

VIDEO LINK:

ATAXIA: Breakdown in normal coordinated execution of movements, maybe associated with adventitious movements like overflow tremor/ dysmetria

VIDEO LINK:

- Peripherally induced movements:
- Myokymia
- Fasciculations
- Hemifacial spasms
- Palmaris brevis syndrome

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HYPOKINETIC MOVEMENTS….

BRADYKINESIA: Slowness of movement and decrement in amplitude, Reduced arm swing, reduced facial expression, micrographia, reduction in dexterity

VIDEO:

PSYCHOMOTOR SLOWING: seen with depression

VIDEO LINK:

- FREEZING OF GAIT: extreme form of akinesia of gait
- VIDEO LINK

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MOST COMMON MOVEMENT DISORDERS

- Essential Tremor
- Parkinsonian syndromes
- Dystonias
- Ataxias
- Myoclonus

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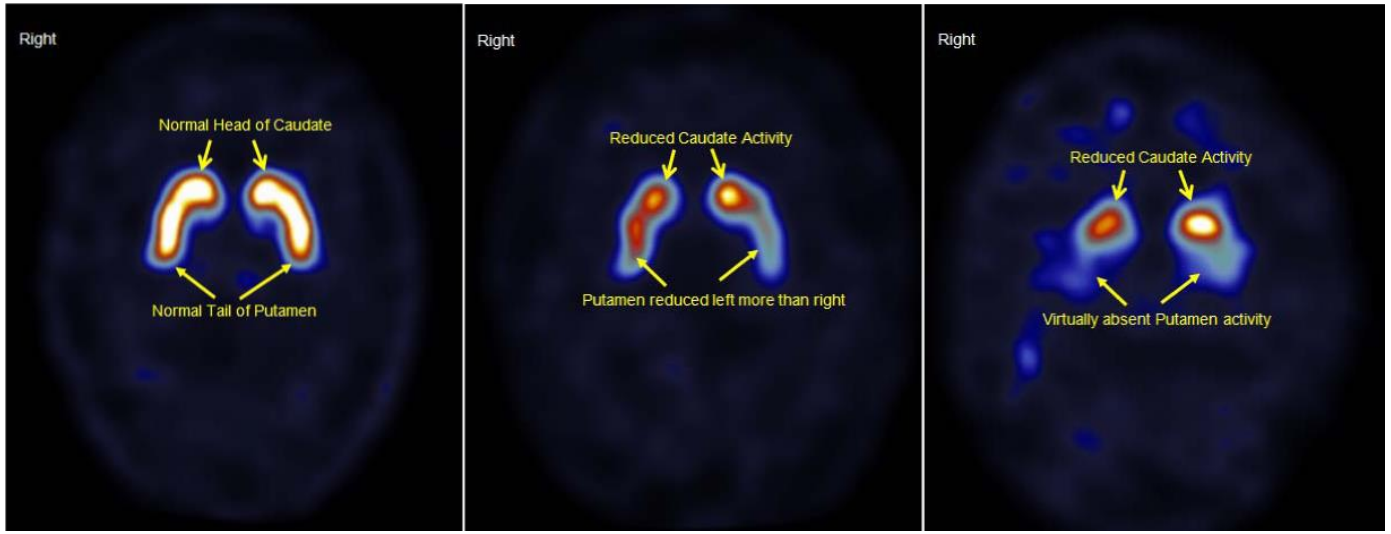
ESSENTIAL TREMOR

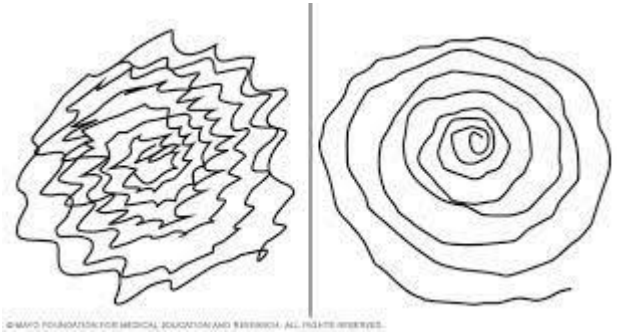
- Isolated action tremor of bilateral upper limb with or without tremor in other places of atleast 3 yr duration
- Soft neuro signs: presence of rest tremor in long standing ET, mild gait instability, elevated tone (cogwheeling),
- + ve family history, Alcohol responsiveness, >14% by age 65
- Slightly higher risk for parkinsons than average population (2 to 3 fold)
- ROLE OF DAT Scan



https://medcraveonline.com/JNSK/ioflupane-i123-injection-datscantm-spect-brain-imaging-in-patients-with-movement-disorders-andor-dementia-preliminary-report.html

DIAGNOSIS AND DIFFERENTIALS:

Demonstrate a postural tremor, spiral drawing, absence of any other Abnormal neurological findings except soft signs



DIFFERENTIAL DIAGNOSIS: Enhanced Physiologic tremor

- Stress/ anxiety/ caffeine
- Toxins/ medications (SSRI/ SNRI/Lithium)
- Endocrine causes: hyperthyroidism

CAVEATS? RED FLAGS:

Strong resting component, rapid worsening, striking asymmetry (<4% asymmetric), significant associated gait disorder

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TREATMENT OPTIONS

MEDICATIONS:

- Primidone upto 400 to 500 mg,
- Propranolol upto 240 mg
- Topiramate upto 200 mg or more,

- OT evaluations
  - Weighted utensils/ tremor cancelling cutlery
  - Devices (speech activated software)
  - Dressing assistance devices

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TREATMENT OPTION UPDATES

CALA KiQ/CALA TRIO

FUS- Focused ultrasound lesioning

DBS UPDATES TO BE DISCUSSED IN PARKINSONS DISEASE MANAGEMENT

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PARKINSONIAN SYNDROMES

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PARKINSONISM/PARKINSONS DISEASE

Clinical diagnosis with the presence of 2 out of the 4 cardinal features one of which must be bradykinesia
Bradykinesia: slowness of movements (essential feature) PLUS one of

- Tremor: resting form (absent 30% of the time)
- Rigidity
- Postural instability

AND

- Absence of red flags like early dementia (within 1 yr of diagnosis), profound autonomic impairment, early severe bladder dysfunction, early severe gait impairment, supranuclear gaze palsy or early bulbar symptoms
- Absence of secondary causes (drug induced, CVA, toxin exposure)

AND

- Robust levodopa response

- All of the above = Parkinson's disease, otherwise would be parkinsonism

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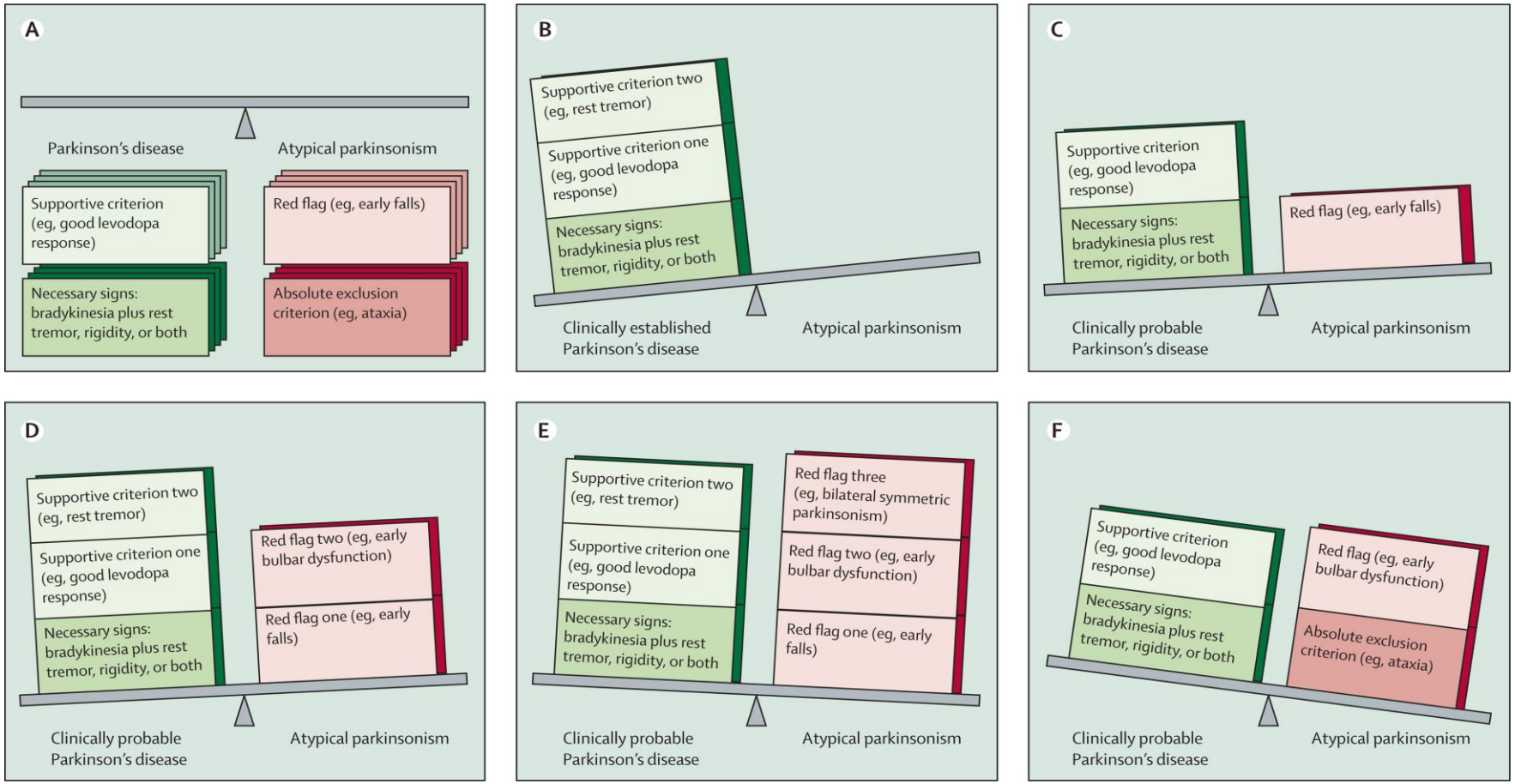
CLINICAL DIAGNOSIS…



Bloem BR, Lancet 2021

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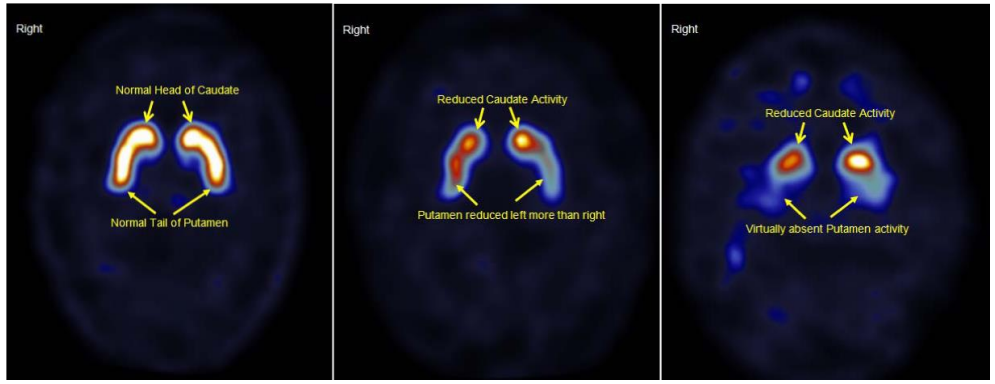
DIAGNOSIS AND CAVEATS



- Diagnosis always clinical, can use DAT scan as adjunct
- LEVODOPA response important for diagnosis (upto 900 to 1000 mg per day for 4 wks, atleast 30 to 40% improvement)
- Red Flags: rapid worsening, early gait disorder, early dyskinesias (orofacial), severe orthostasis, early hallucinations, ocular motility issues, striking asymmetry
- When in doubt, try levodopa,

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NEW IN DIAGNOSIS
SYN ONE/ ALPHA SYNUCLEIN SKIN BIOPSY

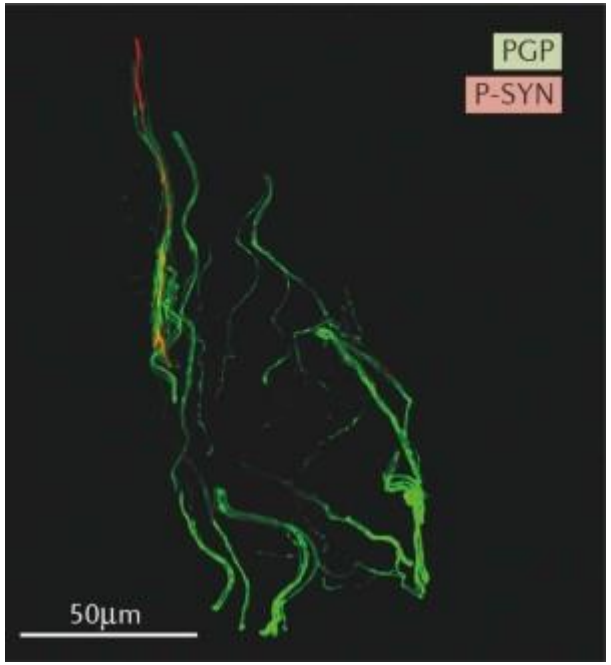
Now available: skin biopsy to detect phosphorylated alpha synuclein

Three biopsy sites: lateral to C7, 10 cm above lateral knee, 10 cm above Medial malleolus

Large study currently enrolling to look at sensitivity and specificity of Syn One

Data so far based on autopsy studies (limited by location of biopsy sites And clinical studies (limited by lack of confirmatory testing) show rather High specificity close to 100% , sensitivities close to 90 to 95%[14]

Does not distinguish between synucleinopathies reliably



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THERAPEUTICS- CURRENT DRUGS

MAOB-Is

- Selegiline, Rasagiline
- Safinamide (Xadago)

Dopamine agonists

- Pramipexole, ropinirole,
- Rotigotine,
- Apomorphine (Kynmobi)

Carbidopa/levodopa

- ER/ IR
- Rytary

- COMT inhibitors: Entacapone, Opicapone (Ongentys)
- Anticholinergics: Trihexyphenidyl,
- Amantadine/ ER (Gocovri)
- Adenosine antagonist:
  Istradefylline (Nourianz)

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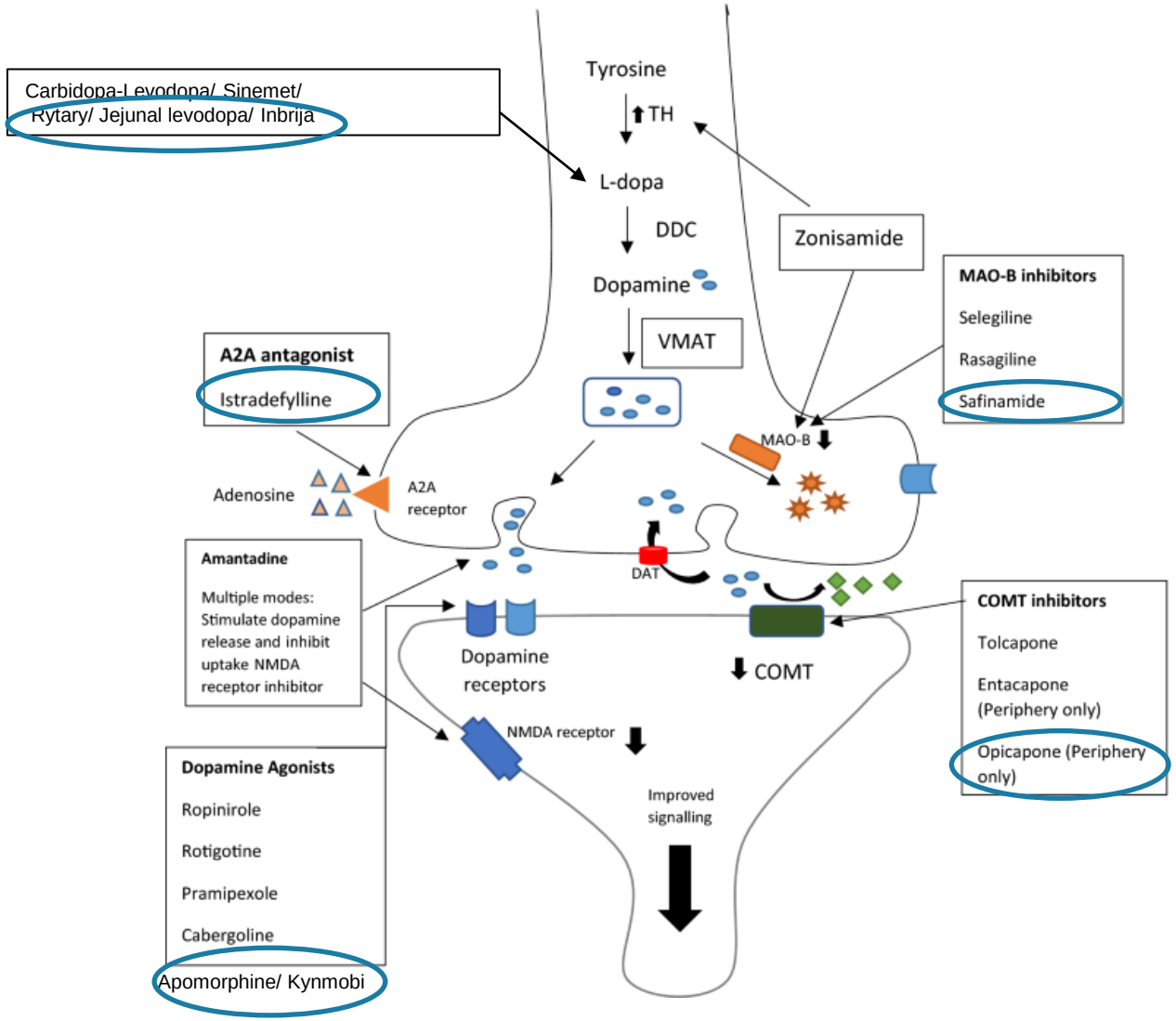
NEW IN THERAPEUTICS

Approved in last 5 yrs

- Opicapone
- Istradefylline
- Extended release Amantadine
- Inhaled Levodopa
- Apomorphine SL



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THERAPEUTICS

- ONGENTYS/OPICAPONE: COMT inhibitor , once daily dosing and potentially a non significant improvement in on time compared to entacapone

- INBRIJA: oral inhaled levodopa, useful as rescue in off periods, onset quick (10-15 min), peak 30 min duration upto 60 min,

- NOURIANZ: istradefylline, adenosine receptor antagonist, reduces off time by 1-2 hrs, +/- dyskinesias

- GOCOVRI: long acting amantadine, NMDA receptor antagonist/ AADC effects, longer acting, QD dosing, less Side effects

- KYNMOBI: sublingual apomorphine, helpful in off phenomenon, strongest dopamine agonist wrt efficacy, onset 10-15 min, dtn upto 60 min, no longer available

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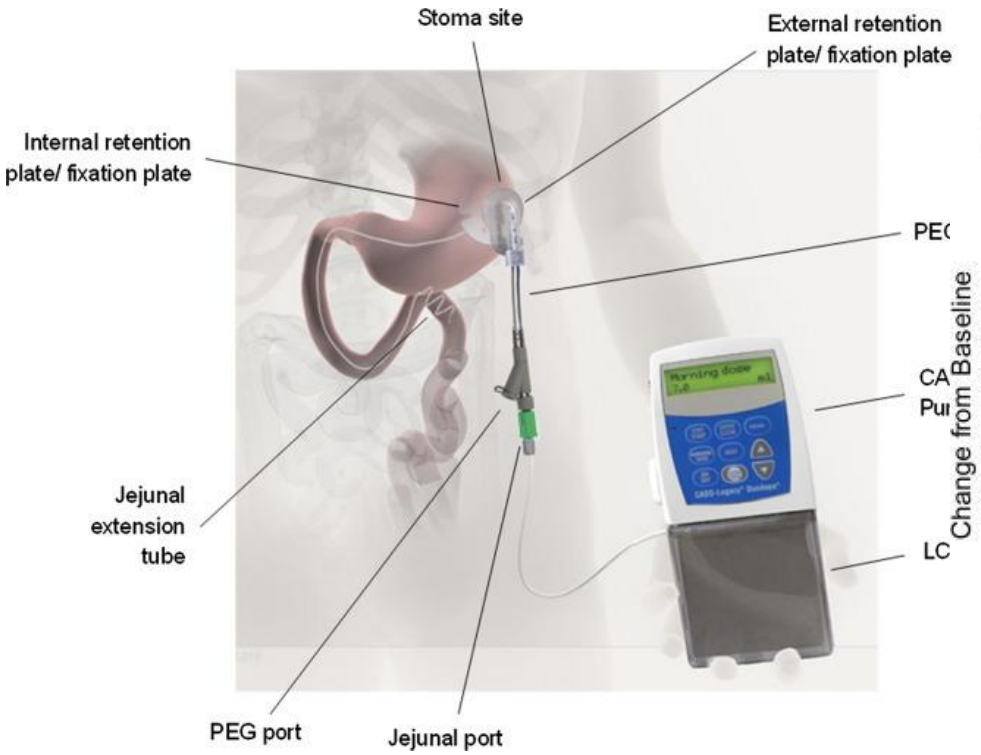
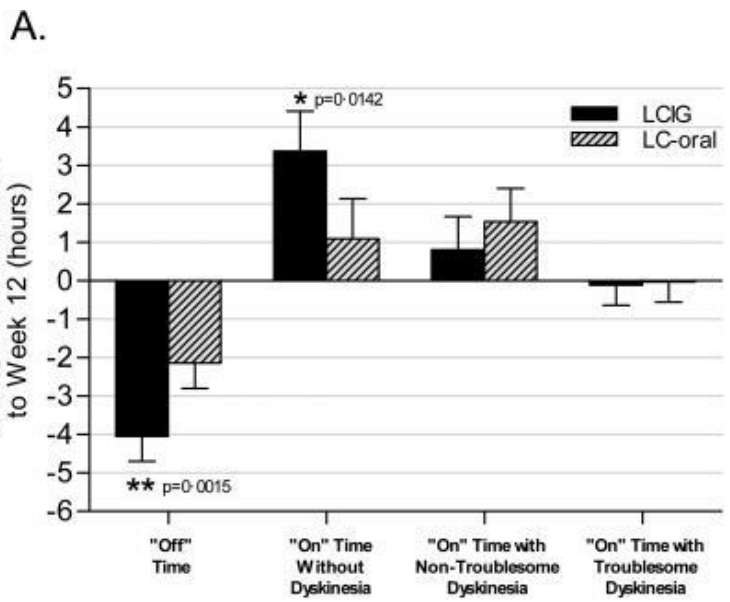
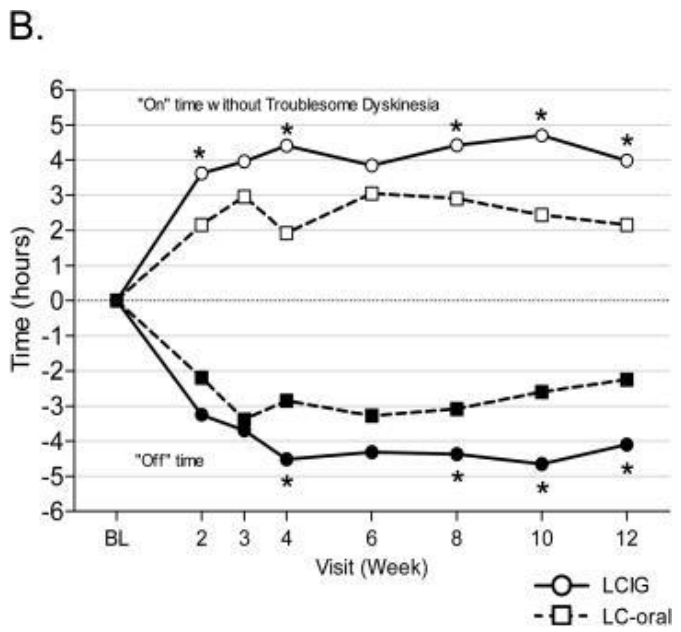
NOT SO NEW DUOPA- INTESTINAL INFUSION







Olanow et al, Lancet 2014

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SURGICAL THERAPIES- DEEP BRAIN STIMULATION

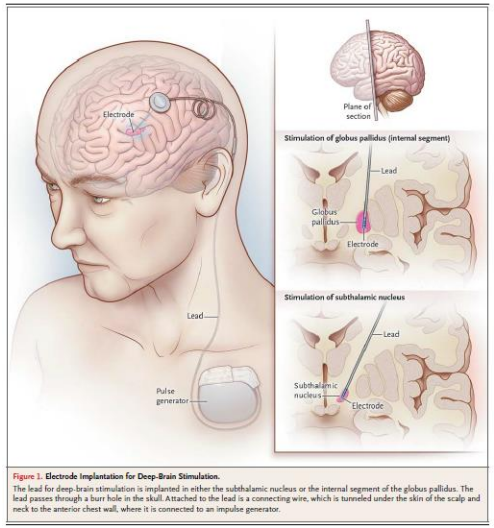
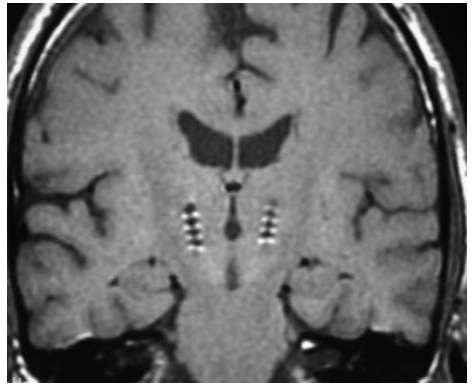
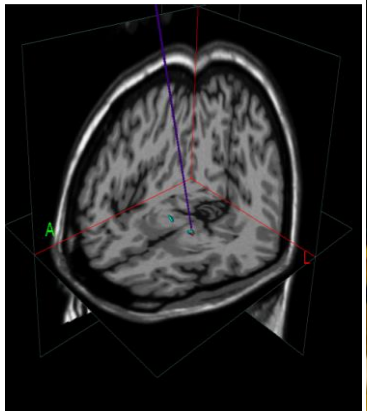
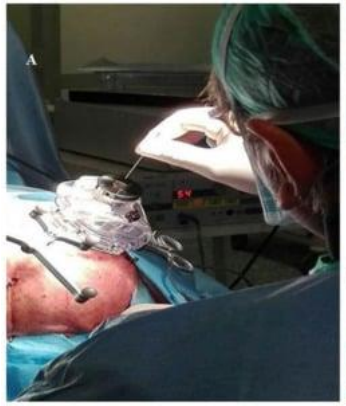
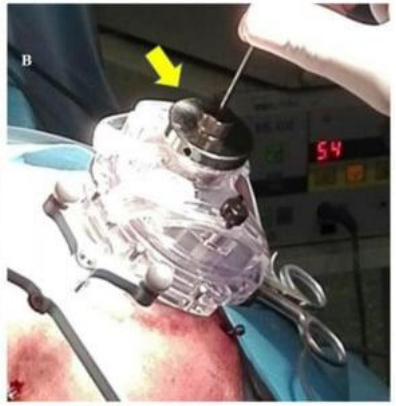


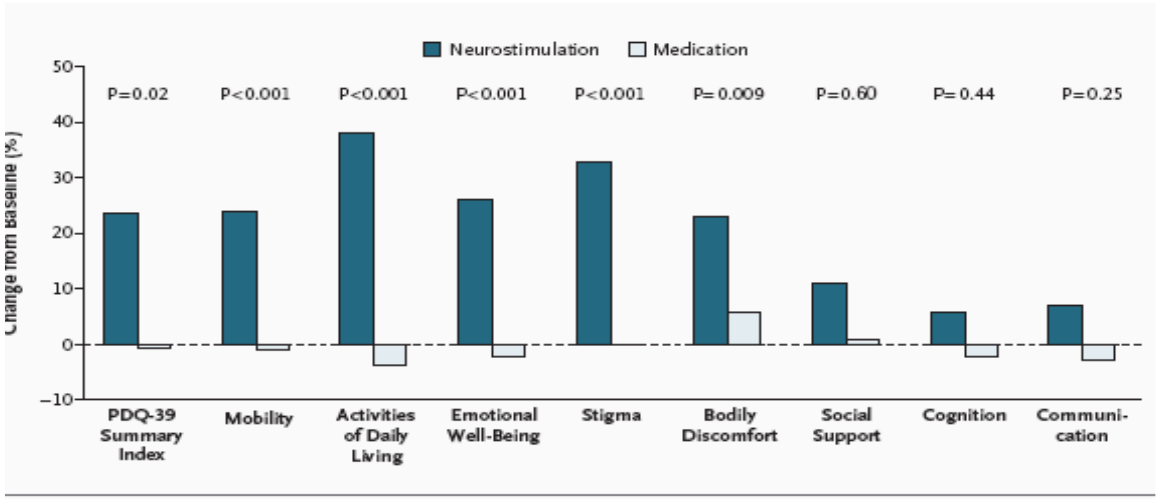
Figure 1. Electrode Implantation for Deep-Brain Stimulation.
The lead for deep-brain stimulation is implanted in either the subthalamic nucleus or the internal segment of the globus pallidus. The lead passes through a burr hole in the skull. Attached to the lead is a connecting wire, which is tunneled under the skin of the scalp and neck to the anterior chest wall, where it is connected to an impulse generator.

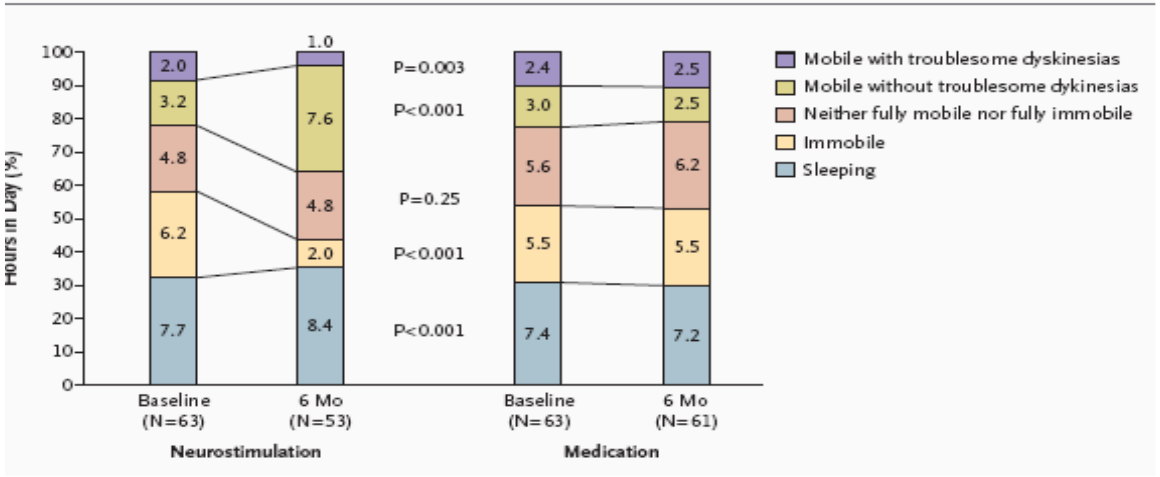












Deuschl 2006

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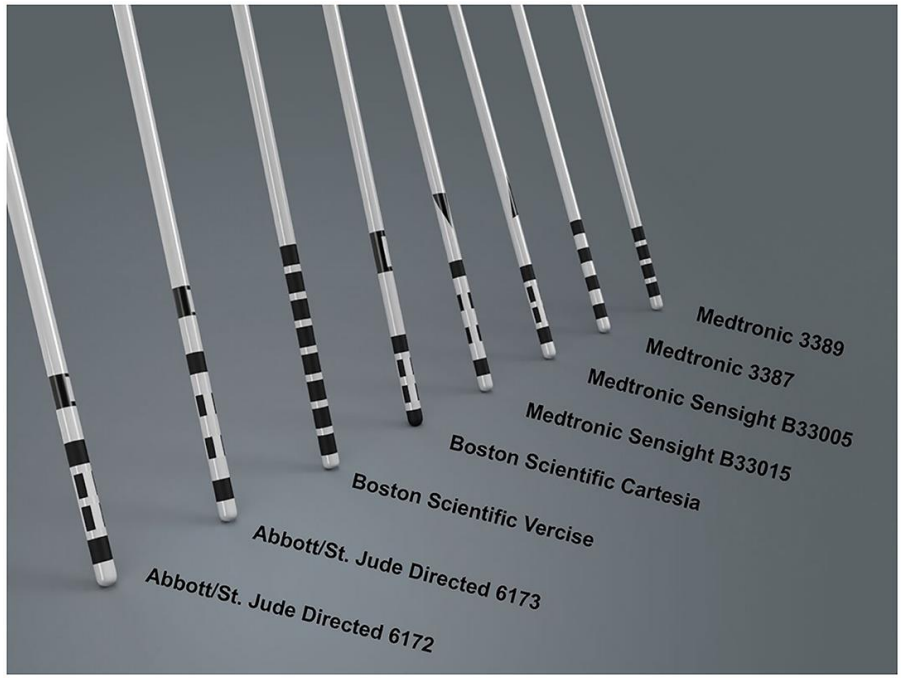
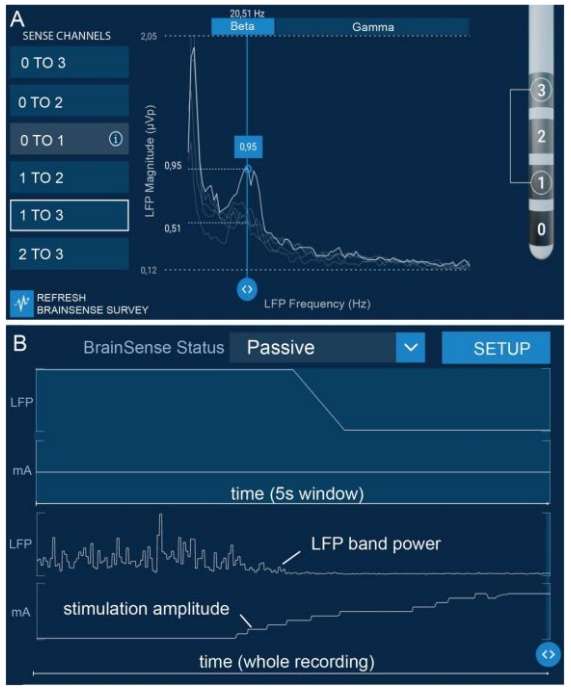
RECENT ADVANCES IN DBS

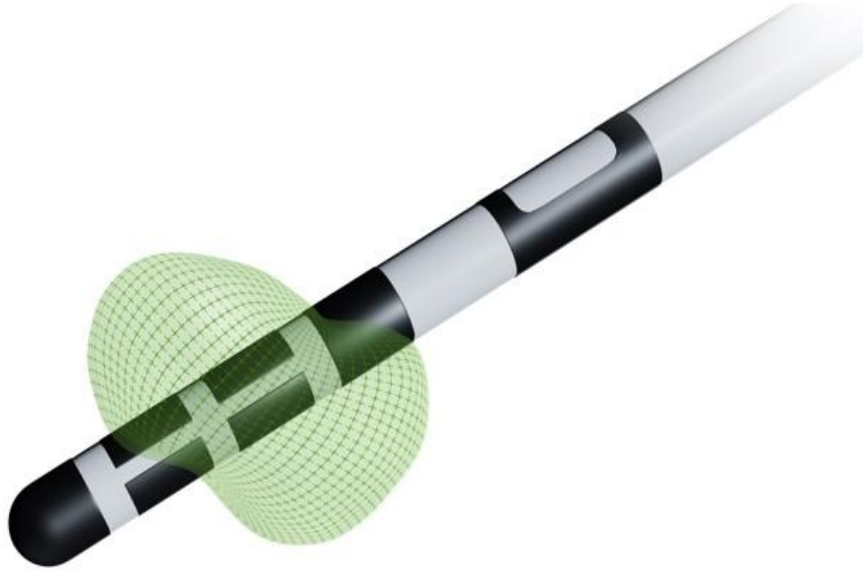


Frey J et al, Frontiers in Neurology, 2022

BRAIN SENSE



CURRENT STEERING



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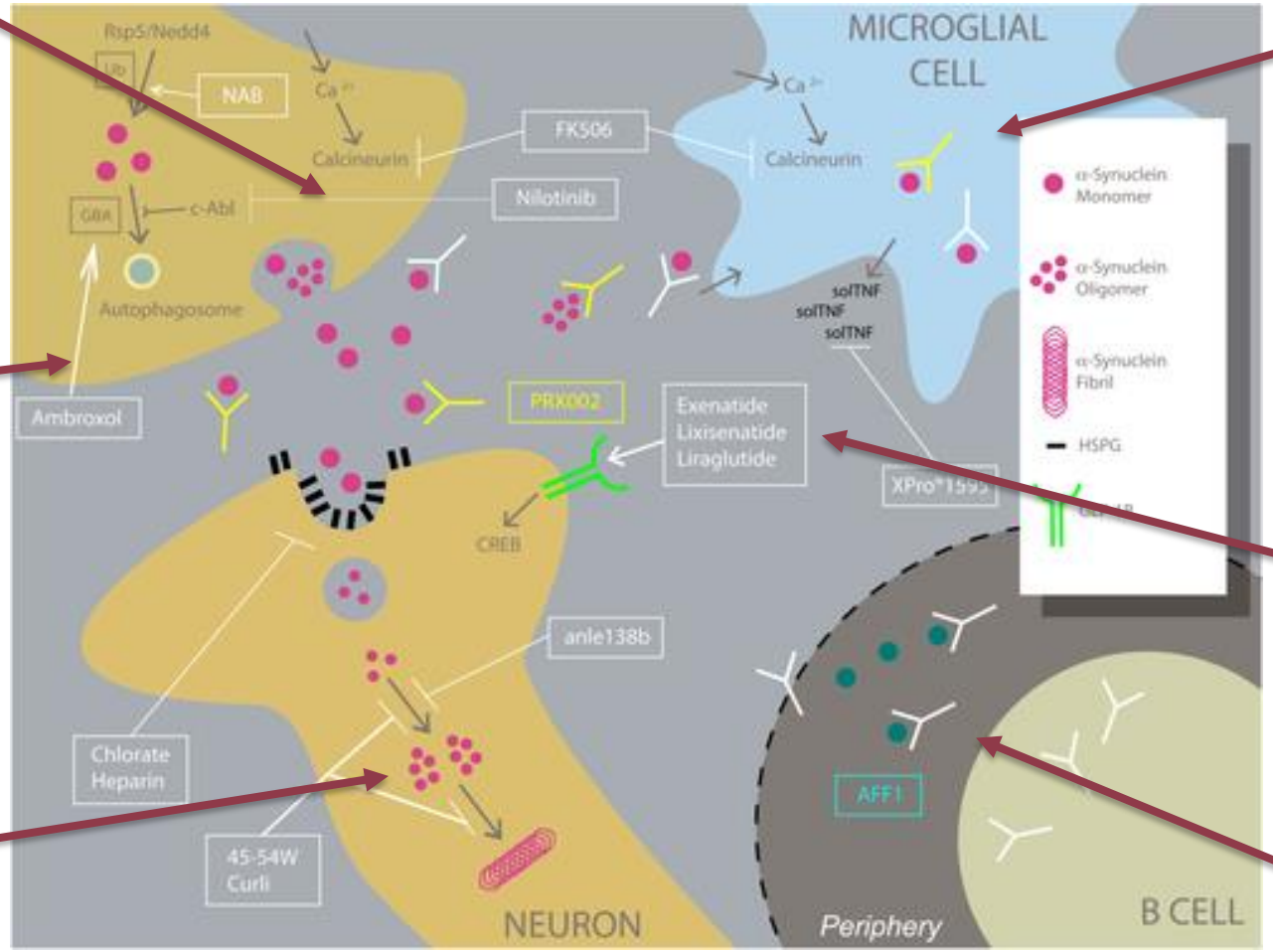
CELL BASED AND DISEASE MODIFYING THERAPIES

c Abl tyrosine kinase inhibitors, nilotinib failed but K0706 is in phase 2 trials

Passive immunization against alpha synuclein: prasinezumab negative trial

Inosine urate precursor negative trial
Deferiprone iron chelator negative trial

GCASE enhancer in GBA associated PD, phase 2 trials in cognitively impaired patients



Positive study with GLP-1 agonist exenatide, SR exenatide, liraglutide being studied, awaiting phase 2 trials

UCB 0599 targeting alpha synuclein misfolding, phase 1 completed, recruiting phase 2 ORCHESTRA trial,

PD03A: phase 1 completed and successfully tolerated,

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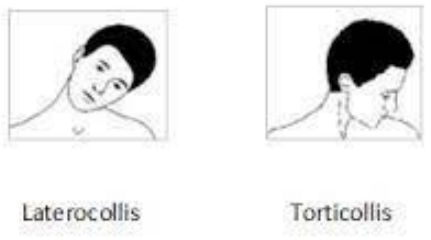
Brundin Mov disorders 2015

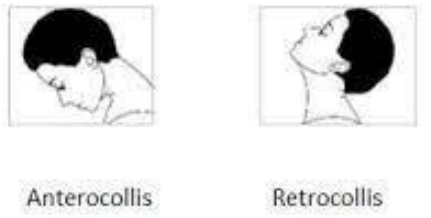
DYSTONIAS

DEFINITION

- Sustained repetitive, twisting movements associated with co contraction of agonists-antagonist
- Types:
  - Focal (cervical dystonia, limb dystonia, writers cramp)
  - Generalized (DYT -1 or genetic forms of dystonia)



- Isolated head tremor without hand tremor and with neck pain/ neck muscle hypertrophy or head tilt should raise suspicion for dystonic head tremor



- Neurolepts can be associated with opisthotonos and retro Collis

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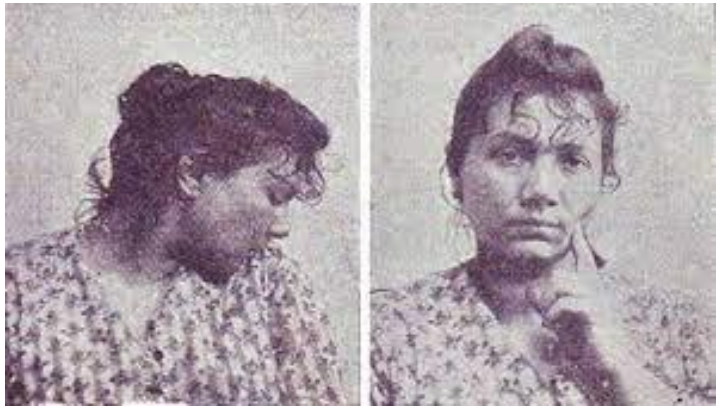
CUES TO DIAGNOSIS

- Often movements maybe more apparent in action (walking, turning, writing)
- Often a dynamic component, on the contrary fixed posturing is usually less likely true dystonia
- Geste antagoniste: sensory trick
- Spontaneous remission can be seen
- Lower limb dystonia in adult, often an early symptom of Parkinsonian syndrome



https://link.springer.com/article/10.1007/s00415-011-6380-7

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TREATMENT

Botulinum toxin injections to affected muscles usually under EMG guidance

Medications limited benefit: trihexyphenidyl, clonazepam can be used

Deep Brain Stimulation to GPi in refractory cases, good response to generalized dystonia especially DYT-1

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ATAXIAS

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DEFINITION AND DIFFERENTIALS:

Breakdown in normal coordinated execution of movements, maybe associated with adventitious movements like overflow tremor/ dysmetria

SENSORY:

- Peripheral neuropathy
- Neuronopathy
- Dorsal column disorders like subacute combined degeneration of cord

SUBTYPES

CEREBELLAR

- Degenerative: Multiple systems atrophy, SCA
- Inflammatory: Autoimmune ataxias like GAD mediated, celiac disease
- Infectious: Whipples
- Paraneoplastic +- inflammatory
- Toxic: Dilantin or alcohol abuse
- Deficiencies: Vit E

CUES TO DIAGNOSIS

- Sensory ataxias often worse in darkness/ low visual acuity situations, worse with eyes closed (pseudoathetosis)

- Cerebellar ataxias can be midline only (alcohol/ dilantin toxicity) or mixed axial and appendicular, often accompanied by eye movement anomalies causing dizziness/ loss of visual suppression with walking (dynamic visual acuity)

- Subacute (progression over weeks) ataxia (sensory or cerebellar) often very concerning for autoimmune disorders/ paraneoplastic syndromes would warrant immediate evaluation

- Standard screening for ataxia (b12, thiamine, folate, celiac, Vit E, RPR, Gad antibodies, TPO-SREAT) would cover most ataxias, consider paraneoplastic screening in subacute progression

TREATMENT/ MANAGEMENT

Often diagnosis specific

- Inflammatory/ autoimmune: if mediated through cell surface Ab (GAD) would respond to immunotherapy, if T cell mediated (like associated with small cell lung cancer) may not respond to treatment
- Celiac: responds to gluten free diet with lack of progression
- Neurodegenerative: MSA-C no clear response to meds, levodopa can be tried for parkinsonian subtype, weak evidence for riluzole in neurodegenerative ataxias
- Deficiencies: supplement
- Toxic metabolic: stop offending med –dilantin, lithium
- Some genetic ataxias now have treatment (Freidrichs: Skyclars)

MYOCLONUS

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DEFINITIONS AND SUBTYPES

Sudden, brief, shock like jerky involuntary movements: positive and negative myoclonus

SUBTYPES:

- Cortical (Juvenile myoclonic epilepsy, Lafora disease, post anoxic myoclonus
- Subcortical (opsoclonus-myoclonus, essential myoclonus, hyperekplexia
- Spinal (segmental and propriospinal myoclonus)

CAUSES

Physiologic: hypnic myoclonus, hiccups

Epileptic myoclonus: Myoclonic epilepsies, Juvenile myoclonic epilepsy

Neurodegenerative disorders: Corticobasal syndrome, Alzheimers, Wilsons, Huntingtons,

Infectious/ post infectious: HIV, lyme, PML, SSPE (measles associated), Creutzfelt Jacob disease

Metabolic causes: hyperthyroid, renal failure, hepatic failure, dialysis

Drug induced: SSRI/ SNRI, Lithium, Opiates, Gabapentinoids, Amiodarone, penicillin group of drugs

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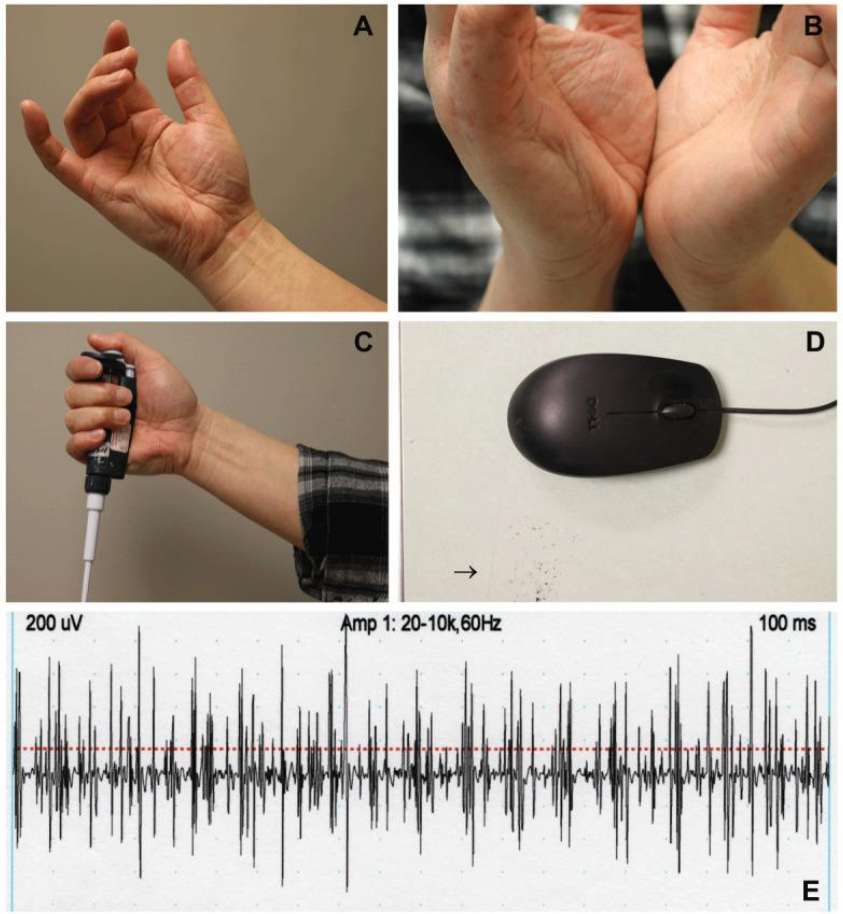
TREATMENT

- Remove offending medications
- Fix metabolic changes in possible
- Rule out deficiencies contributing
- Evaluate for epileptic myoclonus (young adult with AM myoclonus-JME)
- Medication options
  - Levetiracetam for post anoxic myoclonus
  - Valproate for epileptic and non epileptic myoclonus
  - Gabapentin and clonazepam for spinal myoclonus

PERIPHERALLY INDUCED MOVEMENT DISORDER

PALMARIS BREVIS SYNDROME



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FUTURE DIRECTIONS

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FUTURE DIRECTIONS

- Targeted gene therapies for monogenic Parkinson’s
- In advanced Parkinson's, newer drug delivery systems not reliant on gut motility
- Closed loop deep brain stimulation akin to responsive neurostimulation in epilepsy
- PRAX-944 for ET (T type calcium channel blocker) phase III
- Skyclarys Approval for Freidrich’s ataxia, Troriluzole in Ataxia

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When to refer to Neurology

- For diagnostic clarity of any of the listed movement disorders
- Essential tremor not responding to first line treatment, consideration for DBS or additional meds vs devices
- Any rapidly progressive movement disorders: would warrant an urgent/ emergent evaluation!
- Question of functional movement disorders
- Anytime there is a question of a drug induced movement disorder
- Pathologic gait not explained by musculoskeletal issues

Thank you.

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