Advances in Management of Parkinson's Disease and Essential Tremor

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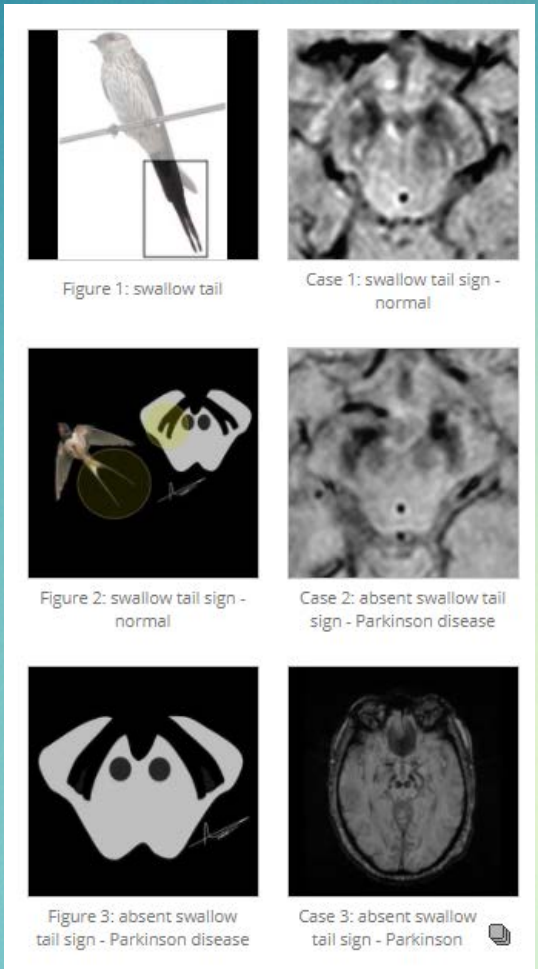
Outline

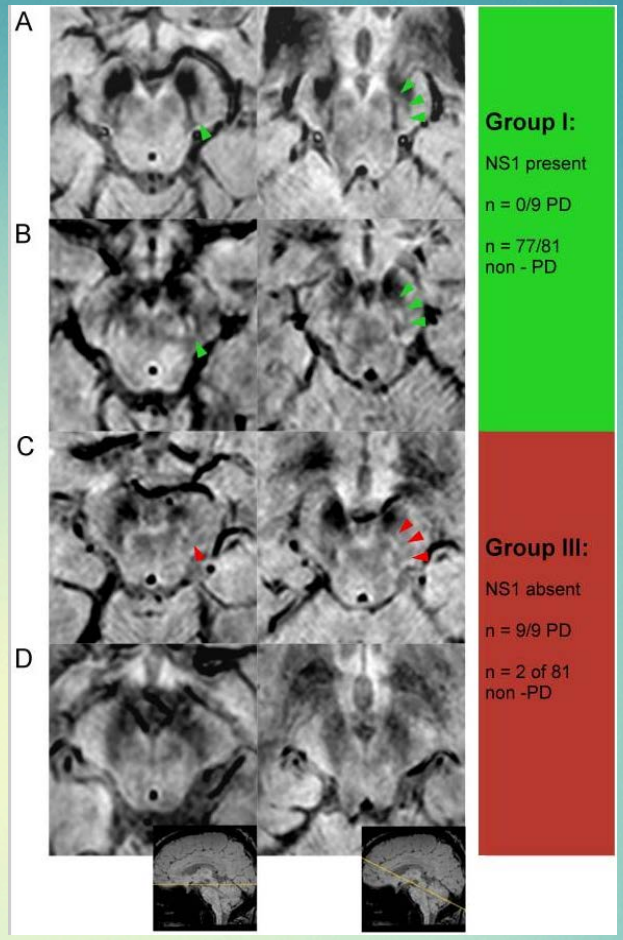
- Parkinson's (PD) updates
  - Diagnostic
    - SWI-MRI
    - DaTscan
  - Medication
    - Motor complications
      - Xadago
      - Gocovri
    - Non-motor symptoms
      - Nuplazid
      - Northera
    - Coming down the pipeline
      - Inhaled levodopa
      - Subcutaneous apomorphine patch/pump
      - Update on disease modifying therapies
  - Non-medication
    - PT, speech therapy
    - Exercise
- Essential tremor (ET)
  - Management options
  - Surgical options

Diagnosis of Parkinsonian syndrome

- Clinical exam
  - Motor scale (MDS-UPDRS)
- MRI brain
  - Typically normal in idiopathic PD, especially early
  - Recent data on high-resolution SWI to assess for loss of neuromelanin
  - Conventional Can be very useful when atypical parkinsonism is suspected
    - Vascular parkinsonism
    - Progressive supranuclear palsy (PSP)
    - Multiple system atrophy (MSA
- DaTscan
  - I^{131} Ioflupane brain SPECT
  - FDA approved for ET vs parkinsonian syndrome
  - Cannot differentiate between idiopathic PD vs atypical parkinsonism

Absent swallow tail sign on high-resolution 3T SWI-MRI in diagnosis of PD





Detection of nigrosome 1 of the SNpc – in clinically well established patients

Sensitivity 100%, specificity 90%, PPV 50%, NPV 100%, accuracy 91%

Schwarz et al., 2014, PLoS One

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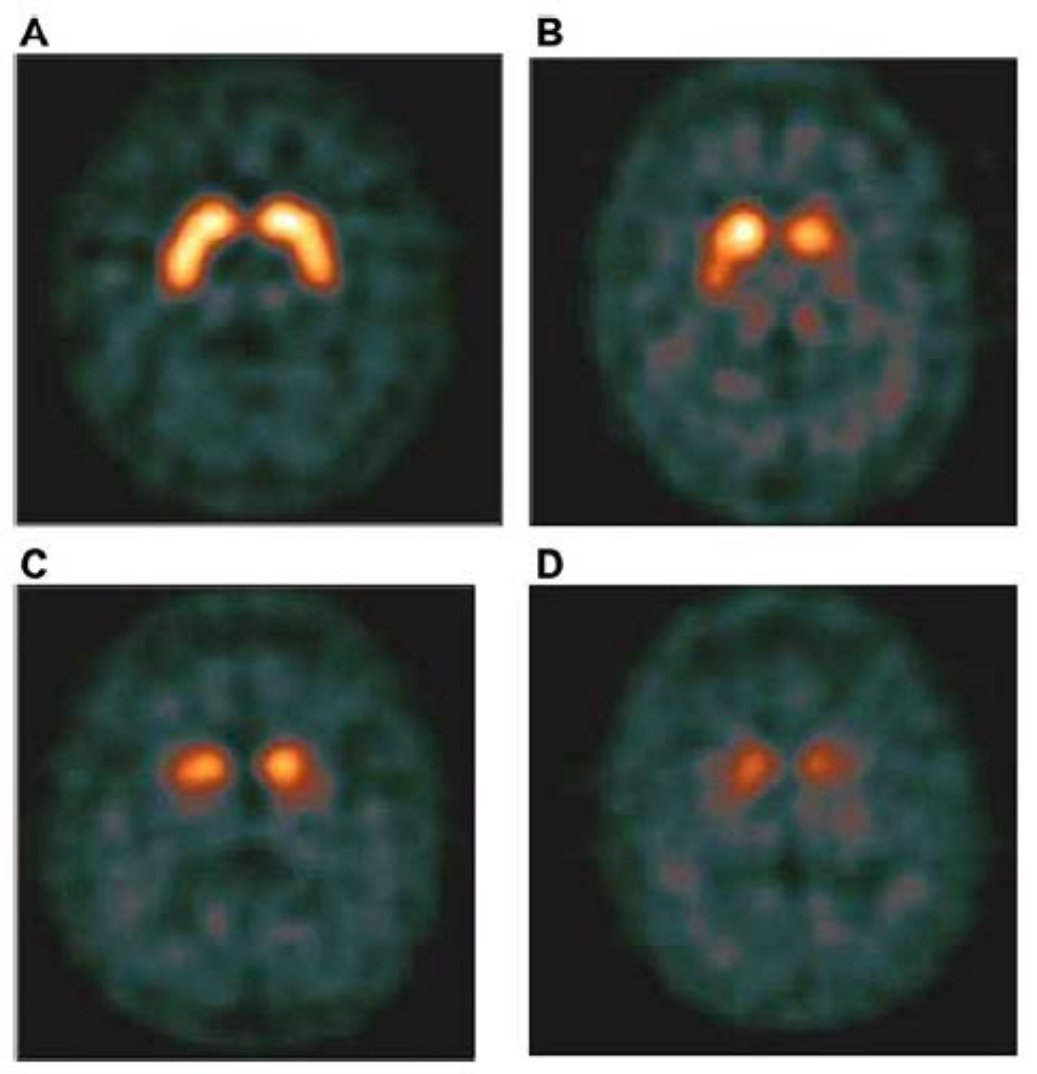
DaTscan



A. Normal: “largely symmetrical; approximately equal bilat”. Two commas.

B. Abnormal 1: asymmetrical; almost normal or reduced putamen activity in one hemisphere and a more marked change on the other side w/ significantly lower or no uptake in the putamen. One comma, one circle.

C. Abnormal 2: included significantly reduced putamen bilat. Activity was confined to the caudate nuclei. Two circles.

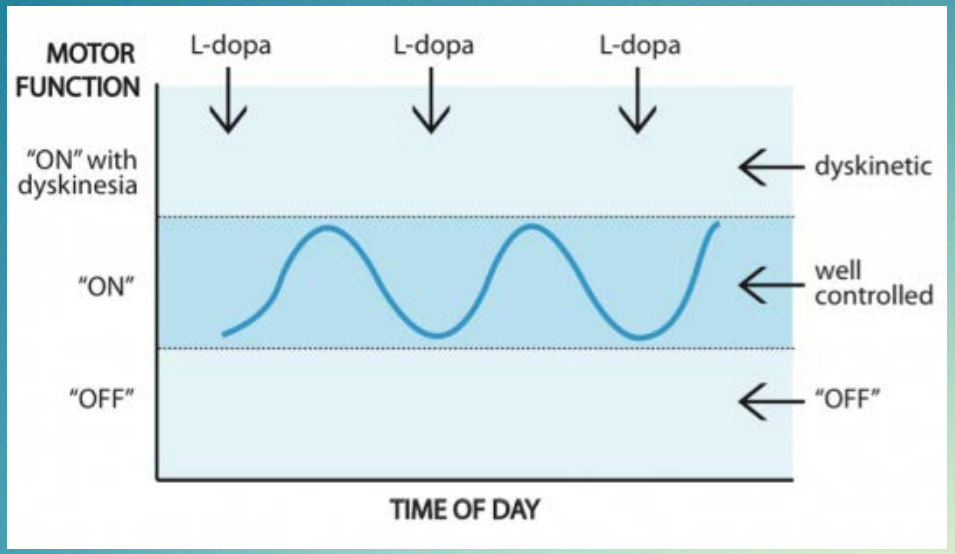
D. Abnormal 3: virtually no uptake bilat. No circles.

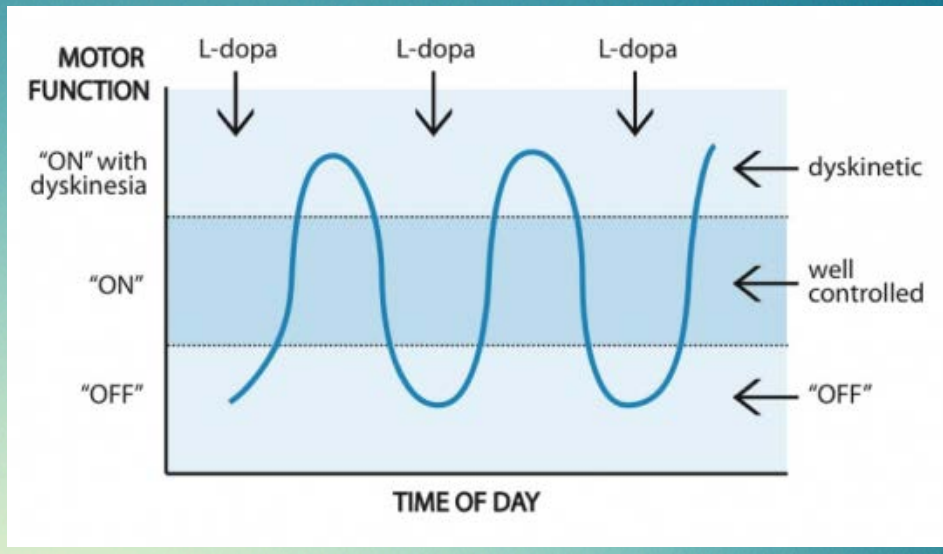
Kupsch et al. 2011 BMJ

DaTscan accuracy

- Clinically established ET vs PD vs healthy control
  - 95% Sensitivity
  - 93% specificity for the consensus blinded read
  - Benamer et al. 2000 Movement Disorders
- Clinically unclear parkinsonian syndrome
  - Baseline DaTscan vs diagnosis after 3 years
  - 78% positive percent agreement
  - 97% negative percent agreement
  - Hauser et al. 2011 J Neuroimaging
- 3T SWI-MRI vs DaTscan: PD, PSP, MSA, healthy control, ET
  - 89% sensitivity
  - 84% specificity
  - 86% concordance with DaTscan with false positives and false negatives
  - Bae et al. 2016 Movement Disorders

Motor complications of PD





- ON time = feeling well, muscles are loose, movements are smooth
- OFF time = feeling stiff, rigid, stuck, frozen, slow, fatigued
- DYSKINESIAS = abnormal involuntary movements (does not include tremor)
- Non-motor fluctuations
- Within 5 years of treatment with levodopa:
  - 50% of patients experience dyskinesias, but only 20% find them troublesome
  - About 40% of patients experience troublesome on-off fluctuations

Safinamide (Xadago)

- FDA approved March 2017
- MAO-B inhibitor (similar to rasagiline (Azilect) or selegiline (Eldeprys), reducing metabolism of dopamine
- Phase III study 2017 JAMA Neurology
  - Patients with 1.5 hours of OFF who were taking levodopa
  - 50-100 mg once daily
  - Improved ON time by 1.4 hours (compared to 0.6 hours in placebo)
  - Dyskinesias in 15% vs 5% in placebo

Safinamide

- Other biochemical effects:
  - Blocks Sodium channels
  - Blocks Potassium channels
  - Reduces abnormal Glutamate release
    - In rats this controlled the neurodegenerative process
    - Has not been proven clinically useful in humans
- No evidence of use as monotherapy
- No head-to-head comparison vs other MAO-B inhibitors or vs COMT inhibitors for clinical data
  - More specific to MAO-B (vs A) compared to rasagiline and selegiline
- Some pts had transient confusion as a side effect
- Was also noted to have insomnia, dizziness, headache and nausea (similar to placebo)
- Not effective in reducing dyskinesias
- Is being studied to see if initiating safinamide early could prevent dyskinesia
- Drug interactions with SSRIs, SNRIs, and TCA's

Extended-release amantadine for dyskinesia (Gocovri)

- FDA approved August 2017
  - NMDA antagonist
  - Mildly anticholinergic
  - Dopamine releasing
- Positive phase III:
  - 30% reduction in dyskinesia compared to placebo
  - Increased ON time without dyskinesia 2.4 hours
  - Reduced OFF time 1 hour
  - Approx 20% stopped due to AE's (vs 7% in placebo)
- Same side effects as regular amantadine other than insomnia
  - visual hallucinations, dry mouth, dizziness, peripheral edema, falls, constipation, nausea, anxiety, decreased appetite, livedo reticularis, auditory hallucinations and orthostatic hypotension

Opicapone (Ongentys)

- Available in Europe
- In pipeline for FDA approval
- Long-acting (once daily)
- COMT inhibitor similar to currently available entacapone (Comtan)
- Reduces metabolism of levodopa, making levodopa last longer
- 2015 Phase III study
- 2-hour reduction in OFF time vs 0.9 hours for placebo
- 2014 study compared opicapone to entacapone
  - Opicapone once daily significantly improved duration of levodopa action compared to 3 times daily entacapone
  - No urinary discoloration or diarrhea (seen in entacapone)
  - May have higher risk of dyskinesia (16%) compared to entacapone (8%)

Non-oral levodopa treatment

Table 1: Existing and "in development" levodopa-based treatment strategies

From: Non-oral dopaminergic therapies for Parkinson's disease: current treatments and the future

Route	*Agent*	*Clinical positioning*
Subcutaneous	Levodopa belt pump	In development (phase 2 CT)
Subcutaneous/transdermal	Levodopa patch–pump	In development (phase 2 CT)
Intrajejunal infusion	Levodopa-carbidopa gel	In clinical use
	TriGel	In development (phase 1 CT)
Inhaled	Levodopa powder (CVT-301)	In development (phase 3 CT)

Abbreviation: CT, Clinical trial; TriGel, levodopa carbidopa entacopone (liquid form).

Duopa (levodopa intestinal gel infusion)

- Reduces OFF time ~ 4 hours (vs 2 hours in placebo)
- Improves ON time w/o dyskinesia ~ 4 hours (vs 2.2 hours in placebo)
- No reduction in dyskinesia
- 16-hour administration via a cartridge into a PEJ tube
- Same benefit as levodopa, but a smoother concentration over the course of the day
- Complications include tube malfunction, ileus, pulled tube, neuropathy, usually only in the first 2 weeks
- FDA approved 2015
- Used in Europe since 2004 (Duodopa)
- Consideration for those who are not candidates for DBS and/or refuse brain surgery

Inhaled levodopa (CVT-301)

- Inhalable levodopa (CVT-301, Acorda)
- The lung has good absorption for levodopa – higher peak compared to oral
- Rapid and predictable onset, lasting 4 hours
- Pure levodopa so pts still have to take oral carbidopa
- Doses 35 mg and 50 mg
- Pulmonary safety study ongoing

Inhaled levodopa (CVT-301)

- Phase III trial results presented
- 271 PD pts without chronic lung disease
- CVT-301 84 mg vs placebo up to five times daily
- Improvement in motor function compared to placebo at 30 minutes
- No lung safety issues noted
- Adverse effects: Mild cough or URI
- No increase in dyskinesias

Subcutaneous levodopa

- ND0612, Neuroderm
- Patch form of carbidopa/levodopa
- Phase II trial (open label)
- Met primary and secondary endpoints of pharmacokinetics

Subcutaneous apomorphine

- Pen / Pump similar to an insulin pump
- Highly selective dopamine agonist
- Phase III TOLEDO trial: 106 patients, 12 weeks, OFF time reduction 2.5 hours (vs 0.5 hours with placebo)
- Reduced dyskinesias
- Risk of new ICD ~ 19% in an observational study
- Typically patients can reduce but not stop levodopa

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5HT1a agonists for dyskinesia

- Buspirone
  - Phase III trial to start soon
- Sarizotan
  - Phase II/III ongoing
- Eltoprazine: 5HT1A/B agonist
  - Proof of concept study
  - double blind, placebo controlled, dose finding: some efficacy at 7.5 mg
- Dipraglurant: mGluR5
  - phase IIa study: mAIMS positive results

When to consider DBS

- Good initial response to levodopa
- On-off fluctuations (improves ON by 5 hours (vs 0 in best medical therapy group); reduces OFF by 2.4 hours (vs 0 in BMT group)
- Dyskinesias (reduces by 70%)
- Disabling tremor (reduces by 60-70%)
- Absence of dementia/severe depression
- PD > 4 years and motor fluctuation x 4 months
- MRI normal for age
- Good medical health
- Realistic expectations

Non-motor symptoms

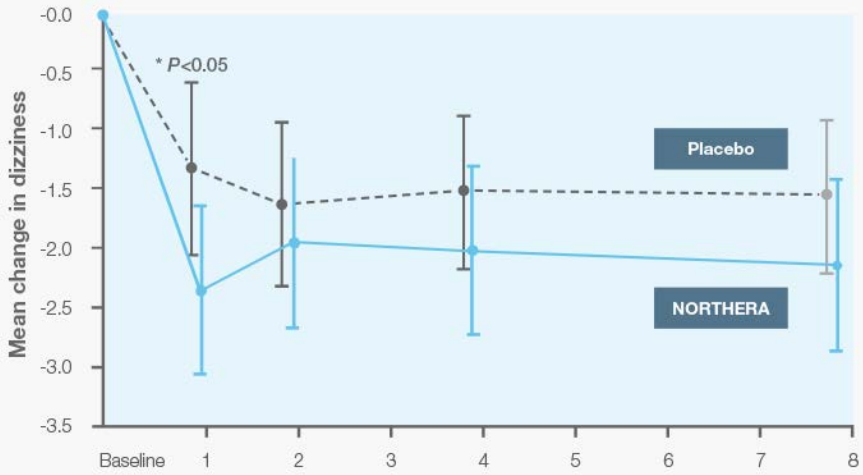
- Autonomic symptoms
  - Constipation
  - Delayed gastric emptying
  - Orthostatic hypotension
  - Urinary dysfunction
  - Sexual dysfunction
  - Diaphoresis
- Cognitive symptoms
  - Memory issues
  - Executive function trouble
  - Processing speed
  - Personality change
- Psychiatric symptoms
  - Depression
  - Anxiety
  - Apathy
  - Hallucinations / Delusions
  - Impulse control disorders (ICD)
- Sleep issues
  - Insomnia
  - Fatigue
  - REM sleep behavior disorder

Droxidopa (Northera) for orthostatic hypotension in PD/MSA

- Metabolized into norepinephrine
- Improve symptoms of OH by 2 points on a 0-10 scale (vs 1.5 in placebo)
- 100 mg 3 times per day x 1 week then titrate
- Most end up on 400-600 mg 3 times per day
- Stop midodrine with use of droxidopa
- Less supine hypertension than with midodrine
- Side effects: HA, dizziness, fatigue, which resolve with time and are not dose-dependent

73% of patients receiving NORTHERA vs 59% of placebo patients saw improvement in symptoms by Week 1 as measured by OHSA Item 1 scores (Study 306B)[2]

Mean change in OHSA Item 1 score by week (n=147)[1,2,a,b]



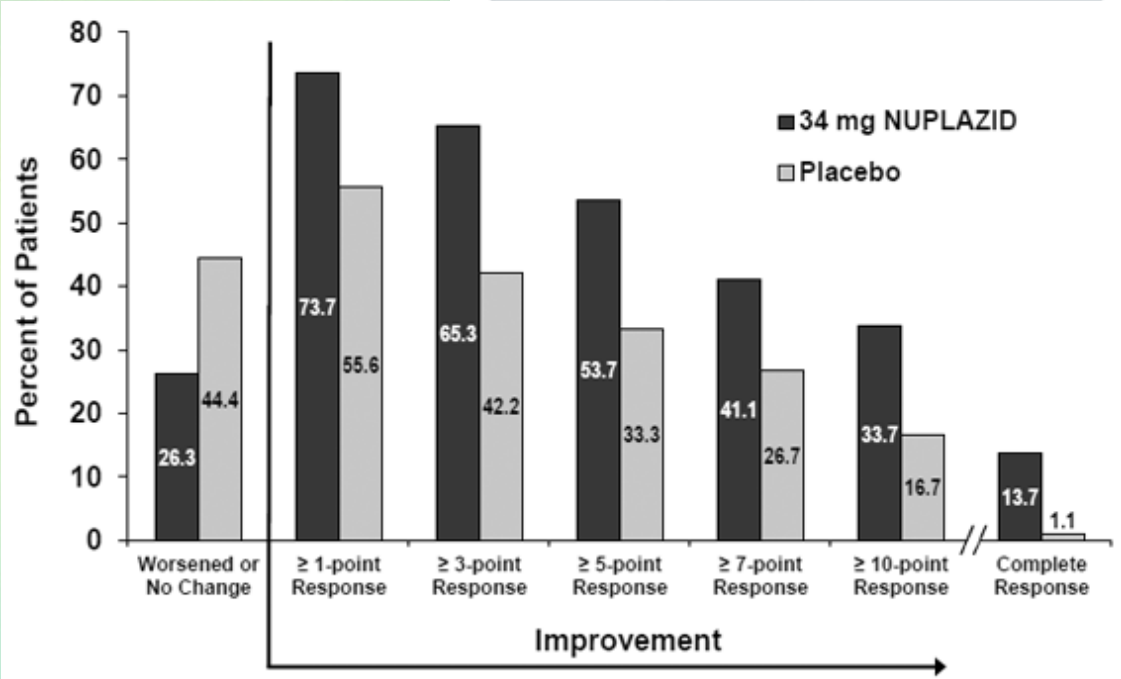
Supine SBP in Study 306[1]

Study 306	During 1- to 2-week titration Phase (% of patients)		At end of 8-week treatment Phase (% of patients)	
	NORTHERA (n=114)	Placebo (n=108)	NORTHERA (n=86)	Placebo (n=93)
Supine SBP >200 mm Hg	2.6%	0%	0%	0%
Supine SBP >180 mm Hg	2.6%	1.9%	0%	0%
Supine SBP >160 mm Hg	16.7%	19.4%	2.6%	8.3%

Nuplazid (pimavanserin) for Parkinson's disease psychosis

- Novel anti-psychotic, not anti-dopaminergic
- Selective 5HT2A inverse agonist
- FDA approved April 2016
- No anticholinergic or histaminergic effect
- Improved SAPS-PD score (0 to 45) by ~ 6 points compared to ~ 3 points on placebo
- Side effects include nausea, constipation, edema, gait issues, confusion

SAPS-PD
Auditory hallucinations
Voices conversing
Somatic or tactile hallucinations
Visual hallucinations
Global rating of severity of hallucinations
Persecutory delusions
Delusions of jealousy
Delusions of reference
Global rating of severity of delusions



Complete response = SAPS-PD score reduced to zero from baseline value.
Patients with missing values were counted as non-responders.

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Updates in disease modification

- Clearing alpha-synuclein
  - cAbl inhibitors e.g., nilotinib
    - Also regulates Parkin gene activity
    - Preclinical data and a small phase I study
    - Phase II studies recruiting
  - Affitope: vaccine to clear alpha-synuclein
    - Phase Ib study safe/tolerable
  - NPT088: human fusion protein
    - Phase I study
- Antioxidants
  - IV and intranasal glutathione showed no symptomatic benefit in well-done trials
  - Inosine increases uric acid
    - Phase III recruiting
- Calcium channel blocker
  - Phase III trial ongoing
- Nortriptyline
  - In vitro reduces alpha-synuclein clumping
  - Reduced levels of alpha-synuclein in rats
  - Delayed time to need levodopa in epidemiological studies
  - Collier et al., 2017 Neurobiology of disease

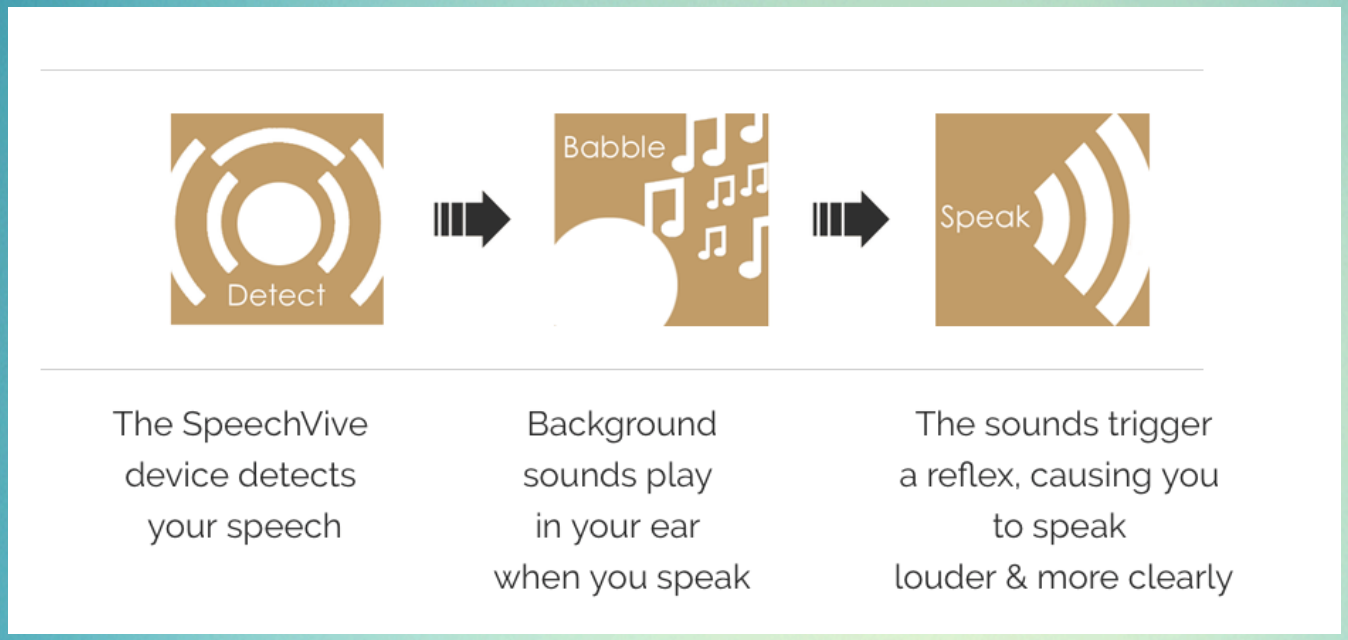
Updates in disease modification

- Diabetes drug exenatide
  - GLP-1 receptor agonist
  - Increase incretin effect
  - Stimulate the release of insulin
  - RCT, N = 62
  - Once weekly vs placebo for 48 weeks, washout x 12 weeks
  - Improved MDS-UDPRS by 1 point compared to worsened UPDRS by 2 points in placebo group
  - Side effects injection site reactions and GI symptoms
  - Does not affect blood sugar levels in non-diabetic patients
  - Athauda et al., 2017 Lancet

- Beta-agonists
  - Alpha-synuclein gene expression (SNCA) correlates with disease
  - Beta-2-agonists modulate epigenetic marks at the SNCA gene
  - Epidemiological studies suggest salbutamol associated with lower risk of PD
  - Propranolol associated with higher risk of PD (but often used for ET which can be misdiagnosis
  - Mittal et al., 2017 Science

Therapy advances for PT

- Ongoing evidence for power of PT, OT, speech therapy, physical activity, dance, exercise, well-being programs
- Speech therapy program:
  - SpeechVive



Technology / Wearable Sensors

- Improve clinical data re:
  - Tremor control
  - Dyskinesias
  - ON vs OFF time
  - Freezing
  - Near falls
  - Medication consistency
- Improve research data especially for subtle aspects of gait in pre-symptomatic gene carriers or RBD patients
  - Could result in shorter study times
- Improve assessment of function, rather than capacity
  - What the patient actually does vs what they can do in the clinic
- A big step for personalization of care

Exercise and PD

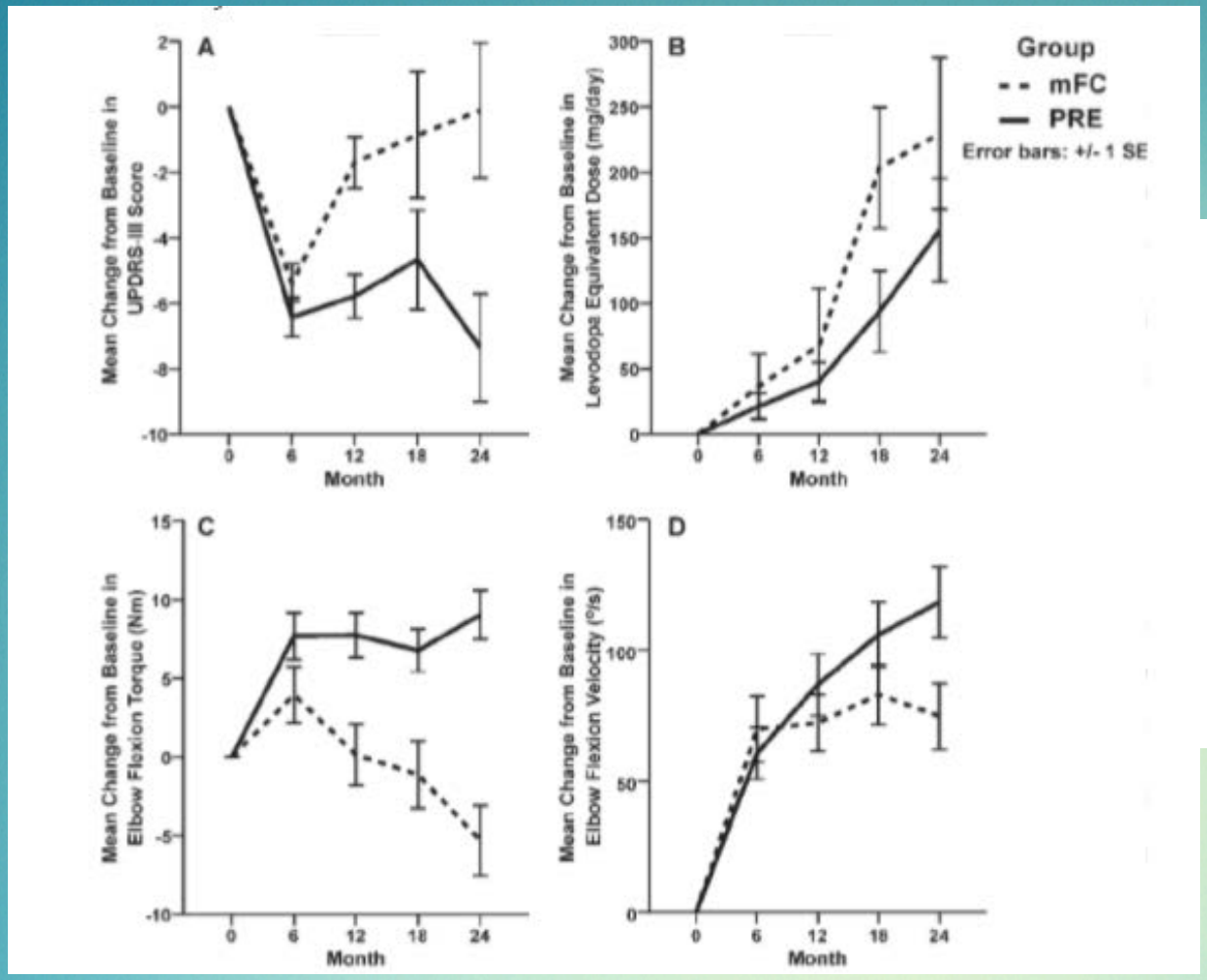
Benefits of Exercise

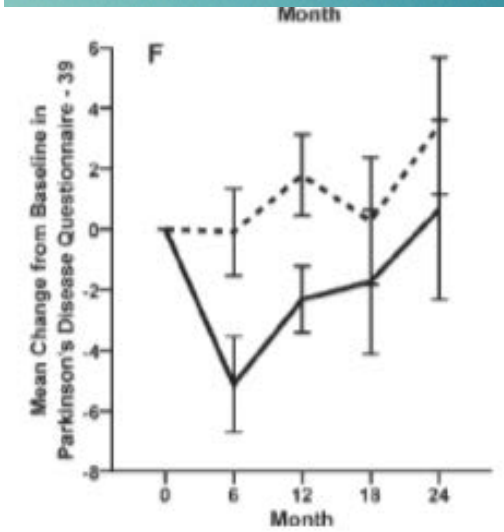
- Improved gait and balance / reduced freezing of gait / reduced risk of falls
- Improved flexibility / reduced rigidity / reduced risk of contractures
- Improved endurance / energy
- Improved ability to complete activities of daily living / improved sense of well-being / improved quality of life
- Improved working memory and decision making
- Improved attention and concentration
- Improved mood / reduced depression and anxiety
- Improved quality of sleep

Direct Effects of Exercise

- More efficient use of dopamine by brain cells (neurons) (making medications more effective)
- Growth of blood vessels, improving blood flow
- Helps neurons make new connections (synapses) by releasing brain growth factors
- Improves neuroplasticity (teaching the brain a new pattern of thinking / functioning)
- Improves cardiovascular health / improves brain metabolism
- Supports the functioning of the immune system / reduces inflammation

Exercise and PD





Corcos et al., 2013
Mov Disorders

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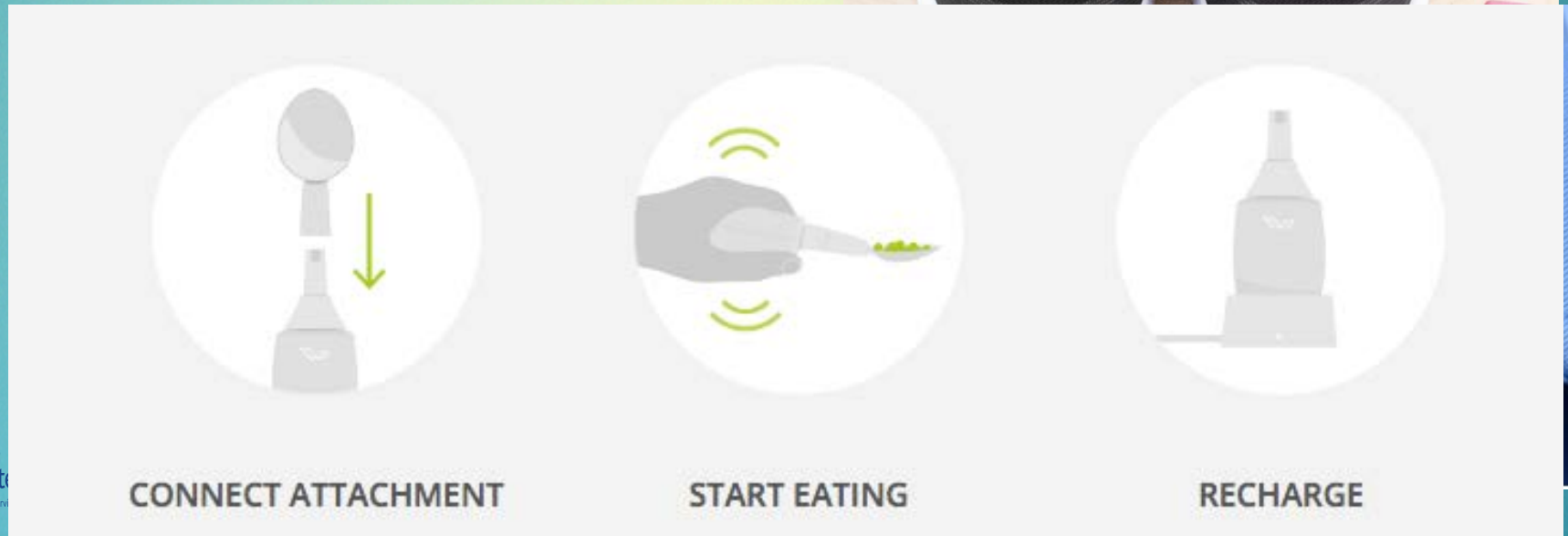
Essential Tremor (ET)

- Slowly progressive condition causing tremor, usually in bilateral hands, head or voice
- Much more common than PD, affects up to 8 million Americans
- Used to be called benign essential tremor to distinguish from PD
- Can be associated with significant disability, limiting writing, dressing, eating, drinking

Essential Tremor (ET) Management

- **Medications**
  - Propranolol up to 240 mg daily
  - Primidone up to 250 mg daily
  - Benzodiazepines (e.g., clonazepam)
  - Gabapentin
  - Topiramate
- **Injection**
  - Botulinum toxin injection for hand and head tremor

- **Non-medication treatment**
  - Use of travel mugs / straws
  - Zubits (magnetic shoelaces)



Advanced Management of ET: comparing options

	Reversible	Laterality	Adjustable over time	Surgery and implant	Battery replacement needed	Frame for surgery	Time to completion	Time to recovery	Time for effect	Hair shaving
Deep Brain Stimulation (DBS)	Yes	Bilateral	Yes	Yes	Yes	Optional	5 hours (+1 hour battery)	Weeks	Immediate	Partial
Focused Ultrasound (FUS)	No	Unilateral	No	No	No	Yes	4 hours	Fast (Days)	Immediate	Full
Radiosurgery	No	Unilateral	No	No	No	Yes	1 hour	Fast	Delayed (months)	No