Geriatric Peer Review:

Parkinson's and Movement Disorders

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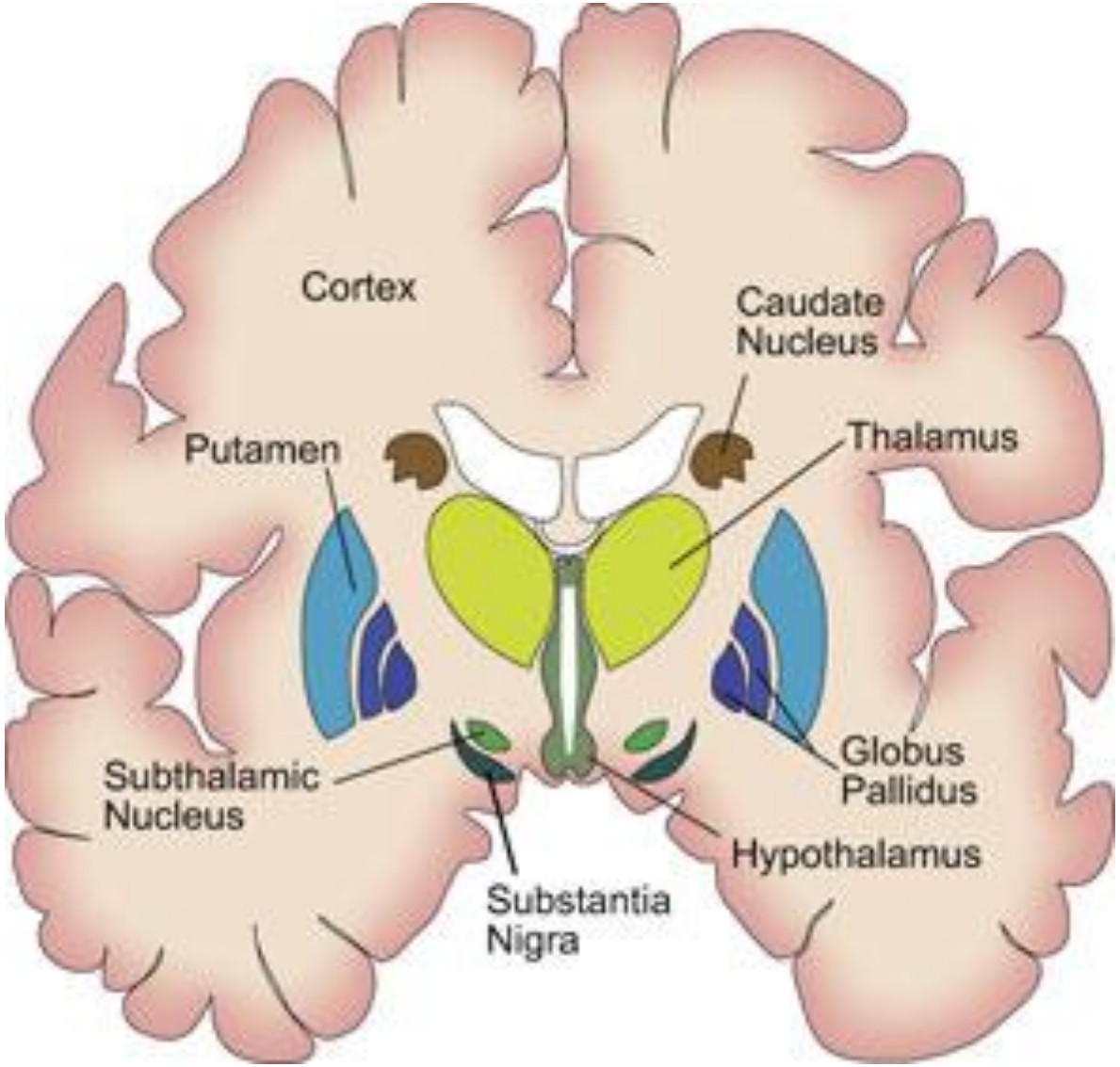
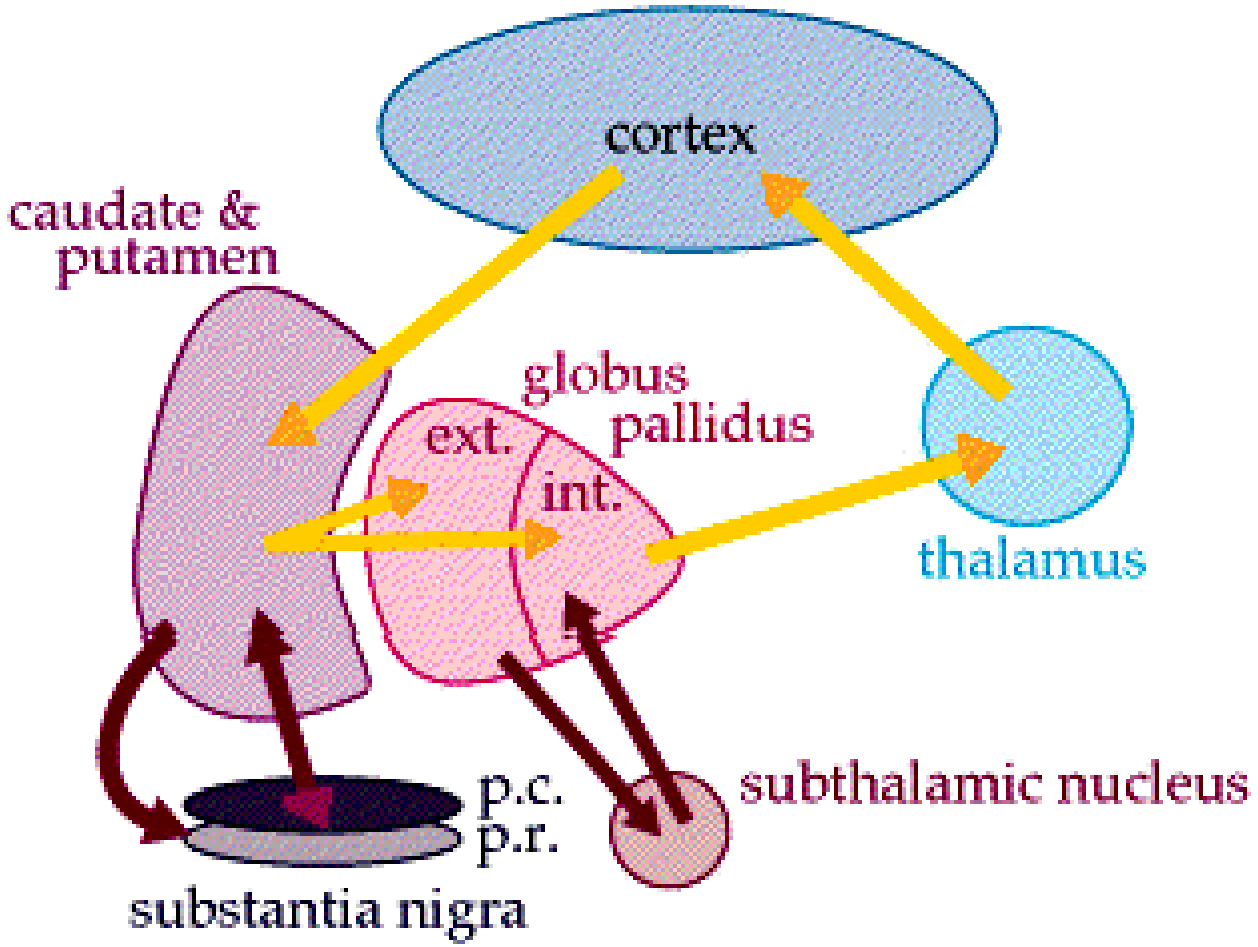
Neurologist

Outline

- Parkinson's Disease
  - Clinical
  - Management
    - Medications
    - Therapy
    - Devices
- Parkinson's plus conditions
- Essential tremor
- Chorea
- Restless legs syndrome
- Neuroleptic malignant syndrome
- Tardive syndromes

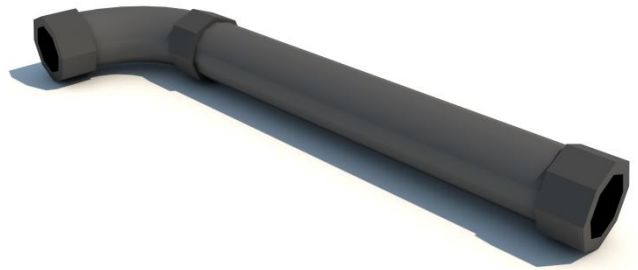
Basal ganglia



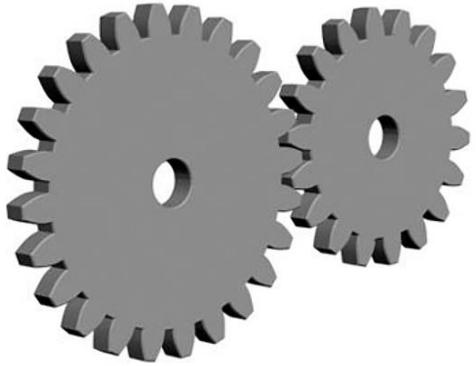

cortex
caudate &
putamen
globus
pallidus
ext.
int.
thalamus
p.c.
p.r.
subthalamic nucleus
substantia nigra

‘parkinsonism’

- Bradykinesia (Akinesia)
  - Slowness of movement, poverty of movement plus fatigue and decrement
  - Slowness alone occurs in many conditions
  - Essential to the diagnosis

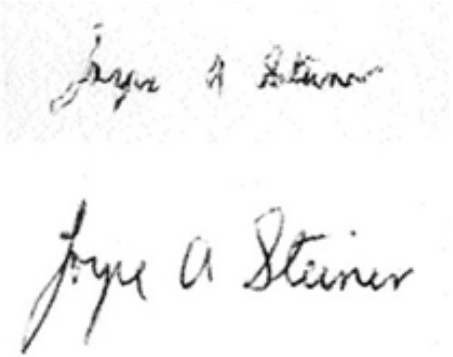


- May or may not have:
  - Rigidity:
    - Lead pipe, worse with synkinesis
  - Tremor:
    - At rest, pill-rolling, cog wheel
  - Postural and Gait disturbance
    - Festinate – small shuffling steps and turn ‘en bloc’
    - Reduced arm swing
    - Freezing and falling



Parkinsonism - examination

- Observation: facial expression, blink rate, frontalis overactivity
- Eye movements and saccades
- Listen to speech: ? monotonous, quiet
- Limbs:
  - Assess for rigidity
  - Look for resting and postural tremor
  - Test for bradykinesia ? asymmetrical
  - Cerebellar signs?
- Gait:
  - Standing, posture, arm swing, step size, freezing?, turning around, heel-toe, pull-back
- Other:
  - BP lying and standing (wait for 1-3 minutes)
  - Handwriting
  - Cognitive assessment



Postural deformities

- Camptocormia
  - Female > male
  - Assoc. with increased motor dysfunction
- Anterocolis
  - Seen in MSA + PD
  - May respond to DBS (STN)
- PISA syndrome
  - 10% lean seen in around 10% of patients

Causes of Parkinsonism

Primary degenerative

- Parkinson's disease (sporadic and genetic)
- Dementia with Lewy bodies (DLB)
- Progressive supranuclear palsy (PSP)
- Multiple systems atrophy (MSA)
- Huntington's disease
- Basal ganglia calcification
- Neuronal brain iron accumulation
- Neuroacanthocytosis
- Multiple other inherited conditions...

Secondary

- Drugs (dopamine receptor blockers)
- Cerebrovascular disease
- Basal ganglia lesions
- Metabolic disorders (e.g. Wilson's, hypoparathyroidism)
- Brain trauma
- Post encephalitic
- Hydrocephalus

Parkinson's disease

- James Parkinson (1755-1824)
- Prevalence 180/100,000
- Men>women
- Weak environmental associations
- Rare genetic causes: LRRK 2 (AD), Parkin (AR)

New MDS clinical criteria 2015

- Early dementia not an exclusion criterion
- Postural instability is not a core feature
- Currently being validated
- Experienced physician is better than the criteria!

Hughes 2001

AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY. (*Paralysis Agitans.*)

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.

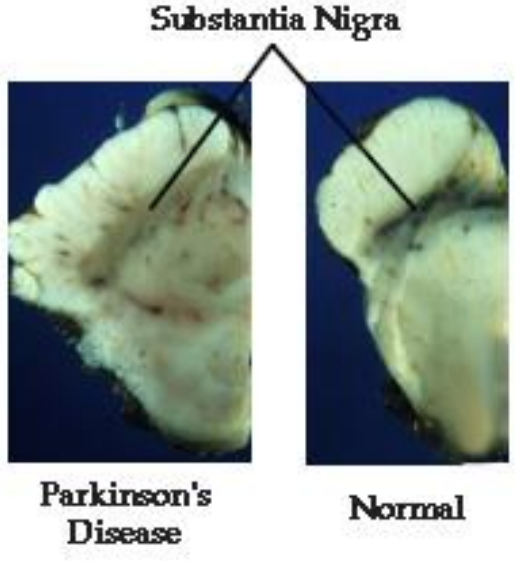
Young vs. old PD

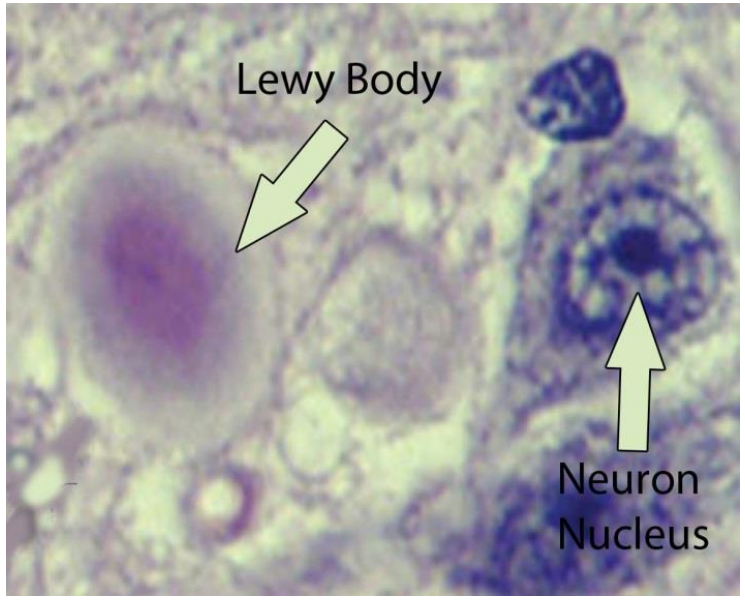
- YOPD < 40y, EOPD <50, LOPD >50
  - Older tends to be more severe
  - Rigidity more common in younger patients
  - PARK2 most common cause of early onset PD (50% < 40y)
    - Lower limb dystonia
    - Axonal neuropathy
    - Early dyskinesias
  - LRRK2
    - similar to standard IPD
  - Pain, rigidity, dystonia, dyskinesia and depression increased in YOPD

Lynch 2016

Pathology

- Lewy Bodies:
  - cytoplasmic inclusions composed of alpha-synuclein and ubiquitin
  - In the basal ganglia (substantia nigra), brainstem and cortex
- Depletion of dopaminergic cells in the substantia nigra pars compacta (SNc)
- Braak hypothesis
- 50% of neuronal loss before we get motor symptoms






Non-motor features

Non-motor features of PD

- Neuropsychiatric
  - Dementia
  - Depression + Apathy
  - Anxiety
  - Loss of libido
- Autonomic
  - Constipation
  - Urinary incontinence
  - Erectile dysfunction
  - Excessive sweating
  - Postural hypotension
  - Excessive salivation
- Sleep disturbance
  - REM sleep behaviour disorder
  - Periodic limb movements of sleep
  - Restless legs syndrome
  - Vivid dreams
  - Daytime somnolence
- Sensory symptoms
  - Pain
  - Paraesthesiae
- Other
  - Fatigue
  - Loss of smell – 2.5 years before on average

Sleeping problems

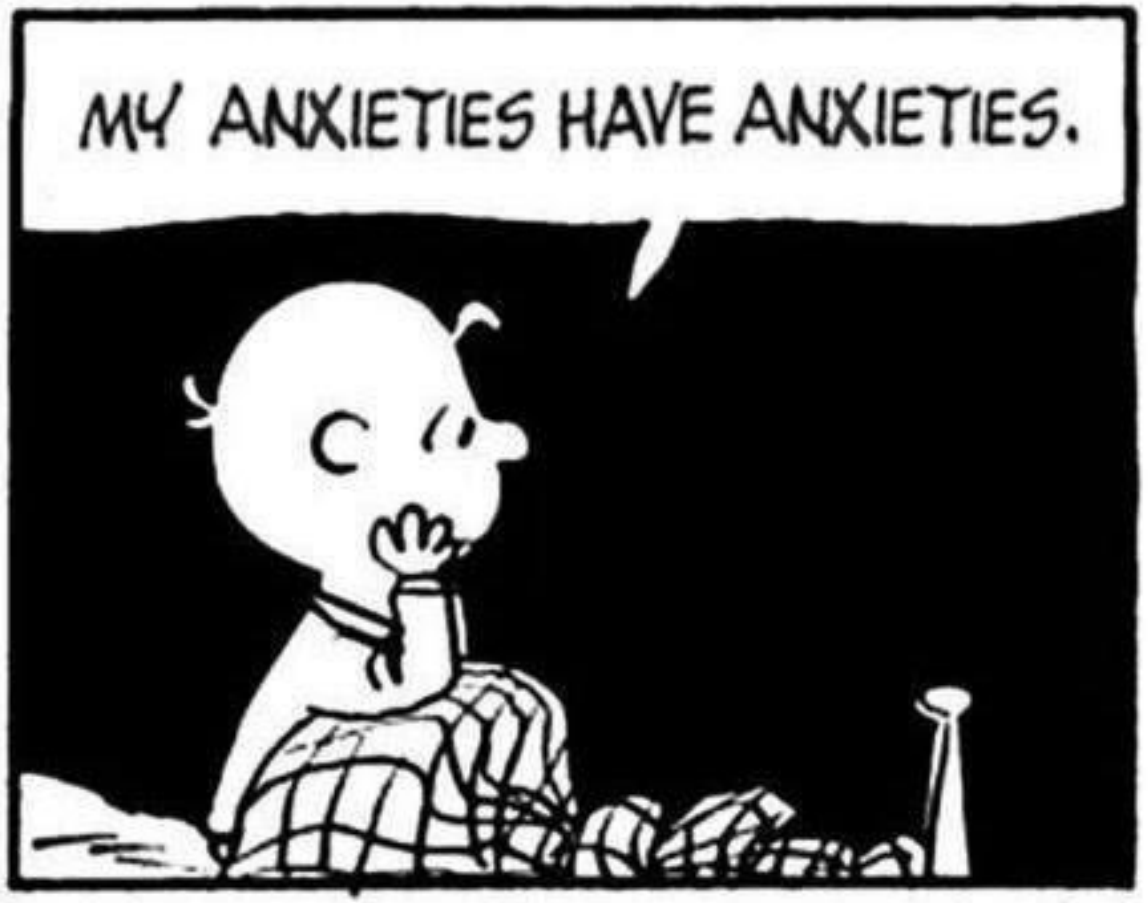
- Vivid dreams
- REM sleep behaviour disorder
  - Risk of developing PD:
    - 33.1% at 5 years
    - 75.7% at 10 years
    - 90.9% at 14 years
- Restless legs syndrome
  - Exclude iron deficiency
- Periodic limb movements of sleep
- Painful leg spasms
- Daytime somnolence

Autonomic

- Constipation
- Urinary incontinence
- Erectile dysfunction
- Excessive sweating
- Postural hypotension
- Excessive salivation

Neuropsychiatric

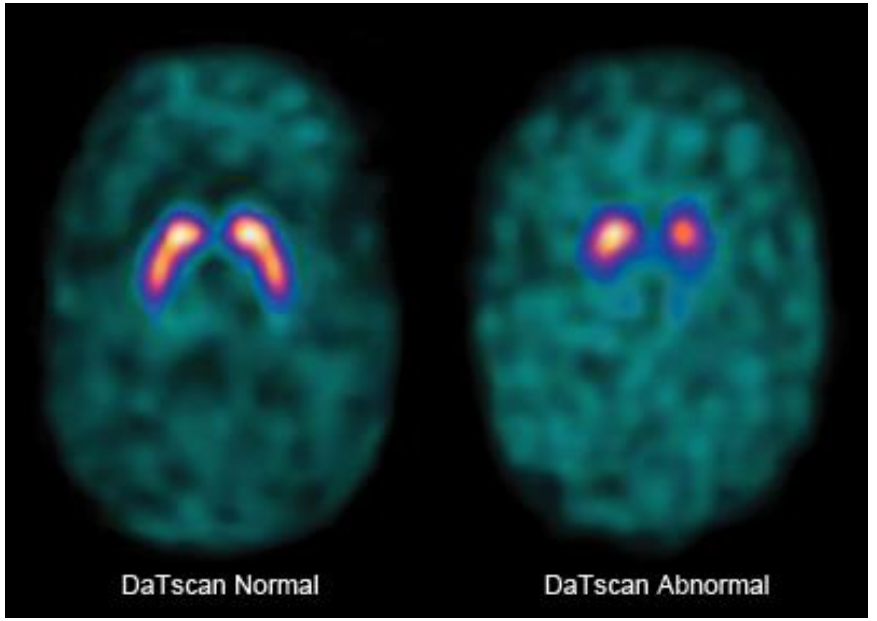
- Cognitive
- Depression + Apathy – ask!
- Anxiety
- Loss of libido



Cognitive dysfunction

- Recall, visuospatial processing, attention affected early in PD.
- Dopaminergic and cholinergic deficits at onset
- 40% prevalence of dementia (poor prognosis)
  - Often predates the diagnosis
- DLB and PDD part of a spectrum
- Cause similar type of impairment:
  - Fluctuating alertness and cognition
  - Visual hallucinations
  - Parkinsonism – often without tremor in DLB
  - Early falls
  - Sensitivity to dopamine receptor blocking agents

Investigations in PD



- PD is a clinical diagnosis, but consider the following:
  - Neuroimaging:
    - To exclude a secondary structural cause, e.g. tumour
    - Further define syndrome if atypical
  - Levodopa challenge:
    - The response to levodopa is very useful diagnostically
    - Limitations as ‘one-off’ test, better as ongoing treatment trial
  - Dopamine transporter scan (DAT scan)
    - Tracer binding to dopamine transporter protein
    - Reduced in some parkinsonian conditions
    - Normal in drug-induced PD, essential tremor
  - Genetic testing

TREATMENT

Much more than just giving pills…

- **PD nurse + community educators**
- Neurologist/geriatrician
- Psychiatrist
- Physiotherapist
- Occupational therapist
- Speech and language therapist
- Social worker
- Neuropsychologist/counsellor
- +/- Neurosurgeon

Options for treating motor symptoms

- Levodopa
  - Co-careldopa (Sinemet)
  - Co-beneldopa (Madopar)
- Dopamine agonists
  - Pramipexole
  - Ropinirole
  - Rotigotine (not currently available)
- Catechol-O-methyltransferase (COMT) inhibitors
  - Entacapone
  - Tolcapone
- Monoamine oxidase (MAO) inhibitors)
  - Selegiline
  - Rasagiline
- Amantadine
- Anticholinergics
  - Trihexyphenidyl

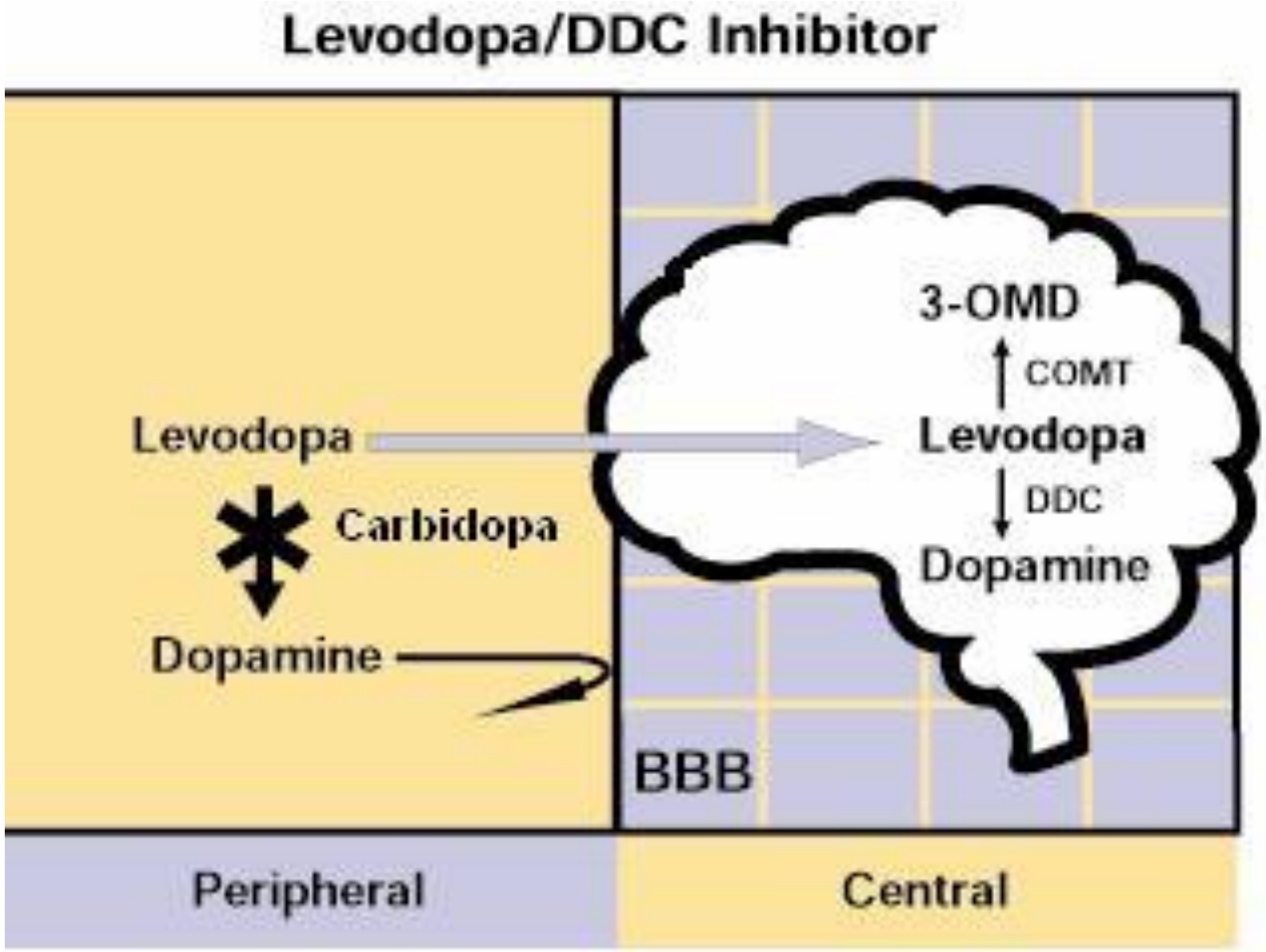
How to start?

- Controversial and individualised
- Start as soon as develop functional disability (better response early on)
- Some use combination at the outset, but NO clear evidence any agent has disease modifying effects

What to start with?

- Levodopa
  - Moderate motor symptoms, over 70 years
- Dopamine agonist
  - Moderate motor symptoms under < 70 without dementia
- Anticholinergic
  - Under 60-65 when tremor is the only motor symptom causing disability
  - Young onset PD, particularly if dystonia present
- Consider MAO inhibitor
  - Consider if only mild motor symptoms

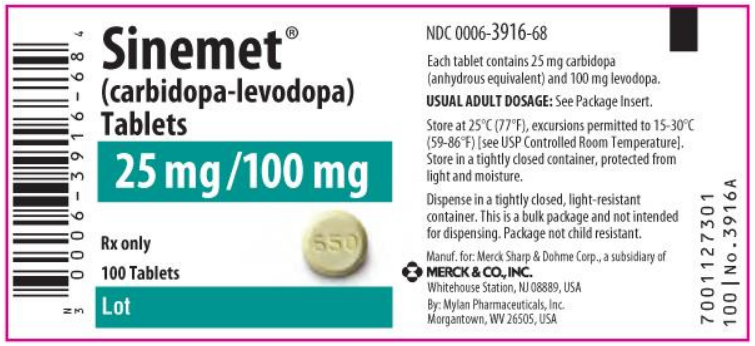
Levodopa

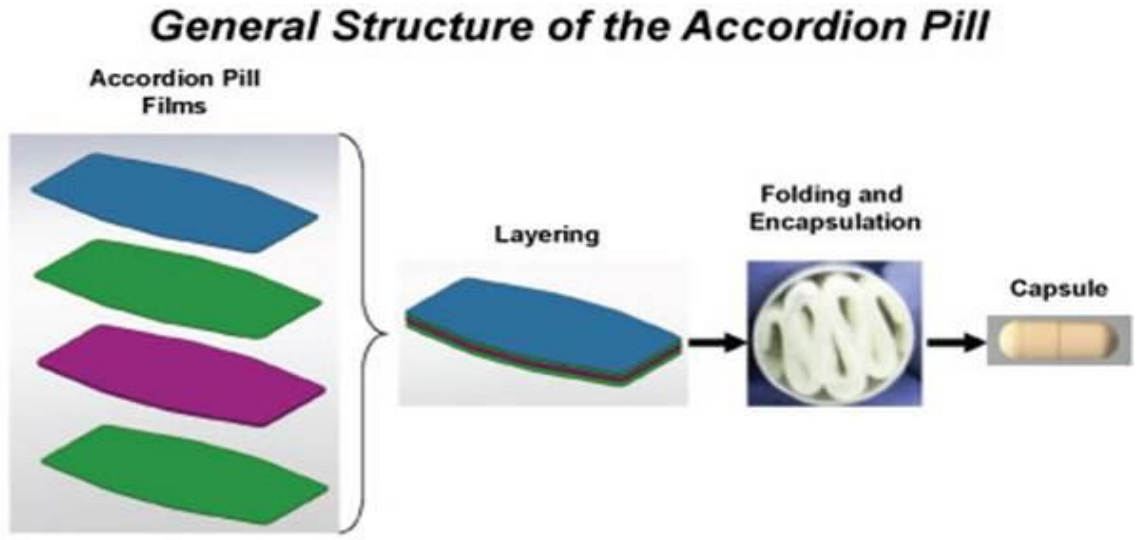


DDC = dopamine decarboxylase enzyme (blocked by Carbidopa)

Levodopa

- Most effective treatment for motor symptoms
- Given with a peripheral dopa decarboxylase inhibitor (DDCi) to prevent breakdown in the periphery
- Written as DDCi/levodopa dose
  - E.g. co-careldopa (Sinemet) 25/100 = 25mg of carbidopa and 100mg of levodopa
- Different formulations
  - Modified release (e.g. Sinemet CR) have a longer duration of effect, but less predictable (low bioavailability)
  - Dispersible (e.g. Madopar dispersible) are faster acting, e.g. as PRN for 'off periods'
  - Duodopa – for direct infusion into the small intestine
  - With COMT inhibitor (Stalevo) - not in NZ



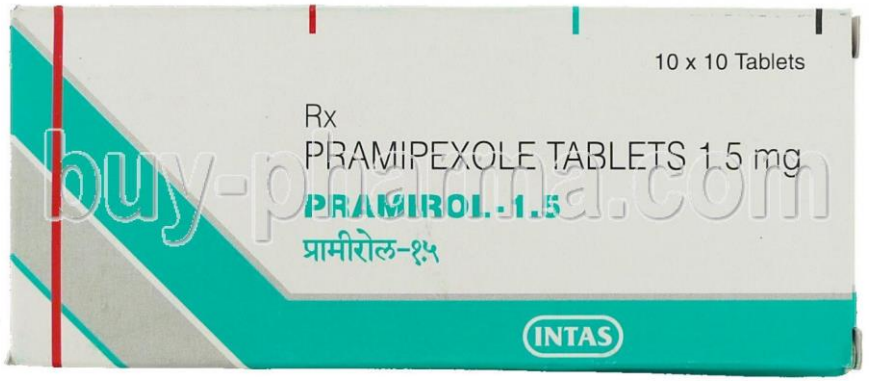


Possible side effects of levodopa

- Nausea and vomiting (most common) – use domperidone
- Postural hypotension
- Hallucinations
- Somnolence and sleep attacks
- Later on develop on-off fluctuations (levodopa-induced dyskinesia)
- Sudden withdrawal rarely causes neuroleptic-malignant syndrome

Dopamine agonists

- Directly stimulate post-synaptic dopamine receptors
- Effective as monotherapy, only rarely cause dyskinesias (on-off)
- Older dopamine agonists were associated with fibrotic reactions in the heart, lung and retroperitoneal space
- Newer ones are not, e.g. pramipexole, ropinirole
- Apomorphine is an injectable form – infusions and ‘rescue’ injections



Possible side effects of dopamine agonists

- Less motor complications
- Nausea, vomiting
- Postural hypotension
- Excessive sleepiness/sleep attacks
- <u>Impulse control disorders 5-20% - 4As:</u>
  - Androgen (male)
  - Age (young)
  - Addictive tendency
  - Angry personality
- Hallucinations/confusion
- Initial worsening
- Dopamine agonist withdrawal syndrome

Monoamine oxidase inhibitors

- Prevent breakdown of dopamine increasing its effect
- Selegiline and rasagiline
- NEW = safinamide; only reversible MOAb inhibitor, may modulate glutamate

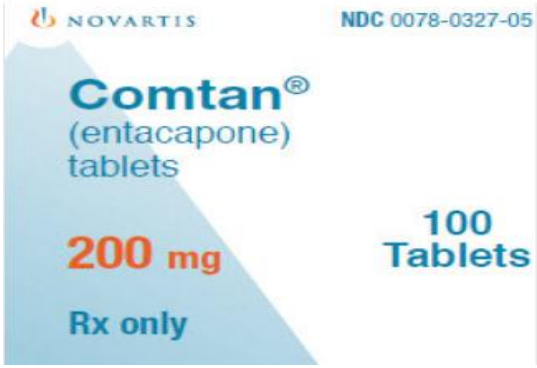
Indications:

- Very occasionally used for monotherapy (if mild motor symptoms only)
- Adjunctive therapy (with levodopa)

Side effects:

- Dry mouth, depression, gastrointestinal (not with GI ulcers)
- Selegiline metabolised to amphetamine derivatives (rasagiline is not)
- Very rarely can cause ‘serotonergic crisis’ with SSRIs
- Potential for hypertensive crisis with tyramine-rich foods

COMT-inhibitors

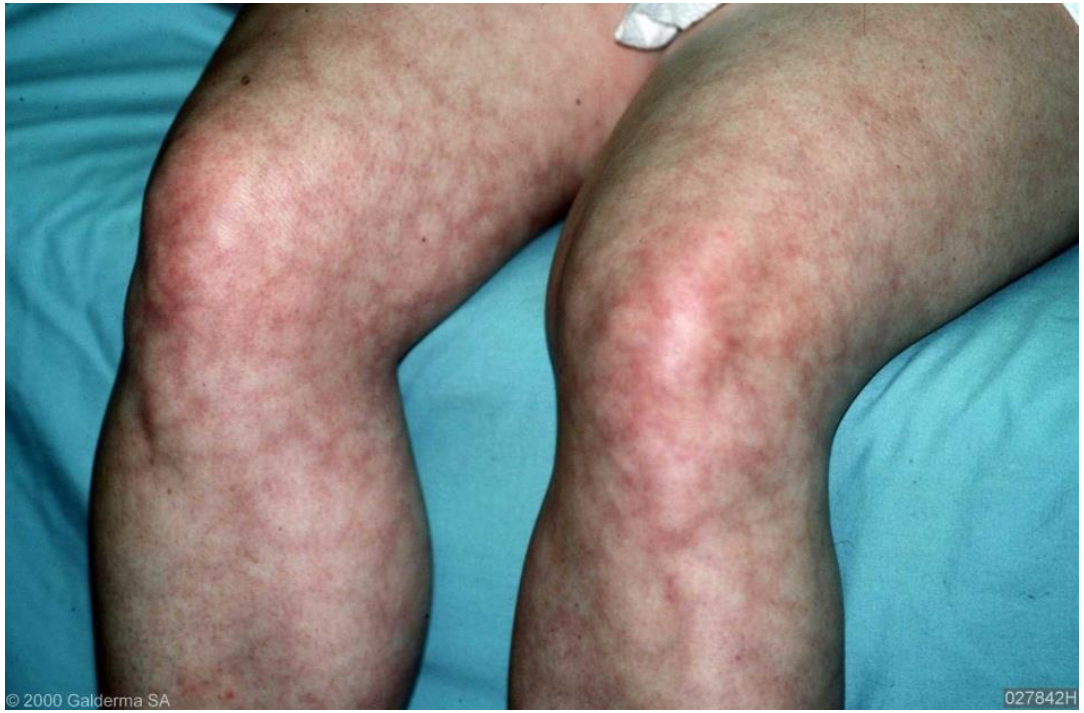


- Decreases breakdown of levodopa by the COMT enzyme increasing dopamine levels
- Can prolong the effect of each dose of levodopa
- Options:
  - Entacapone
  - Tolcapone – more effective, rare liver failure
  - Opicapone (NEW – not in NZ)
    - Strong inhibition and given daily dose = much better than TDS
    - 50mg non-inferior to entacapone and ‘tendency’ to greater effect – *Ferreira*
- Potential side effects:
  - GI: nausea, diarrhoea, abdominal pain
  - Increased dyskinesia
  - Red/brown urine

Amantadine

- Works on multiple neurotransmitter pathways
- Main indication = reducing levodopa-induced dyskinesia
- Minor effect on bradykinesia, rigidity and gait disturbance

- Side effects:
  - Peripheral oedema
  - Rash – livedo reticularis
  - Confusion and hallucations
  - Stimulating effect



Anticholinergics

- Used to treat tremor
- Side effects limit their use in elderly:
  - Confusion
  - Dry eyes, mouth
  - Constipation
  - Urinary retention
- Contraindicated with:
  - Closed-angle glaucoma
  - Cognitive impairment
  - Prostatism

Cognitive dysfunction

Treatment

- PD involves multiple neurotransmitter pathways – NA, Chol, serotonin, dopamine
  - Cholinesterase inhibitors can improve cognitive function and reduce hallucinations
    - Rivastigmine and donepezil
    - One meta-analysis positive, but mild effect – Rolinki M
    - RCT of rivastigmine showed only trends – not significant
  - Dopamine important for working memory, executive function, but all work together.
- Insufficient evidence for DAs – *Neurotherapeutics 2014*
- Avoid anticholinergics
- CBT/cognitive training – only mildly effective
- Nintendo Wii can improve reaction times
- Memantine
  - NMDA antagonist
  - Effect very slight

Depression/anxiety

Treat the mood disorder first – occasionally resolves parkinsonism…

- SSRIs
  - Paroxetine and Venlafaxine effective and well tolerated – *Richard IH, Neurology 2012.*
- Mirtazapine
  - Noradrenergic and serotoniergic activity
- Limit daytime benzodiazepine use – can increase falls
- Counselling + support

Hallucinations/psychosis

- Quetiapine and clozapine have less extra-pyramidal side effects
- Clozapine more effective
- Pimavanserin
  - New antipsychotic specific for PD (not schizophrenia)
  - Selective 5-HT2A antagonist with 58h t1/2 (no effect on dopamine)
  - Therefore (possibly) dopamine not necessarily related to hallucinations in PD

Restless legs syndrome

- Don’t treat if only mild or sporadic given significant side effects
- Levodopa
  - Works, but augmentations occurs – monitor – more common at doses >200mg.
  - No trials to support intermittent use
- Ropinirole + pramipexole
  - Also watch for augmentation: overall rate low in study
- Rotigotine
  - 4 new studies, 2-3mg patch efficacious
- Gabapentin
  - Need higher doses, up to 1200mg not very effective, i.e. 2400mg
- Pregabalin
  - Doses 150-450mg/d, 1-3h before bed
  - Non-inferior to pramipexole: Allen R P NEJM 2014.
- Oxycodone-naloxone

Other treatments to consider

- Chewing gum for sialorrhoea
- Melatonin for REM sleep behaviour disorder, along with clonazepam and rivastigmine
- Rotigotine for nocturia (RECOVER study)
- Antidepressants good for rapid ejaculation (SSRI)
- Caffeine:
  - Activity on adenosine receptors
  - 100-200mg daily works a little bit to improve the UPDRS
  - Adenosine A2 antagnoists showing some effect – Hauser, Lancet Neurology 2014
- Postural instability – not much evidence:
  - Methylphenidate: 1 +ve and 1 -ve trial
  - Donepezil: may reduce falls
  - PPN DBS

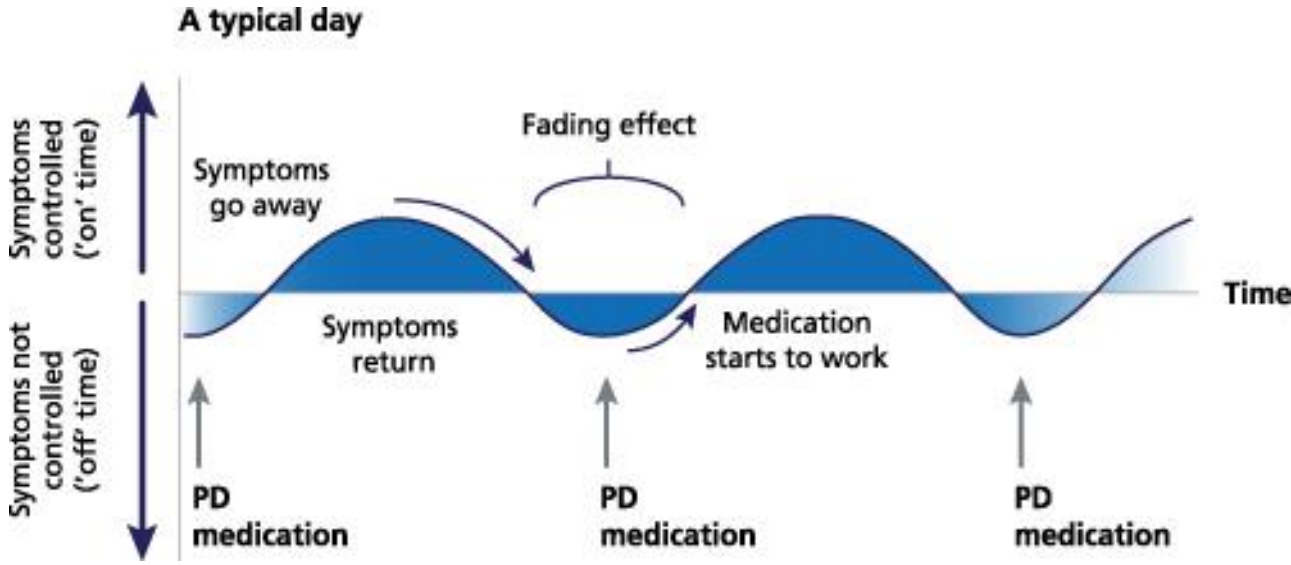
Non-pharmacological treatments

- Exercise
  - 2 RCTs show benefit for the Argentinean Tango
  - PRET – PD study: *David JA et al*.
    - 24 month of Progressive Resistance Exercise Training improved attention and working memory
    - No control group – ? Just learned to do tests
  - Park-fit study: progressive resistance and brisk walking; fit bit
- Neuropsychology:
  - Predictors of positive coping: self transcendence, freedom, responsibility, personality.
- Stem cells
  - Pro Savin – vector to transform glutamate
  - One patient with a graft 24 ya – Wen et al 2016

- *Nonpharmacological treatments for patients with Parkinson's disease – Mov Disor 2015*

Treatment of advanced PD

- Motor fluctuations with 2h of 'off time', some non-motor features and functional decline.
- Most get within 5-10 years
- On-off fluctuations:
  - Take ½ hour before meals
  - Regulate timing
  - Increase frequency +/- dose
  - Add DA, COMTi
  - Amantadine for dyskinesia + alerting
  - Slow-release formations – not great in practice
- Watch out for:
  - Dopamine dysregulation syndrome
  - Impulse control disorders
  - Psychosis – *better to be slow and sane*

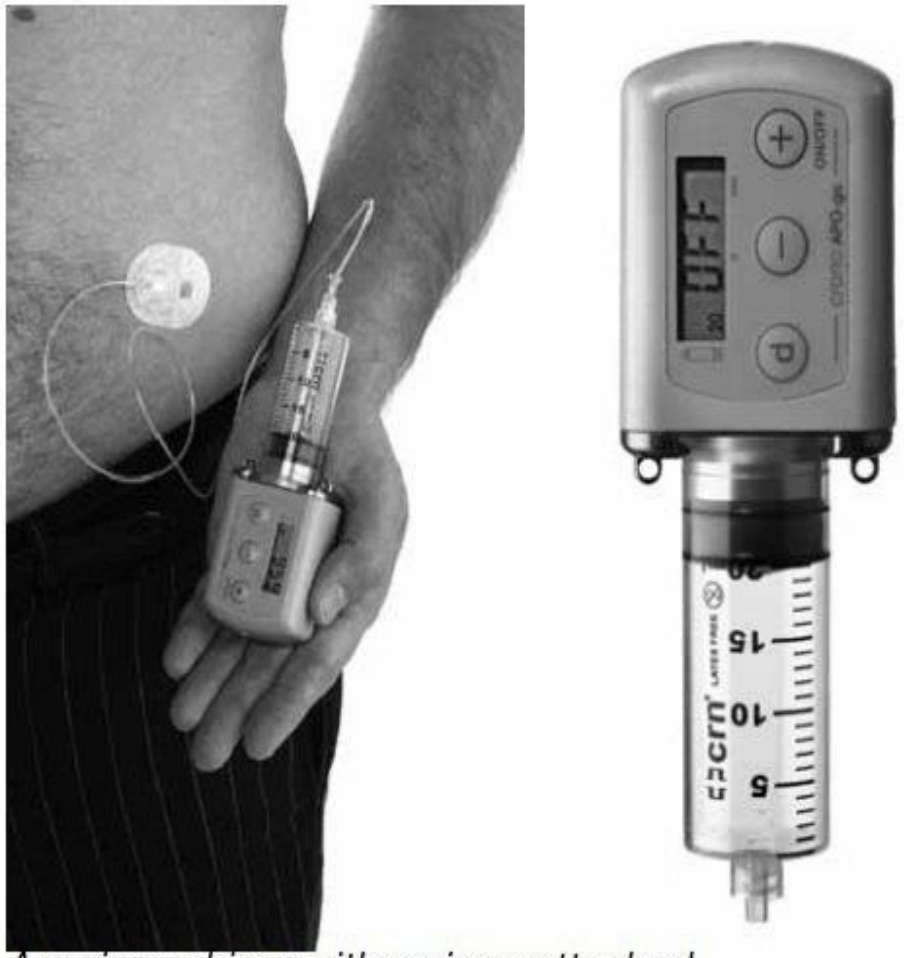


- Consider Device-based therapies in selected patients

Transl Neurodegener. 2015; 4: 3. Treatment of the later stages of Parkinson's disease – pharmacological approaches now and in the future – Peter Jenner

Apomorphine

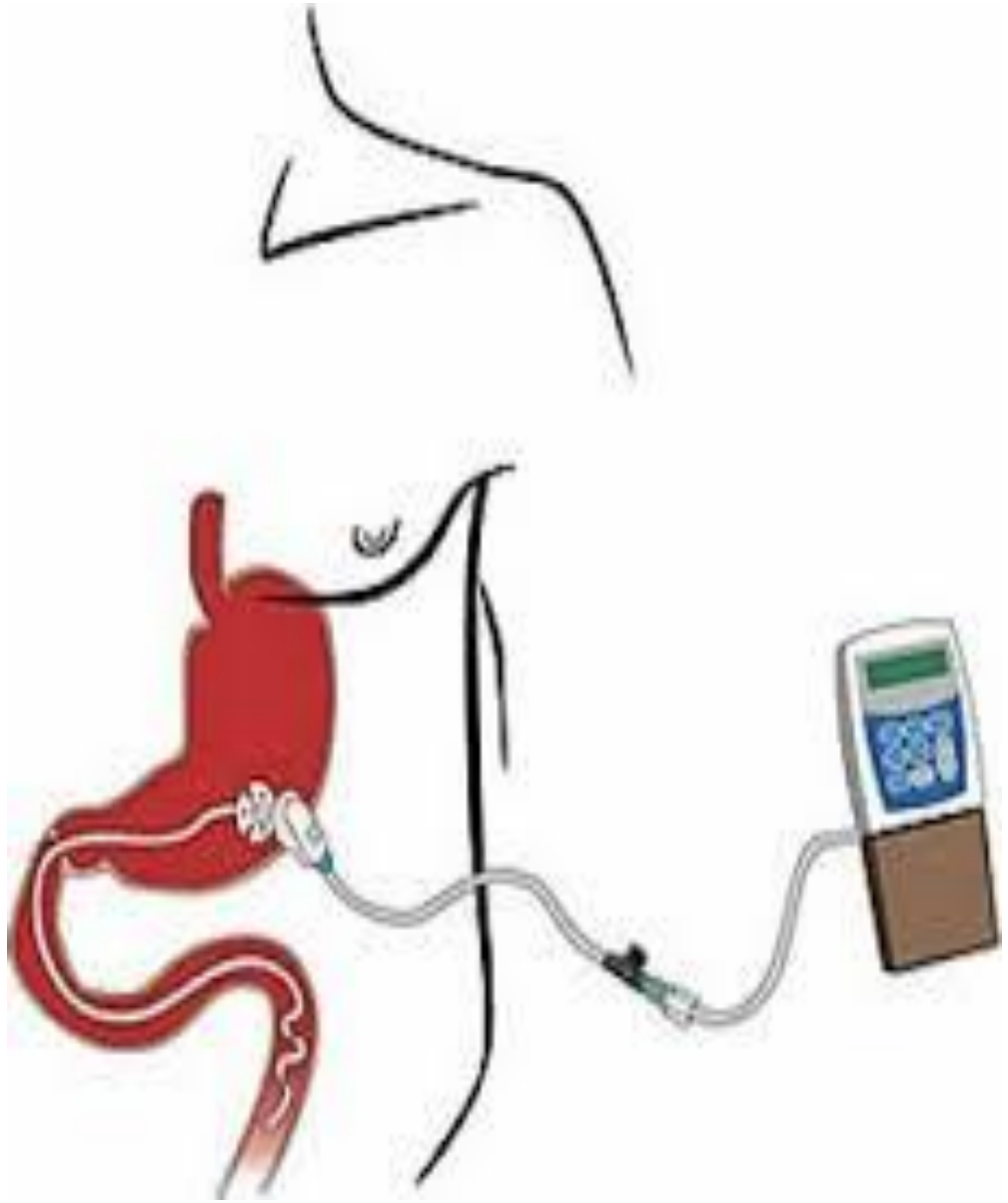
- Continuous infusion of DA
- Infusion and bolus injections
- Reduces off time and dyskinesias
- Notes from MDS conference:
  - Improves mood, apathy, urinary dysfunction and QOL
  - May be a modifier of amyloid (basic science).
  - Side effects: DA side effects plus…
    - Nodules at injection site
    - Possibly increases systemic hypertension.



A syringe driver with syringe attached

Duodopa pump (LCIG)

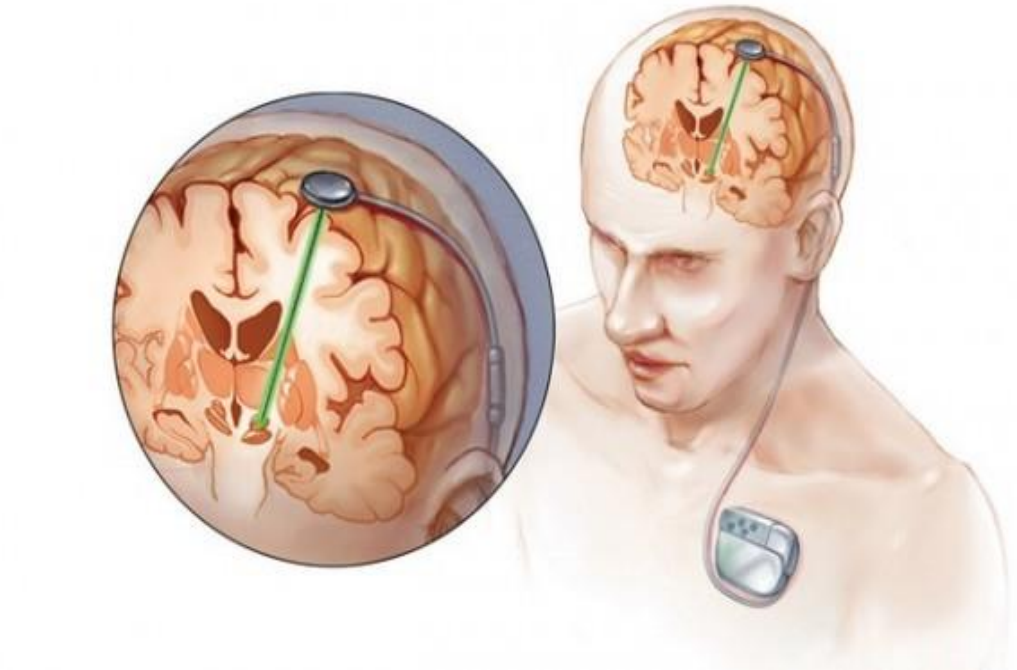
- Only available in research setting
- Jejunum is where LD is absorbed
- Reduces dyskinesia and increases on
- Effect in > 65y is similar (unlike DBS)



Deep Brain Stimulation (DBS)

- Potential candidate:
  - IPD
  - Continued response to levodopa - *can still modulate the network*
  - Significant disability
  - Not demented
  - No significant surgical risk factors
  - Realistic expectations
  - Consider earlier in: severe dyskinesia, severe tremor

- Improves on/off, dyskinesias, tremor
- Different targets: STN, GPi, thalamus
- Specific risks
- Benefit to non-motor symptoms



Palliative care

- Judge when appropriate
- Questions at palliative interview:
  - How intensely would you like to be treated?
  - What are your goals?
  - How much participation can the family/spouse have? (including later on)
- 70% want to die at home
- 80 – 90% wanted to talk to their doctor more about this
- Hard truths:
  - PD does kill people eventually
  - Demented patients don't do well in ICU – 55% dead within 1 year
  - False public perception (70% on ER show survive out of hospital cardiac arrest)
  - 70% lack the capacity near the end of life to communicate their wishes
  - Relatives tend to want more aggressive treatment than patients.

- All patients with late PD should probably have an advanced care plan

Mimics

Not everything that looks like Parkinson’s is Parkinson’s

Progressive supranuclear palsy (PSP)

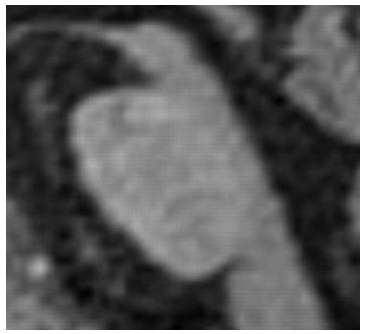
Clinical

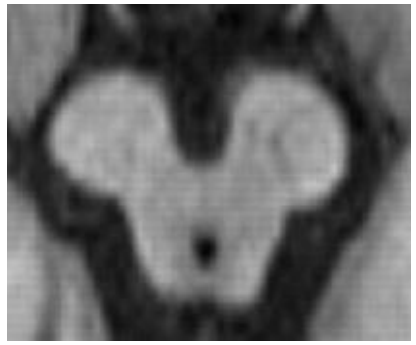
- Parkinsonism with **early falls** and **axial dystonia**. Symmetrical, tremor
- **Supranuclear ophthalmoplegia**
- Pseudobulbar palsy (speech strained/slurred, dysphagia)
- Cognitive dysfunction

Pathology

- Abnormal tau protein accumulates as ‘tangles’ in brainstem + basal ganglia

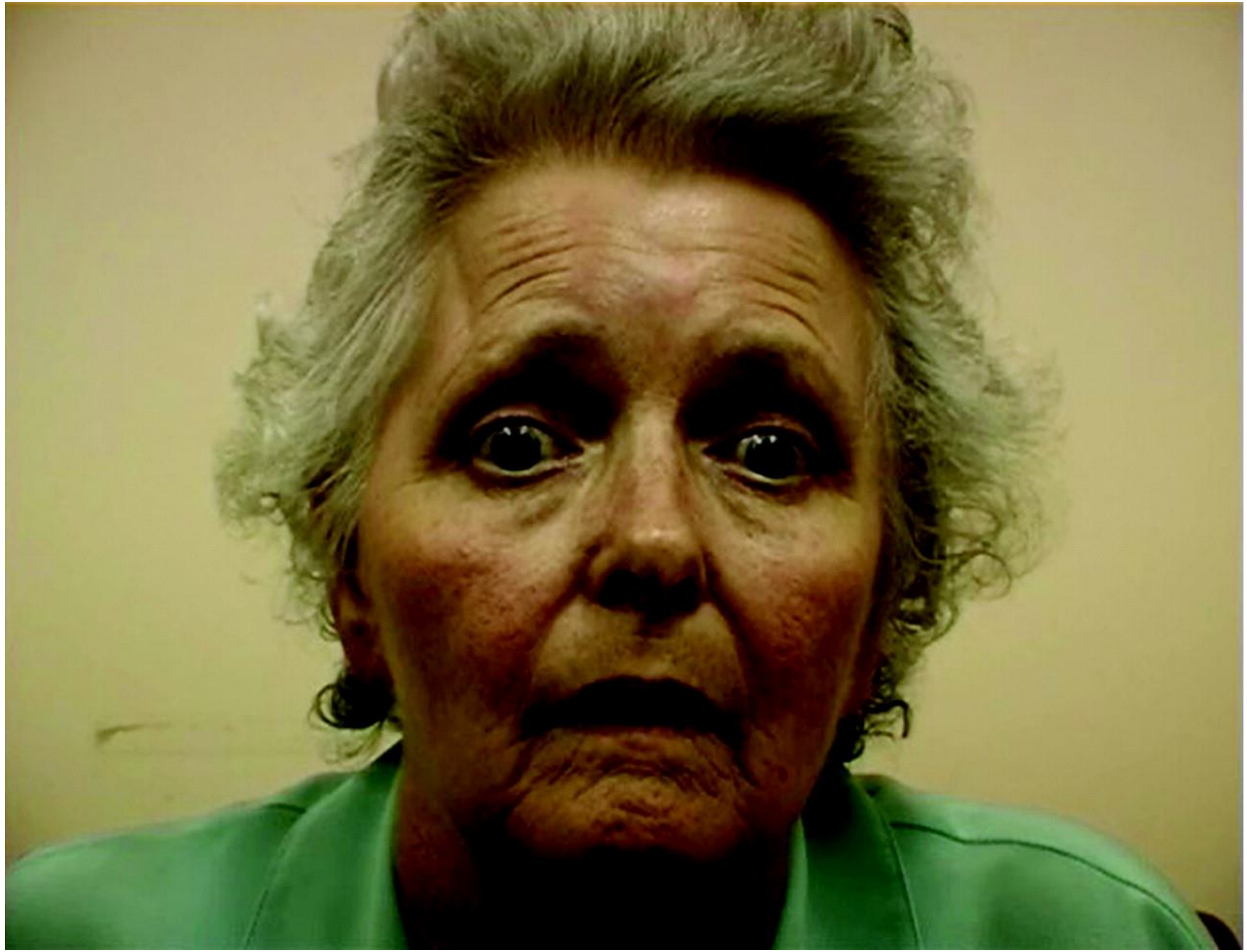
MRI shows midbrain atrophy (hummingbird and mouse ears!)





Treatment

- Levodopa may have some effect
- Supportive



Multiple systems atrophy (MSA)

Triad:

1. **Parkinsonism:** more symmetrical, tremor usually present (MSAp)
2. **Cerebellar dysfunction:** limb and gait ataxia, speech (MSAc)
3. **Autonomic dysfunction:** postural BP, urinary, sweating changes

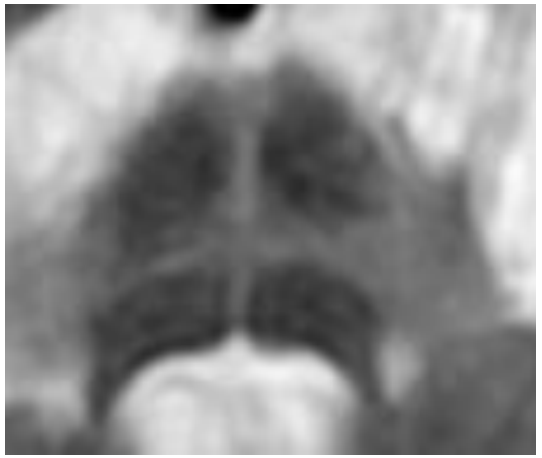
+/- cortical myoclonus and lower limb spasticity

Pathology:

- alpha synuclein inclusions in cytoplasm of neurons

Treatment:

- Don't respond as well to levodopa, but some can – *32/87 Gilman*
- Manage postural hypotension:
  - Getting up slowly, fluids, salt, stockings (to hip)
  - Drugs: fludrocortisone, midodrine…



Neuroleptic malignant syndrome

- Side effect of dopamine receptor blockers, e.g. haloperidol, phenothiazines
- Rarely after levodopa withdrawal

Clinical:

- Hyperthermia
- Hypertensive
- Rigidity
- Stupor progressing to coma

Key investigations:

- CK (markedly elevated), renal function + myoglobinuria

Differentials:

- meningitis/encephalitis, drug intoxication/side effects, malignant hyperthermia…

Treatment:

1. Intensive care
2. Bromocriptine 5mg TDS
3. Dantrolene sodium 0.25-3mg IV

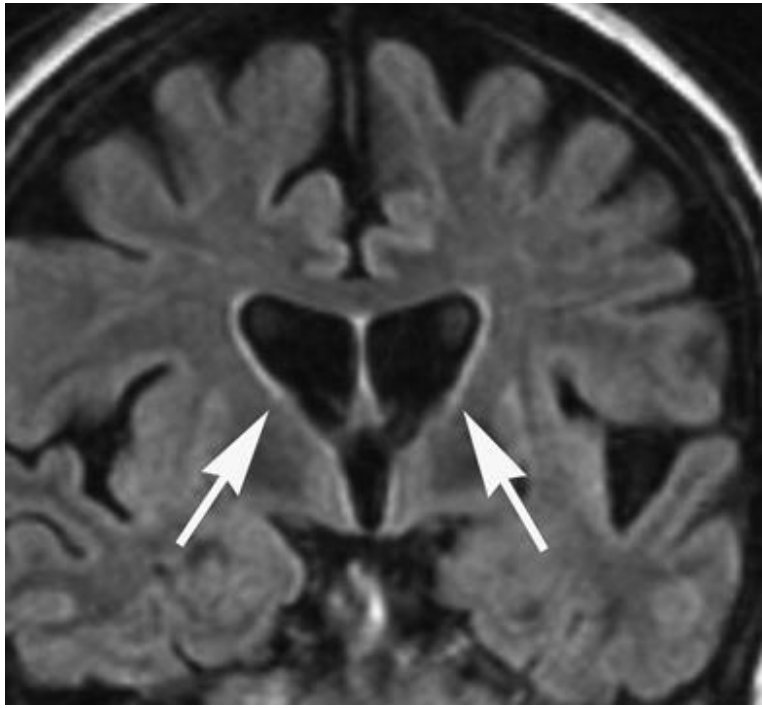
‘Essential’ tremor

- Reasonably common, increases with age
- Autosomal dominant inheritance
- Clinical:
  - Postural tremor, not present at rest
  - Worse with movement , e.g. holding a cup of tea
  - Usually involves both upper limbs, can affect head (nodding) and voice
  - Transiently improves with alcohol
  - Don’t have parkinsonism or dystonia
- BUT, a small percentage do eventually develop signs of parkinsonism
- Treatment
  1. Beta blockers: propranolol
  2. Primodone
  3. Topiramate
  4. Deep brain stimulation

Orthostatic tremor

- Typically present with unsteadiness on standing and/or fear of falling
- Faster than others (around 16Hz) that can be seen on EMG or heard with the bell of a stethoscope (helicopter)
- Treatment:
  - Minimally effective
  - Gabapentin, clonazepam and primidone

Huntington's Disease



- Average onset around 40-50y, rarely <15y (Westphal variant).
- Progressive and eventually fatal

Clinical

- Behavioural: personality change, impulsivity, depression
- Chorea: random, slow, writhing movements 'dancing' between body parts
- Motor impersistance: tongue, posture
- Oculomotor: impaired initiation, slow pursuit and voluntary saccades
- Dystonia and parkinsonism later
- Dementia: usually severe by 10-15 years
- High suicide and subdural haematoma rates

Huntington’s Disease

Genetics

- Autosomal dominant CAG repeat disorder (chromosome 4).
- ≥ 40(or 42) repeats = definitely get the disease
- 35-39 possibly get a milder, later-onset form
- Anticipation: repeat size increases over generations -> earlier, more severe
- Worse if inherit from the father in HD
- Ethical issues ++

Treatment

- Supportive, should be under HD service ideally
- Haloperidol (and other dopamine blockers) for chorea +/- emotional lability, but side effects may outweigh benefit

Patient 2

- 45 year old woman with a longstanding alcoholism
- Having increasing falls despite stopping drinking
- Feeling unsteady
- Normal sensation in lower limbs