The Complex Parkinson's Disease Patient: When to Consider Advanced Therapies

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Declaration of interest:

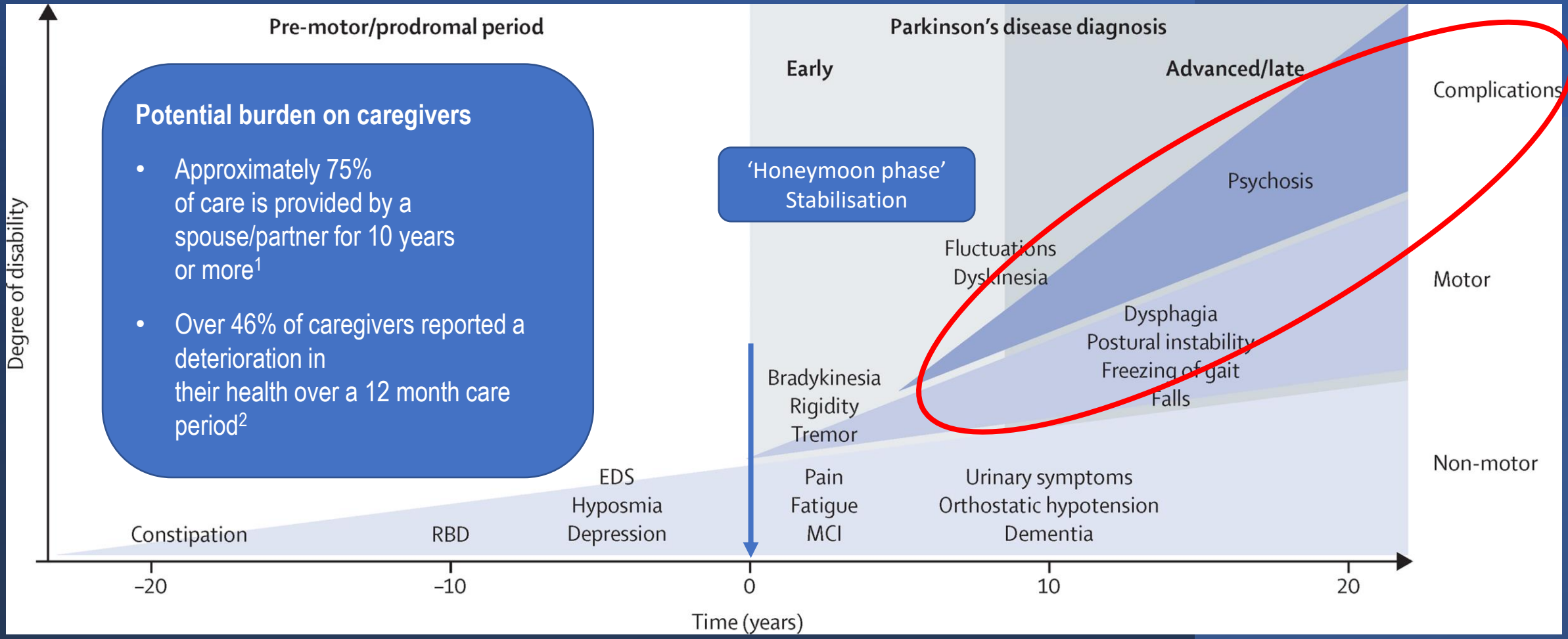
I have no financial interests or relationships to disclose with regard to the subject matter of this presentation.

Overview & Learning Objectives

- What is ‘Complex Parkinson’s Disease’
- Pharmacological approaches to managing motor fluctuations
- When should we consider non-oral therapies?
- Advanced therapies: Cases
  - Who should be considered
  - What can be expected
  - Which non-oral therapy should be selected
- Acute presentations in PD – ‘Troubleshooting’
- Future directions

Complex Parkinson's Disease

- Defined as the stage when standard therapies are unable to consistently control symptoms, or patient has developed troublesome dyskinesia
  - Impacting **quality of life**
  - Oral medications are **less effective** in controlling PD symptoms
  - **Side effects** are outweighing their benefits

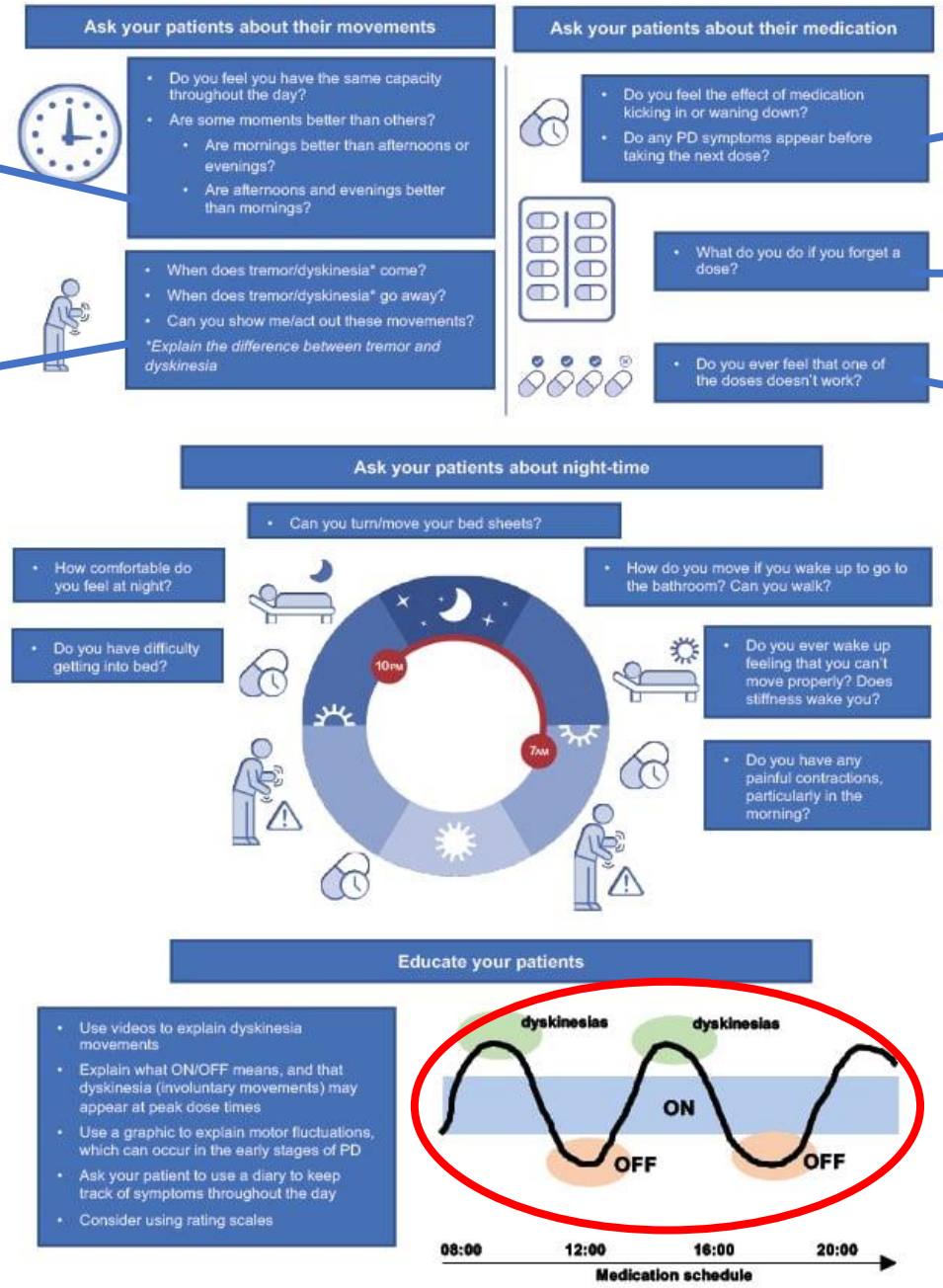


1. Odin *et al. Parkinsonism Relat Disord* 2015
2. Hassan *et al. Parkinsonism Relat Disord* 2012

Kalia & Lang, *Lancet* 2015

Map out their day
Do they have a typical day?

Is there true dyskinesia .v. tremor



Response to the medication as prescribed

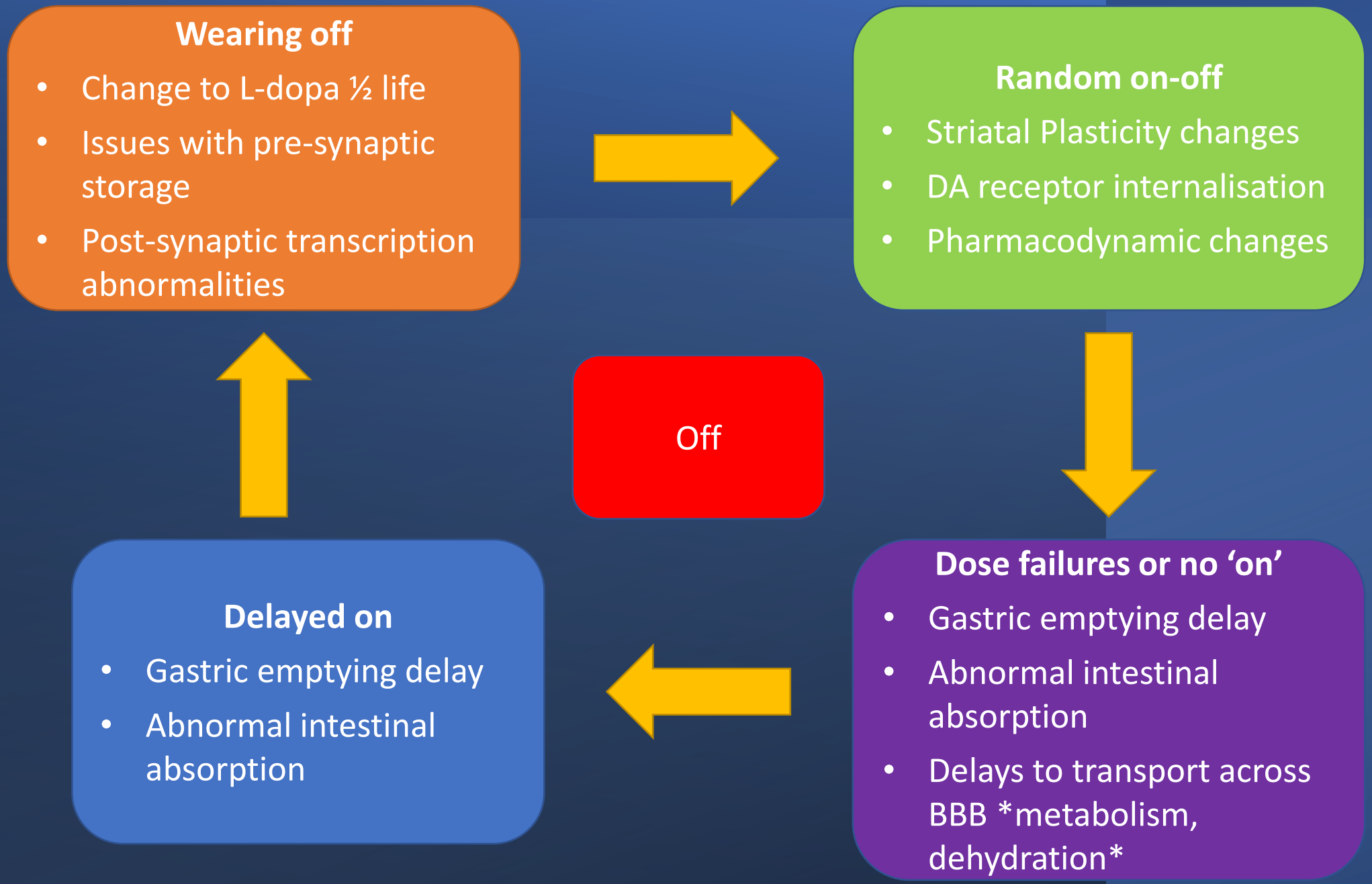
What happens if a dose missed?

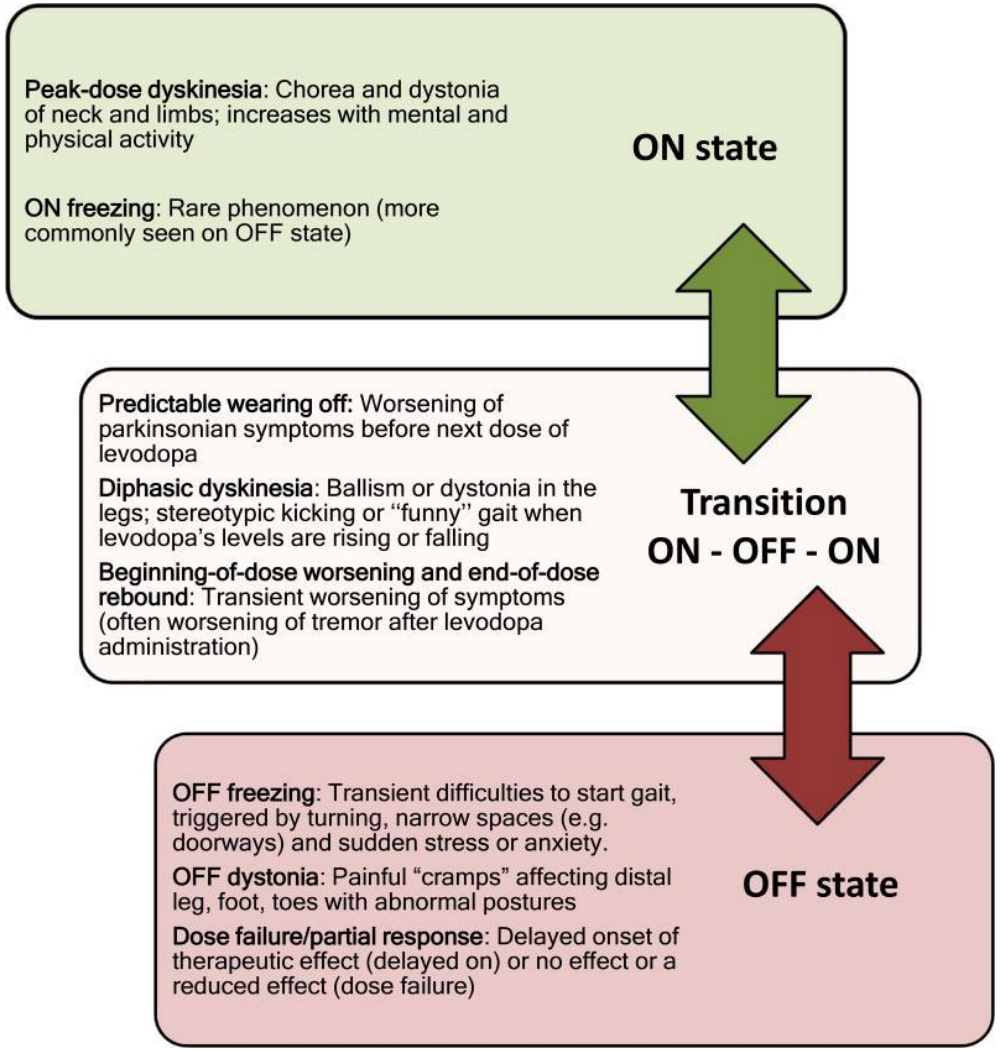
Do all the doses work?

Educate & empower your patients

- What do we mean by ‘dyskinesia’
- What do we mean by ‘on’ and ‘off’ states
- Symptoms diary (Hauser)
- Check compliance

Stocchi, Kurtis, Morgante, *EMJ Neurol.* 2021


Wearing off
• Change to L-dopa ½ life
• Issues with pre-synaptic storage
• Post-synaptic transcription abnormalities
Random on-off
• Striatal Plasticity changes
• DA receptor internalisation
• Pharmacodynamic changes
Off
Dose failures or no 'on'
• Gastric emptying delay
• Abnormal intestinal absorption
• Delays to transport across BBB *metabolism, dehydration*
Delayed on
• Gastric emptying delay
• Abnormal intestinal absorption


Peak-dose dyskinesia: Chorea and dystonia of neck and limbs; increases with mental and physical activity
ON freezing: Rare phenomenon (more commonly seen on OFF state)
ON state
Predictable wearing off: Worsening of parkinsonian symptoms before next dose of levodopa
Diphasic dyskinesia: Ballism or dystonia in the legs; stereotypic kicking or "funny" gait when levodopa's levels are rising or falling
Beginning-of-dose worsening and end-of-dose rebound: Transient worsening of symptoms (often worsening of tremor after levodopa administration)
Transition
ON - OFF - ON
OFF freezing: Transient difficulties to start gait, triggered by turning, narrow spaces (e.g. doorways) and sudden stress or anxiety.
OFF dystonia: Painful "cramps" affecting distal leg, foot, toes with abnormal postures
Dose failure/partial response: Delayed onset of therapeutic effect (delayed on) or no effect or a reduced effect (dose failure)
OFF state

The complex PD patient

‘5-2-1’ criteria

- Moderate level of troublesome motor fluctuations
- 2 or more hours with ‘off’ symptoms ★
- 1 or more hours of the day with troublesome dyskinesia ★
- Moderate level of dyskinesia
- Troublesome dysphagia
- 5 or more doses of oral L-dopa per day ★

Antonini A, *et al*. *Curr Med Res Opin* 2018

Aims of a ‘pragmatic’ approach to managing motor fluctuations

Enhance absorption & transport of L-dopa

Stabilising L-dopa plasma levels via changes of drug delivery & L-dopa pharmacokinetics

Non-L-dopa related strategies of continuous DA-receptor stimulation

1. Improve L-Dopa absorption & Transport

- Avoid dosing with protein-rich food
- Enhance gastric motility (avoid anticholinergics or dosing with meals)
- Soluble L-dopa preparation

2. Revise L-dopa Regimen

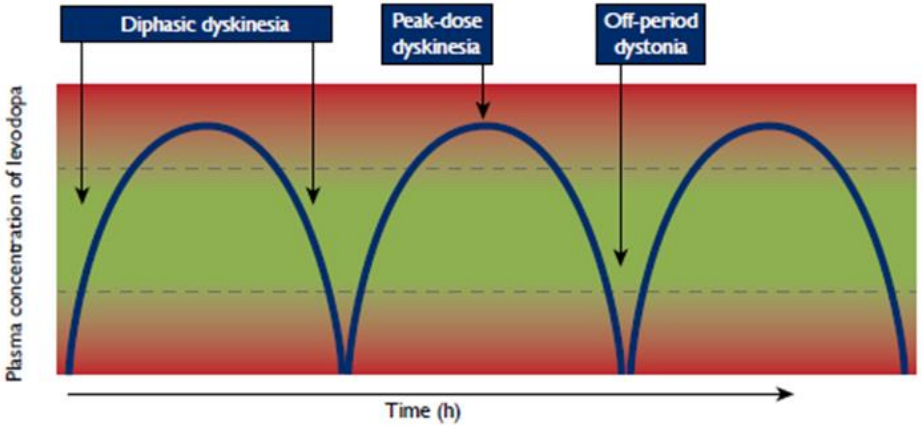
- Increase dosing frequency (decrease time interval between doses <4hrs)
- Introduce sustained-release formulations for nocturnal or early am offs

3. Provide prolonged striatal DA-ergic stimulation

- Add COMT inhibitors – Opicapone (**Epsilon trial**)
- Add MAO-B inhibitors - Safinamide
- Add orally active DA-agonists, preferably MR
- Add transdermal DA-agonist delivery

4. Consider advanced therapies

- SC apomorphine rescue injections, up to 3-5 per day
- SC apomorphine infusions
- *Duodenal L-dopa (duodopa)*
- SC L-dopa (produodopa)
- DBS
- *MRgFUS*



Type of Dyskinesia	Levodopa levels in plasma	LID characteristics
Peak-dose dyskinesia *Or improvement-dystonia improvement* Most common form	Peak	Choreic in nature
Diphasic dyskinesia *Or dyskinesia-improvement dyskinesia* Occurs at the onset and/or end of action of levodopa	Rising or falling	Dystonic in nature though chorea and mixed pattern may occur
Off-period dyskinesia *Or wearing-off dyskinesia* Frequently occurs in the morning	Low	Dystonic in nature often painful, distraining, and disabling

AJMC, 2017

Management of L-dopa induced dyskinesias

- Revise L-dopa regimen (reduce individual doses, use more frequent dosing)
- Add/increase dopamine agonists (MR preparations), consider rotigotine
- Add amantadine
- Use continuous drug delivery (Duodopa, apomorphine)
- Consider DBS

Things not to miss…

Patients understanding of terms used

- Motor ‘offs’
- Dyskinesia versus tremor
- Freezing versus ‘off’ periods

Compliance

- Non-compliance can range from 10-67% (Malek & Grosset. CNS Drugs, 2015)

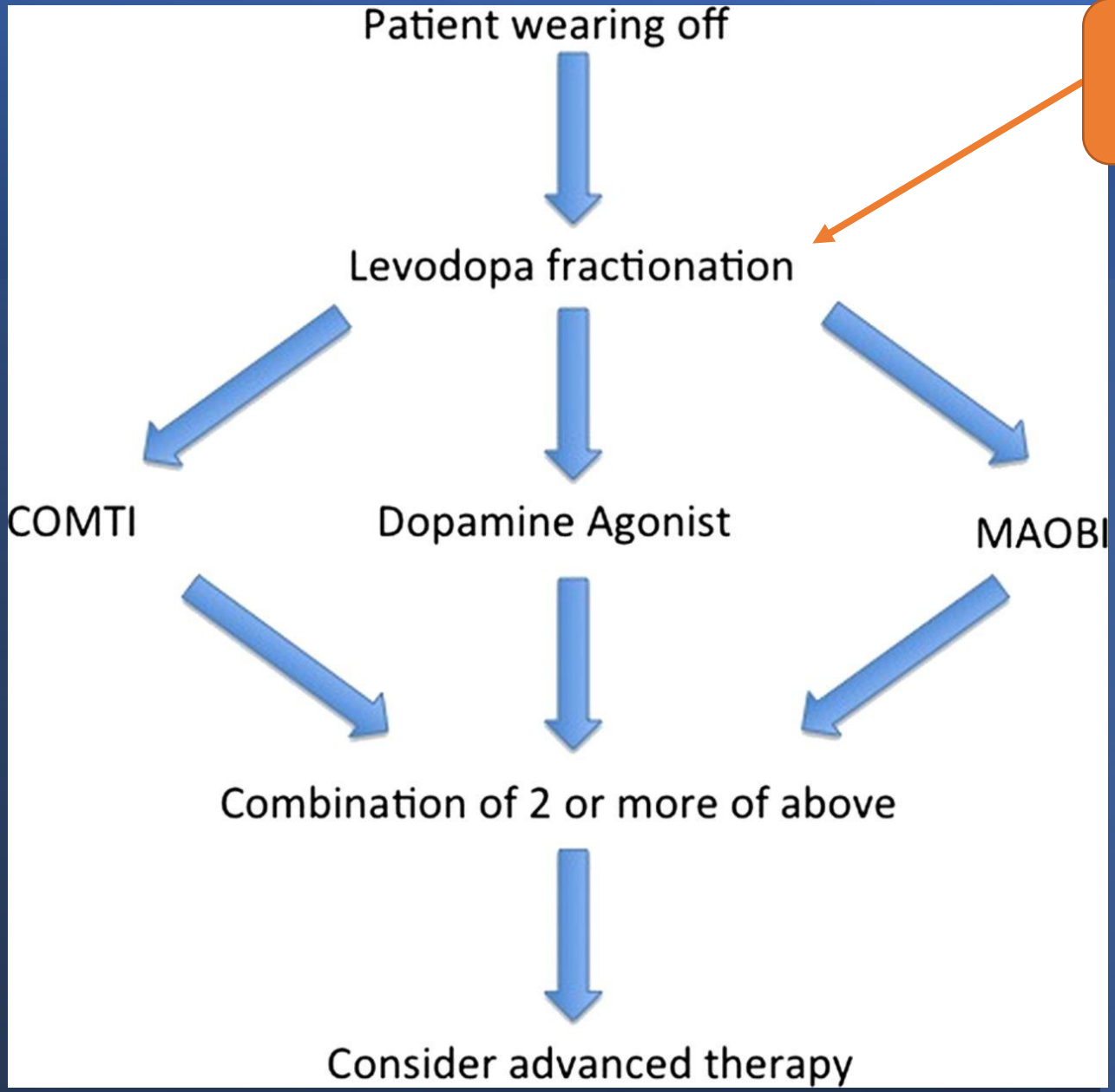
Correct doses at the correct times

Meal content

Gastric emptying & Bowels

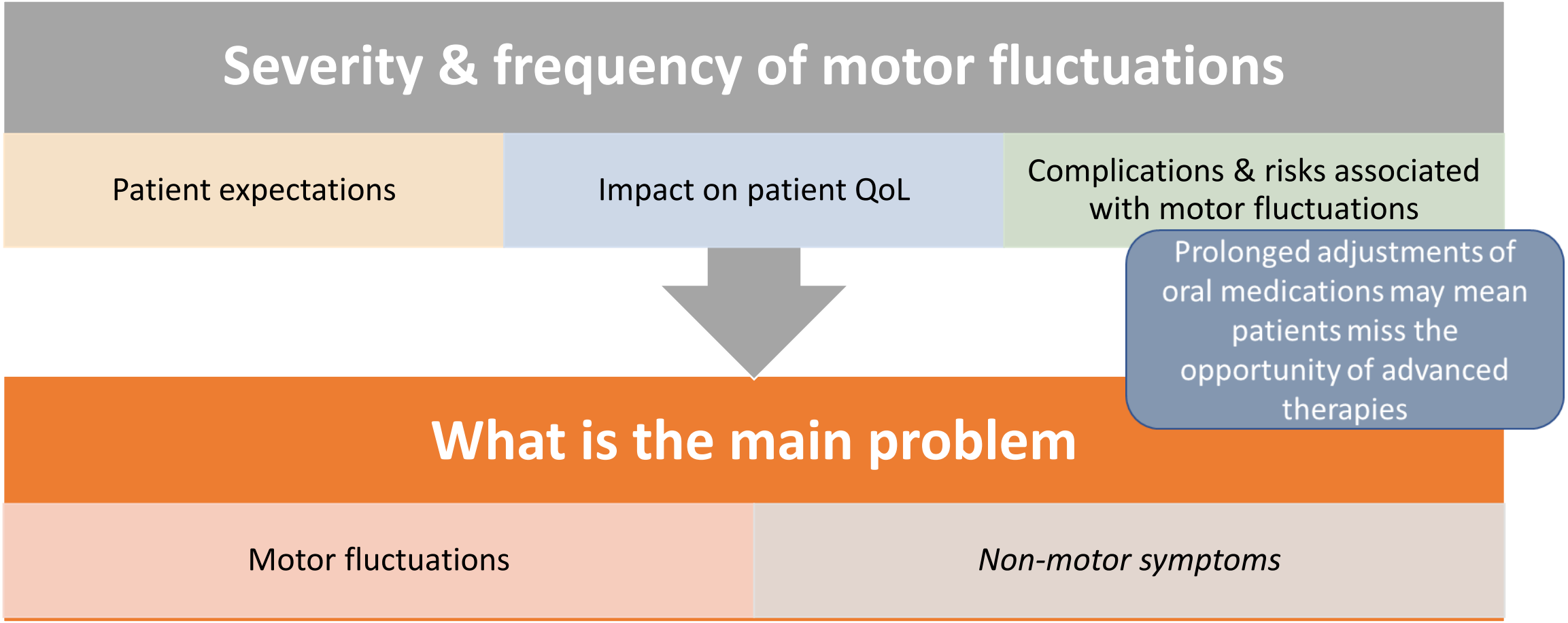
Any evidence of dopamine-dysregulation syndrome

- Compulsive dopaminergic medication use, exceeding the amount needed for adequate symptom control



Worth PF, *Pract Neurol* 2013

Consider your patient…



Classification of levodopa-related motor fluctuations in PD

Clinical pattern	Mechanism	
Wearing-off	Levodopa – half-life Pre-synaptic storage	
Delayed-on	Gastric emptying Intestinal absorption	
Dose-failures (No-ON)	Gastric emptying Intestinal absorption Blood–brain barrier transport	
Random ON-OFF	Striatal Pharmacodynamic Changes	

Which for consideration of advanced therapies?

Patient Expectations

Realistic

Increase ‘on’ time

Reduction in ‘off’ time

Reduction in ‘on dyskinesia’

Reduce unpredictability

Improved confidence

Improve QoL – hopefully!

Unrealistic

They will not be how they were pre-diagnosis

Will not get rid of all fluctuations

It is **not a cure**

Unlikely to improve non-motor symptoms to the same degree

Considerations

- **Postural instability**
  - Frequent falls even in their best on phase
- **‘ON’ freezing of gait**
  - Can be difficult to quantify if FOG only occurs in the off state
  - Detailed clinical examination – consider triggers, e.g. walking through doorways, obstacles, turning
  - May consider examination in on and off states
  - Early physiotherapy assessment – can also help with ways to combat FOG
- **Age of the patient**
- **Timescale**

Case 1

Background

- 62 YO, LH female, diagnosed with tremor-dominant PD (2017)
  - Symptoms started approx. 3 years prior, tremor affecting L-hand
  - DAT scan – reduced uptake in right striatum & was c/o trihexiphendyl – much improved (increased to 8mg/day), SE ++
  - No gait disturbance
- Progression of tremor, unusually marked action component, minimal bradykinesia and rigidity on examination
  - MRI - NAD
- C/o madopar 62.5mg TDS
  - Next OPC: using 5 times daily due to wearing off – dose adjusted to 125mg TDS
  - More parkinsonian on examination

Background

- 2019
  - Madopar 125mg TDS + madopar CR 250mg ON
  - Tremor is **L-dopa responsive**
  - C/o on rotigotine patch
- COVID strikes
- Telephone review 2020
  - Tremor much worse with n
    improved
  - 'Madopar works well for ab
    'symptoms' creep back in'
  - She increased her madopar t
  - Tremor interfering with eating & drinking ++
  - Diagnosed with early wearing off - can increase to 5/day if needed

Refractory tremor:

- Increase L-dopa
- MAOIs
- Dopamine agonists
- Propranolol
- Topiramate

} Particularly if postural/action element

- Trihexyphenidyl
- Amantadine
- (Mirtazapine)

Background

- 2021/2022
  - Increased madopar 125mg to 5 times daily (7/9.30/12/14.30/17), additional madopar 62.5mg added at 18.30
  - Madopar CR 125mg 19.30 & SR at 21.00
  - Rotigotine 6mg/24hrs
  - Entacapone 200mg BD, gradually increased to all doses
  - Feels meds wear off after 90mins, increasingly anxious & 'jittery' before next dose
  - Nocturia 3-4/night, tremor bad at night – takes additional madopar
  - Tremor starts to wake her at night
- 2022 referred to movement clinic

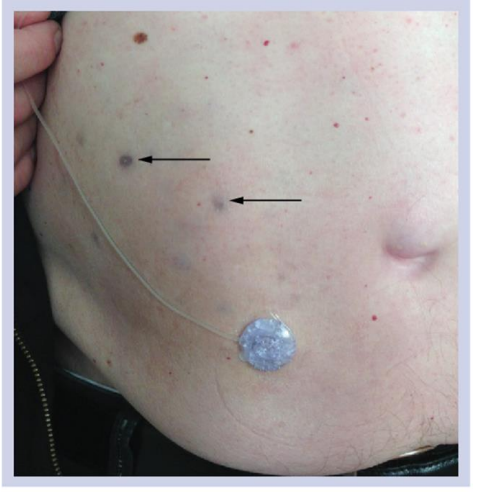
Background

- Dec 2023 movement clinic:
  - **Rationalise medication**
    - Madopar + entacapone at 7/10/13/16/19
    - Stop madopar 62.5mg at 18.30
    - Amantadine added
    - Madopar CR 250mg ON, and additional madopar SR taken at this time stopped
    - ?diphasic dyskinesia
  - Really hard to get a handle on what was going on
  - Dyskinetic in clinic, reporting disabling off periods with prominent tremor
  - As approached time for medication, L-sided tremor returned
  - I felt prominent feature at this stage was dyskinesia when we mapped out her day
  - Asked to video her ‘off periods’ and when medication was working

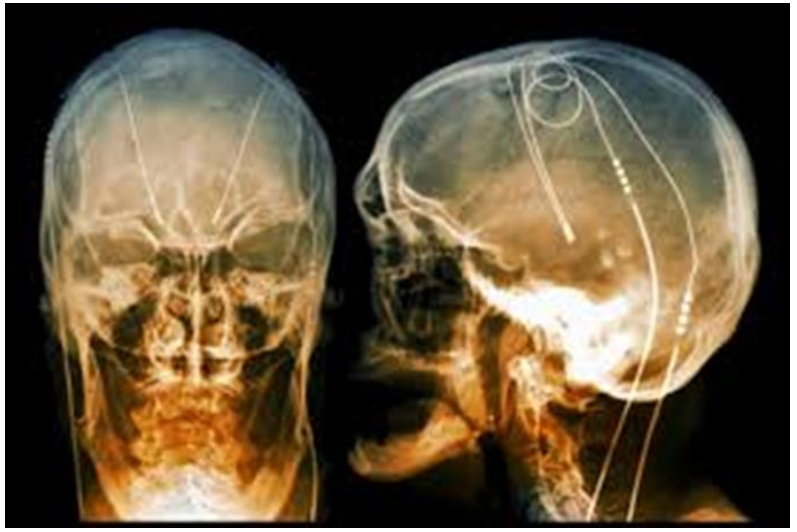
Proceeded to Apomorphine

- No videos forthcoming as lived alone
- **Decision for admission**
  - Disabling off periods, unpredictable & with pronounced tremor
  - Peak dose dyskinesia – not troublesome during admission
  - Main issue: **off periods**
  - Medication adjusted – entacapone → opicapone, amantadine increased
  - No real improvement → apomorphine (neupro overnight)
    - 3 day preparation with domperidone, started to reduce the patch

- 'Got my life back', 'New lease on life. Shopping again, going out & driving'
- Tolerating well: no orthostatic hypotension, no nodules



Case 2



Background

- RH male patient presented to NHS aged 30yrs, by that stage described ~10yrs of symptoms (2009)
- DAT scan in France 2006 was consistent with a Parkinsonian syndrome, formally diagnosed aged 26YO
  - 1st noticed R UL stiffness – noted when doing University exams
  - He stated he also would have noticed stiffness in adolescence when playing piano
  - Started to use LH
  - Started to notice a slight resting tremor, increasing issues with dexterity
  - Hypophonia
  - No gait issues or falls
- Initially started on pramipexole
- No PMH
- FHx – Paternal Grandmother diagnosed in her 80s, Mother had Addison's disease & fibromyalgia

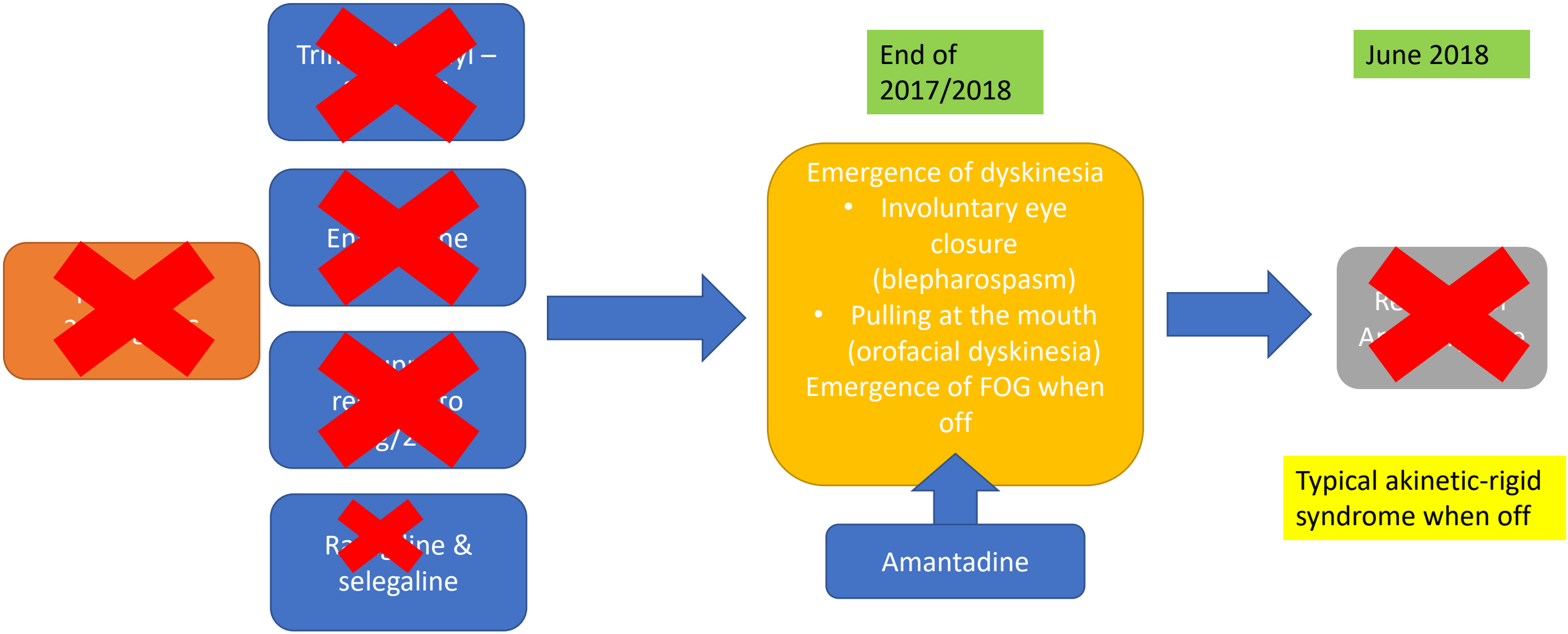
Background

- In 2010 – Rasagiline added
  - Noticed improvement in fatigue
  - No real improvement in R hand function
  - Also prescribed a LA dopamine agonist – not started

- BHSCT MD clinic in 2017, following referral from Prof Lees (London) – 37YO
  - Genetics, incl. PARK2 negative
  - Now working as a film maker – France & Mexico
  - Main symptoms: Pain & stiffness R UL & LL, including R foot posturing, mild tremor
  - Now on Rotigotine – some ICBs reported, so dose downtitrated
  - Trialled L-dopa in the form of Mucana puriens (Zanodopa)

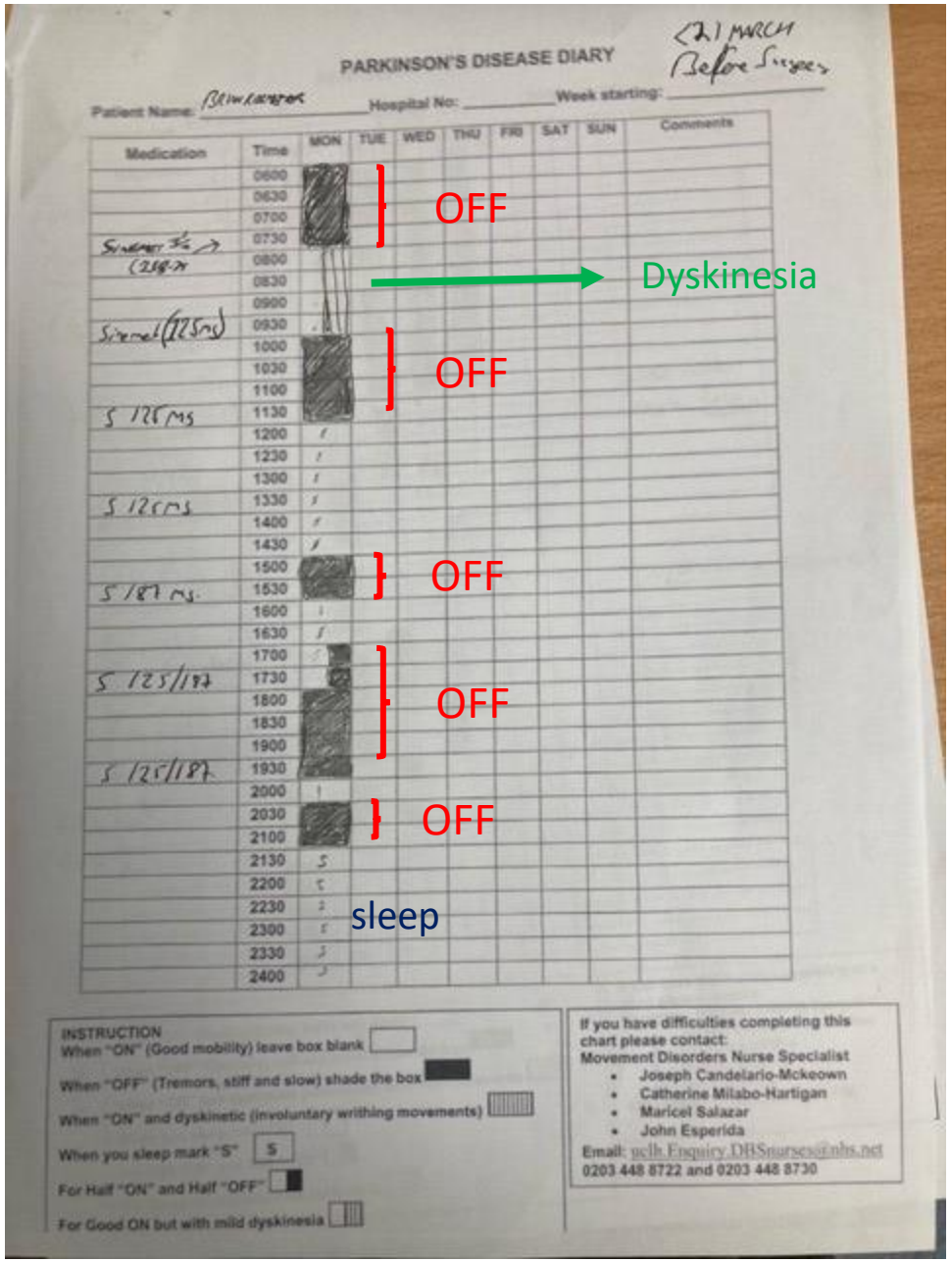
- Every change in PD meds gave him a ‘boost’ for a short period, **but disliked side effects**

Medication adjustment



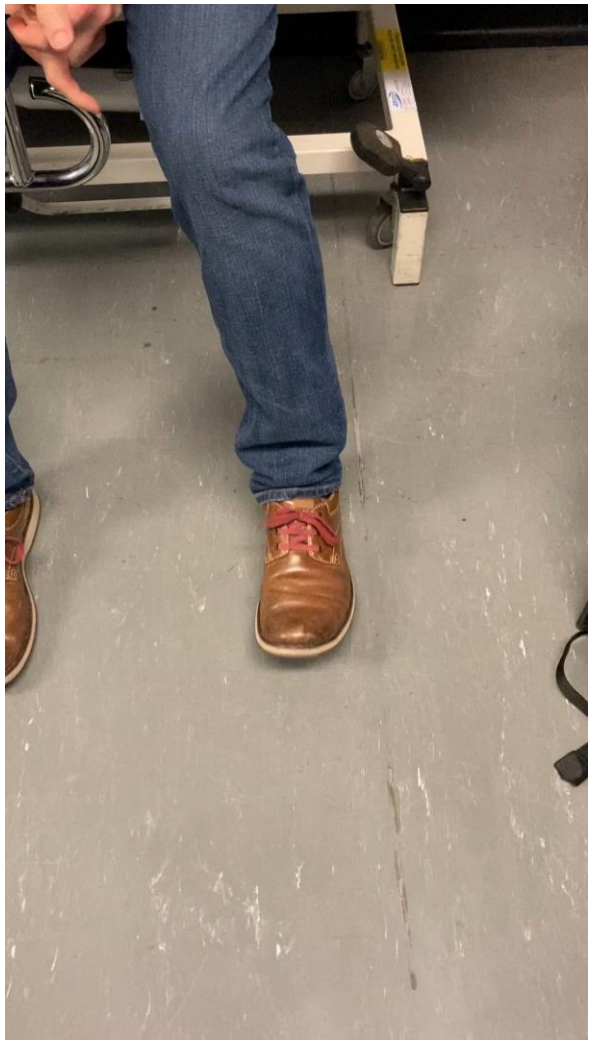
‘Typical’ Pre-operative Day

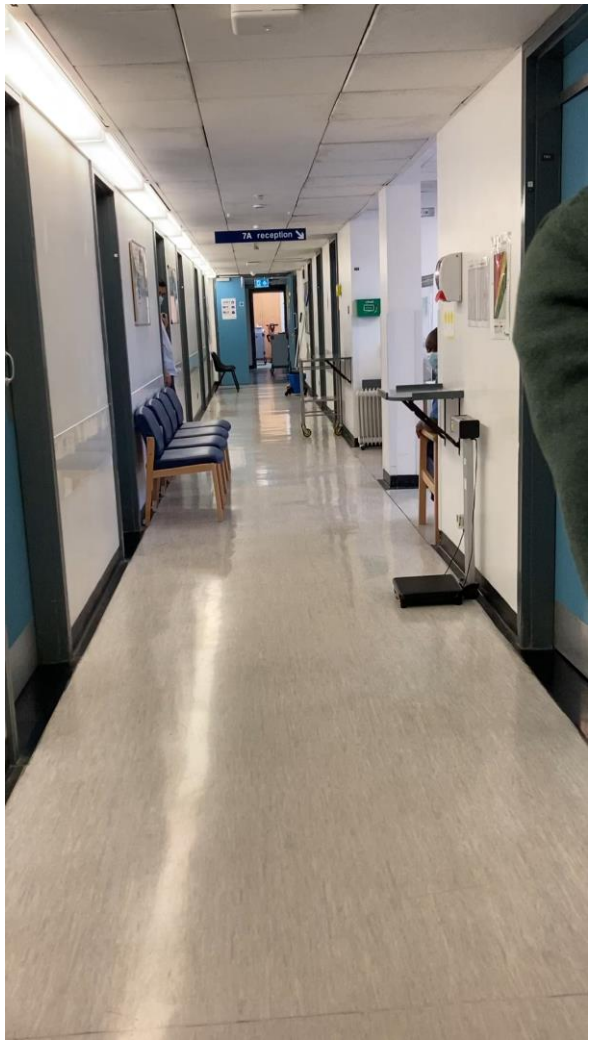
UPDRS-III:
OFF score – 78
ON score – 28
64% improvement
H&Y grade 2

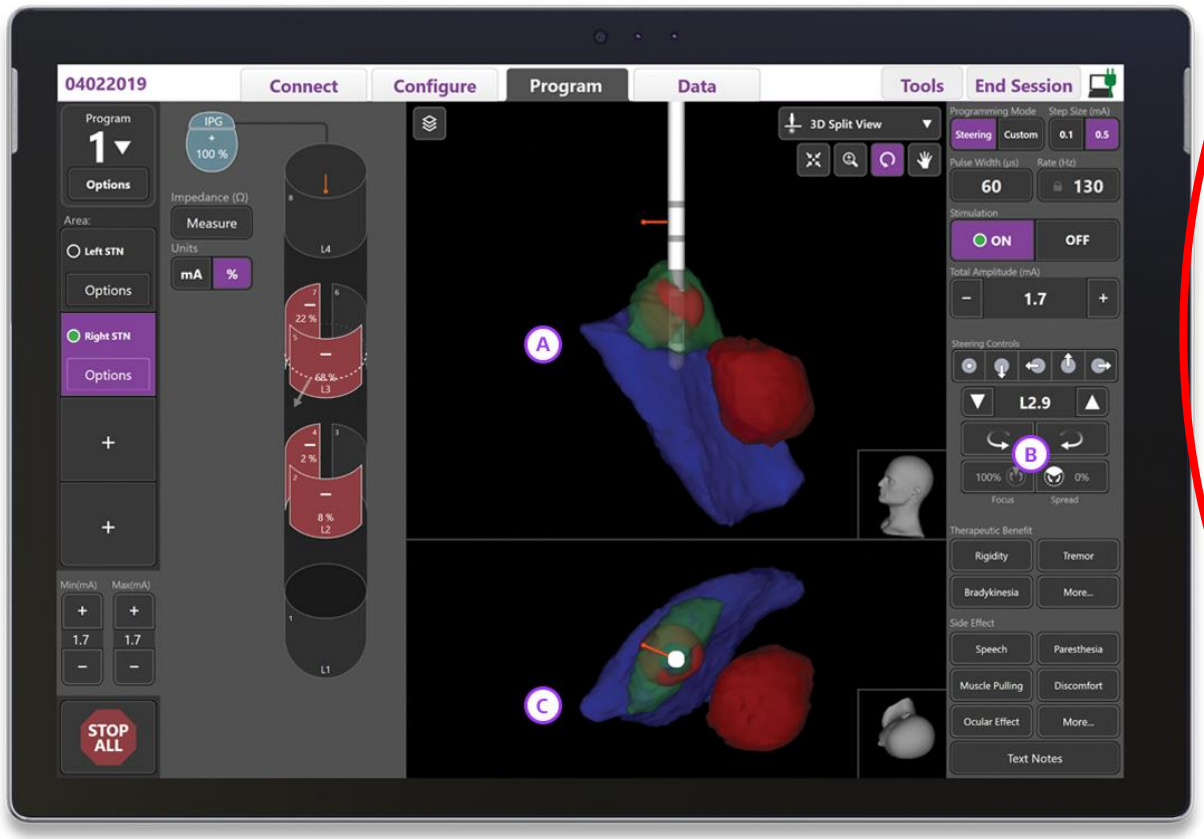


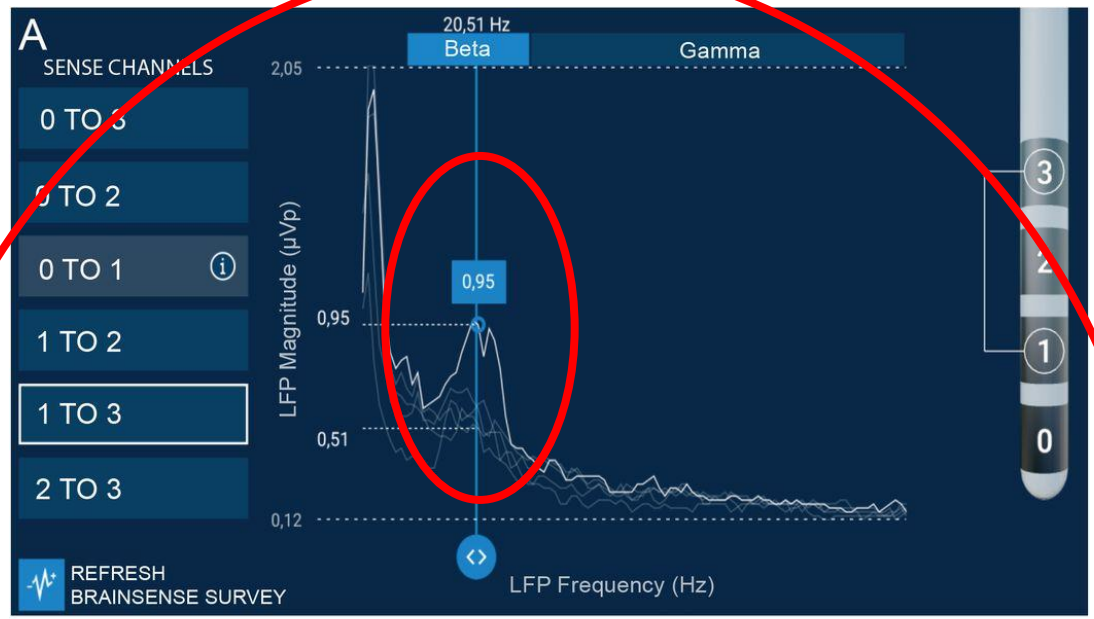
Awake 15 hrs
OFF 9 hours
=60%

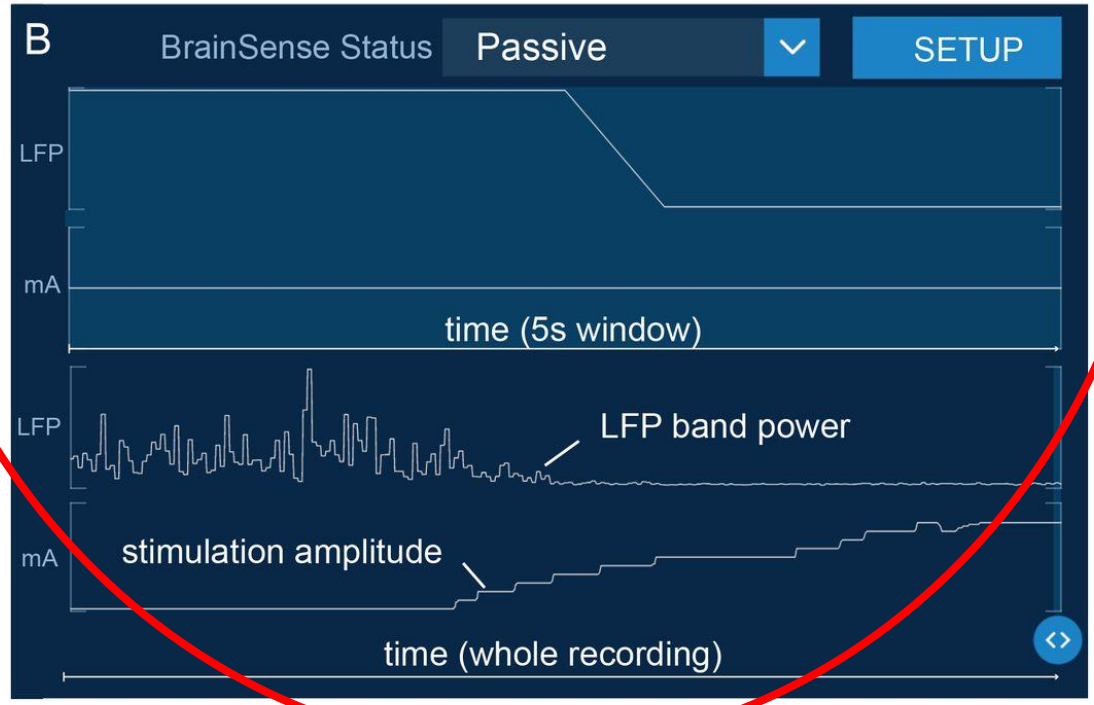

clinell

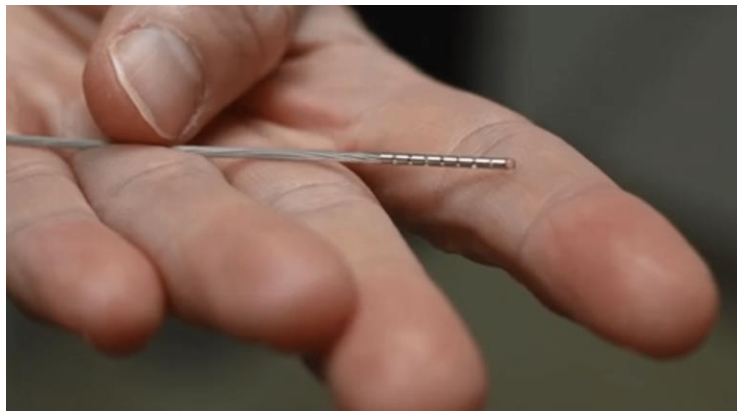


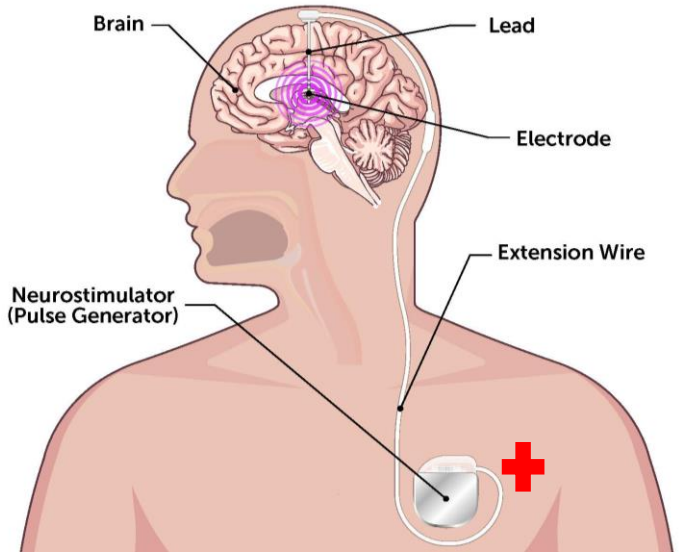

7A reception

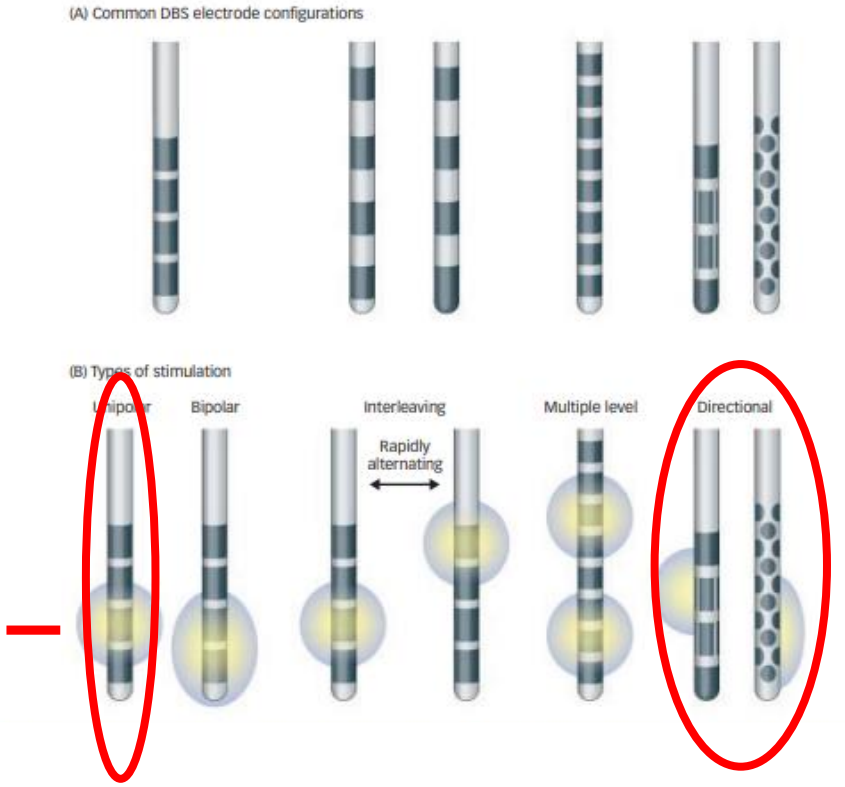

04022019
Connect
Configure
Program
Data
Tools
End Session
Program
1
Options
IPG
100 %
Impedance (Ω)
Measure
Units
mA
%
Area:
Left STN
Options
Right STN
Options
Min(mA)
Max(mA)
1.7
1.7
STOP ALL
3D Split View
Programming Mode
Steering
Custom
Step Size (mA)
0.1
0.5
Pulse Width (µs)
60
Rate (Hz)
130
Stimulation
ON
OFF
Total Amplitude (mA)
1.7
Steering Controls
L2.9
Focus
Spread
Therapeutic Benefit
Rigidity
Tremor
Bradykinesia
More...
Side Effect
Speech
Paresthesia
Muscle Pulling
Discomfort
Ocular Effect
More...
Text Notes
A
B
C


A
SENSE CHANNELS
0 TO 3
0 TO 2
0 TO 1
1 TO 2
1 TO 3
2 TO 3
20,51 Hz
Beta
Gamma
2,05
0,95
0,51
0,12
LFP Magnitude (µVp)
0,95
3
2
1
0
REFRESH
BRAINSENSE SURVEY
LFP Frequency (Hz)


B
BrainSense Status
Passive
SETUP
LFP
mA
time (5s window)
LFP
LFP band power
mA
stimulation amplitude
time (whole recording)




Brain
Lead
Electrode
Extension Wire
Neurostimulator
(Pulse Generator)


(A) Common DBS electrode configurations
(B) Types of stimulation
Bipolar
Interleaving
Rapidly alternating
Multiple level
Directional

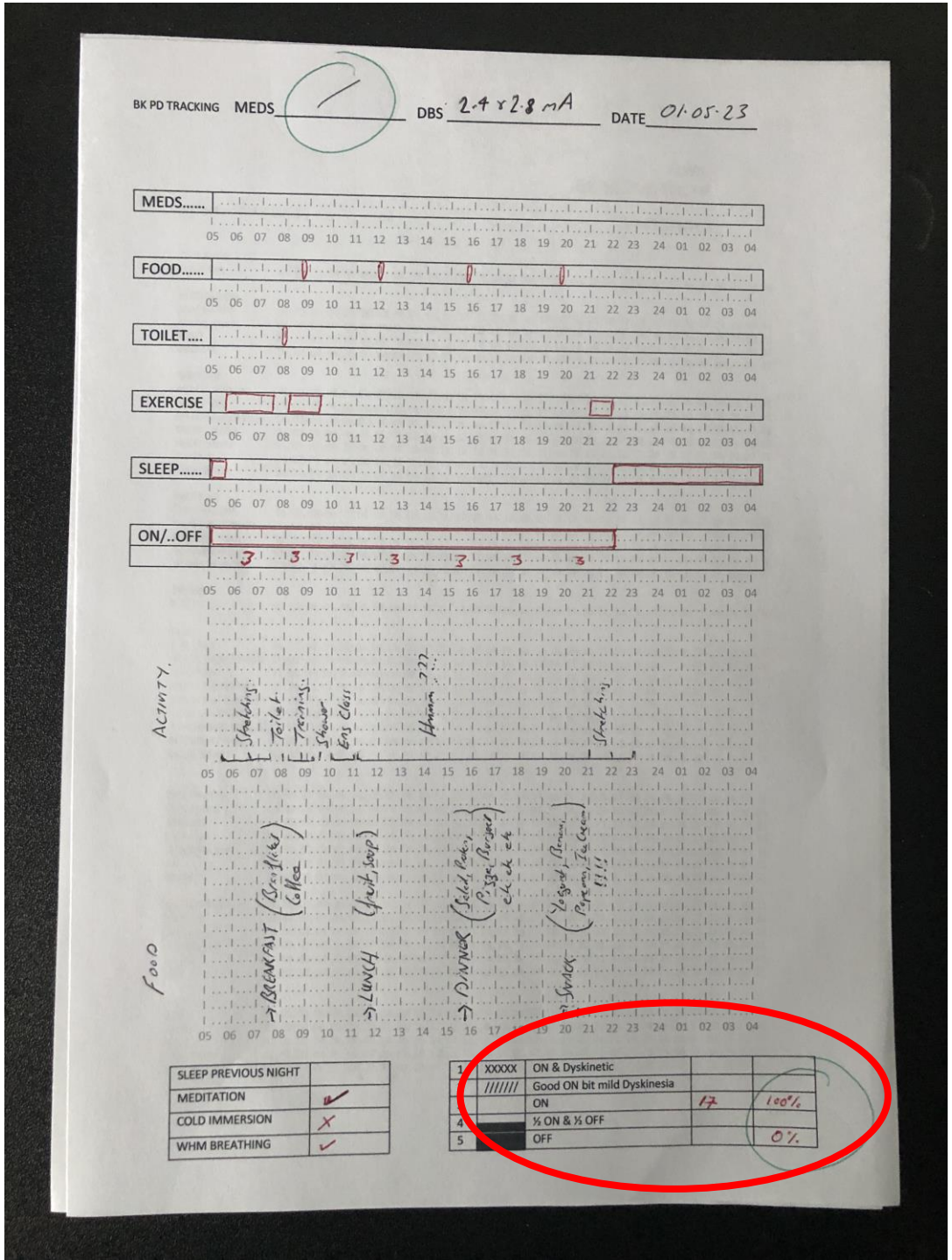

Clinical
Room 3

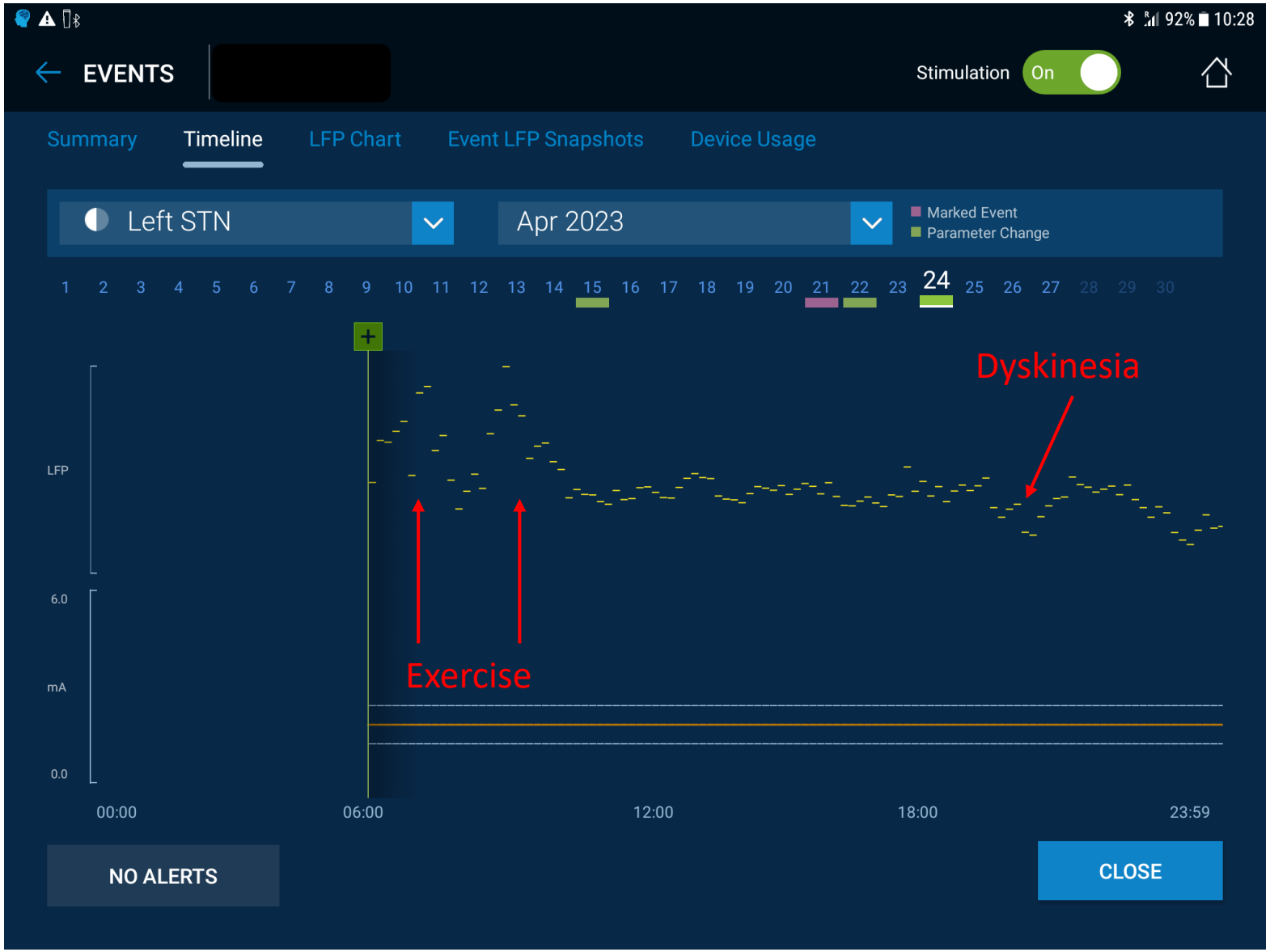
DBS outcomes

L STN: Case +ve, contact 2-; 2.8mA, 60us, 130Hz
R STN: Case +ve, contact 10-, 2.4mA, 60us, 130Hz

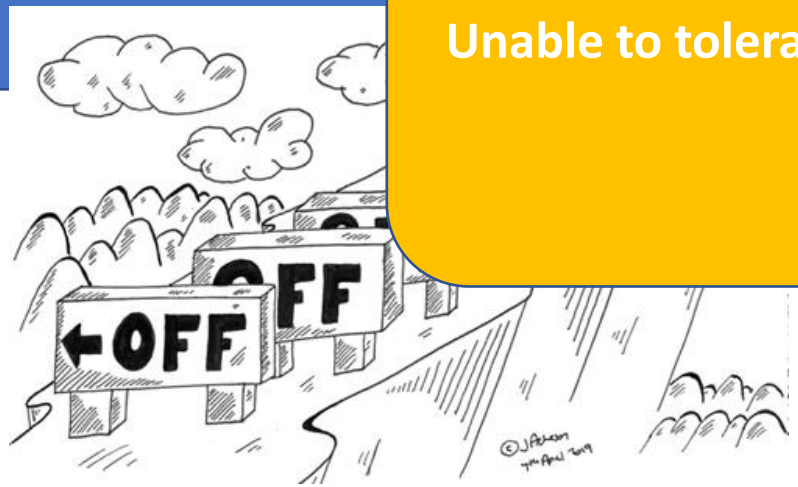
‘It was really nice to see you all last Thursday. I am continuing to do well and slowly getting back to civilised society !

They say that, in the end, everything worthwhile and of consequence is achieved the coordinated work of relatively small teams.’




92% 10:28
EVENTS
[redacted]
Stimulation On
Summary
Timeline
LFP Chart
Event LFP Snapshots
Device Usage
Left STN
Apr 2023
Marked Event
Parameter Change
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
LFP
6.0
mA
0.0
Dyskinesia
Exercise
00:00
06:00
12:00
18:00
23:59
NO ALERTS
CLOSE

Motor fluctuations



Unable to tolerate medications

Refractory tremor

Which advanced therapy?

Patient preference

- If appropriate, all 3 options should be offered

Clinical symptoms

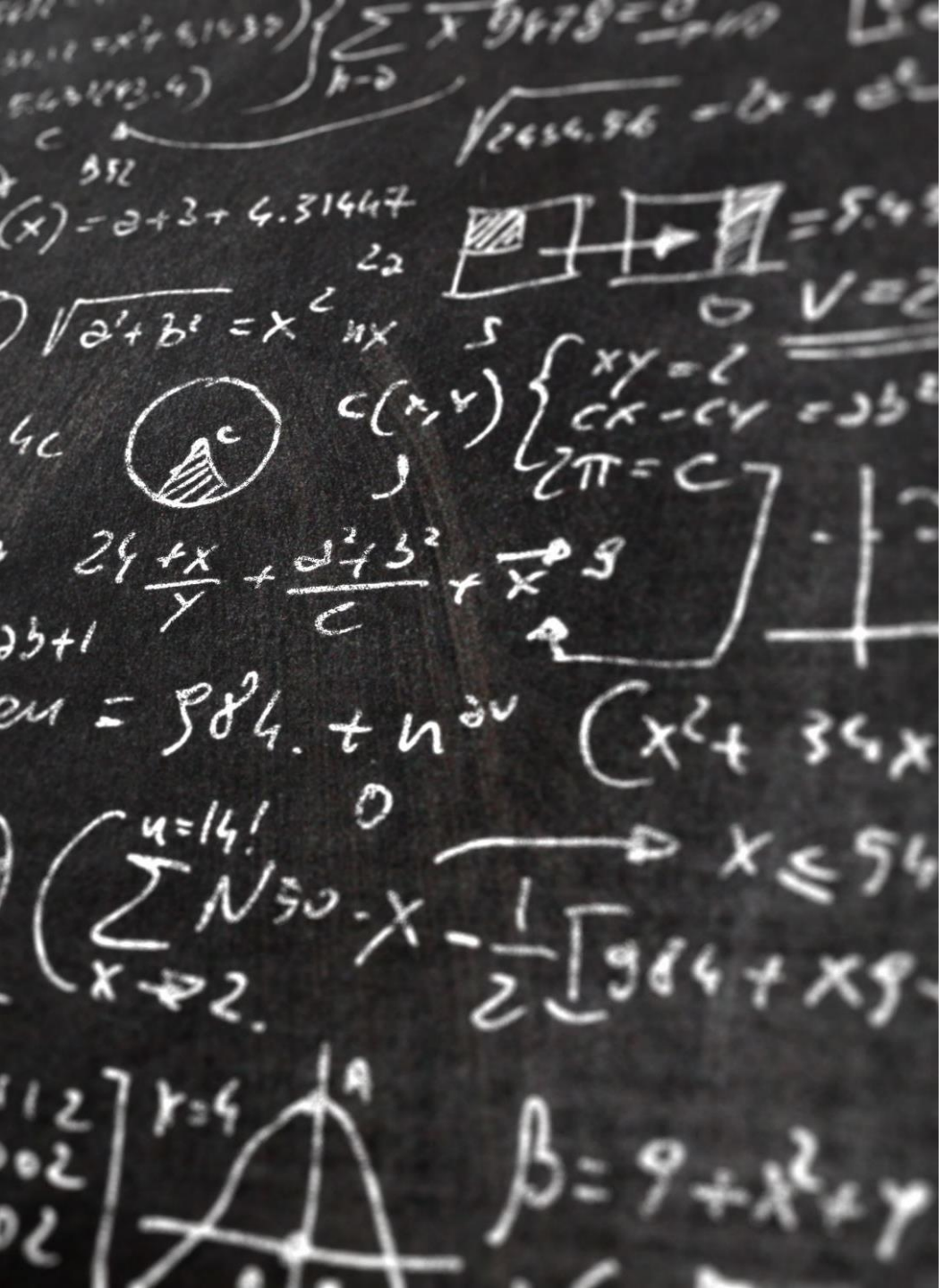
- Nature of dyskinesia – if all in ‘on’ phase, consider DBS (GPi)
- Any early cognitive symptoms
- Gait or balance disturbance

Home situation

- Apomorphine & duodopa/produodopa require patient or family-carers to be able to set up the pump

Convenience

- DBS will require lifelong follow-up, adjustments, battery replacements (however, more rechargeable devices on the market)
- Urgency



Acute Presentations in PD: ‘Troubleshooting’

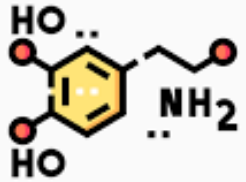
Case 3

Clinical Presentation

- 61YO RH male
  - Presented to Neurology aged 55YO with ‘tension in R knee lasting few secs at a time’, decreased dexterity & fatigue
  - Delayed diagnosis due to an abnormal MRI ??Inflammatory demyelination
  - DAT +ve 2017
- 6/7 Hx of declining mobility, early wakening akinesia & rigidity with painful foot dystonia, weight loss, worsening wearing off & burning pain in limbs
  - Morning of presentation to ED: ‘couldn’t move out of bed’ & severe pain, increasing off time
- <u>Current treatment:</u>
  - Sinemet 125mg QDS – 7/11/14/18:00 (**recent reduction**)
  - Sinemet CR 125mg ON at 22:00
  - Safinamide 50mg OM (not tolerated increased dose – **dyskinesia ++**)
  - Madopar Disp 62.5mg on waking (recent decrease from 125mg) & 2pm ‘rescue’
  - Entacapone 200mg (recent introduction, & was also taking with CR), increasing dose over past few days

- No fever or illness, no missed medication, no unwell contacts
- Constipated ++ - no BO for 3/7 – new for him
- Previously not tolerated requip XL – worsening rigidity, stopped driving & exercising; no Hx of ICBs

- <u>Aug 2022:</u>
  - Seen in OPC & noted to be very dyskinetic
  - Diagnosed with *'Dopamine dysregulation syndrome'*
  - Medications reduced
    - Sinemet x5 → QDS
    - Madopar disp reduced
    - Amitriptyline stopped
  - Sudden switching off between 2-4pm, significant nocturnal akinesia
  - Not sleeping due to pain & increased pain, having to sleep during day 'when DA on board'
  - Cognitive decline 'brain fog'
  - Worsening wearing off
    - Safinamide increased to 100mg →no improvement, perhaps some worsening dyskinesia
    - Entacapone added in September , including alongside CR → no improvement, dyskinesia +



Dopamine Dysregulation Syndrome (DDS)

- Iatrogenic disturbance that may complicate long-term symptomatic therapy of Parkinson's disease
- Patients with DDS develop an addictive pattern to dopaminergic medication
  - Administering doses more than those required to control their motor symptoms
- Prevalence in patients attending specialist PD centres is **3-4%**; diagnosis is clinical
- Behavioural disturbances include
  - Punding - complex stereotyped behaviour
  - ICDs - pathological gambling, hypersexuality, compulsive shopping & compulsive eating
- Levodopa is still considered the most potent trigger, but apomorphine & oral dopamine agonists also responsible
- **Management:**
  - Identify those at risk & use lowest clinically effective doses of DA therapy
  - Avoid rapid acting, 'booster' medications
  - If suspected, dopaminergic dose reduction
  - Stop DA agonists
  - CBT/psychology; social input to control RFs
  - Neuroleptics if presence of psychosis, aggression – psychiatry input advised

What did we do…

- **Mapped out his day**
  - Waking, when he was functional, duration of DA effect, typical wearing off & timing if dyskinesia etc.
  - How long until meds kick in
  - What does wearing off look like for him, 'virtual paralysis'
    - No unpredictable offs, no 'on' FOG
  - Dyskinesia – troublesome v non-troublesome, peak dose
  - No cognitive concerns, hallucinations
- AXR, stool chart, laxatives
- Hauser diary
- Lying-standing BPs – persistent BP drop, safinamide held
- Increased Madopar Disp PRN (with caution) & CR preparation
- Continued with up-titration of entacapone, then switched to stalevo 100 & increased to x5/day

Define therapeutic window

Date (day / month / year): ____/____/_____ Subject ID_____

TIME	ASLEEP	OFF	**ON** without dyskinesia	**ON** with no troublesome dyskinesia	**ON** with troublesome dyskinesia
00:00-00:30					
00:30-01:00					
01:00-01:30					
01:30-02:00					
02:00-02:30					
02:30-03:00					
03:00-03:30					
03:30-04:00					
04:00-04:30					
04:30-05:00					
05:00-05:30					
05:30-06:00					
06:00-06:30					
06:30-07:00					
07:00-07:30					
07:30-08:00					
08:00-08:30					
08:30-09:00					
09:00-09:30					
09:30-10:00					
10:00-10:30					
10:30-11:00					
11:00-11:30					
11:30-12:00					

- Continued with unpredictable ‘frozen episodes’ & complex motor fluctuations
- Variable day to day - ?gastric outlet syndrome, ‘no control’
- Pt fearful to ask for disp, but encouraged to do so; taking x3/day
- More dyskinetic – affecting sleep, not concerning during day
    - Losing weight
- Worsening hand function, increasingly dependent
- Wished to switch back to original regimen pre-August

- <u>Discussed options</u>
    - **Not keen for advanced therapies at this stage**
    - Increased to 187.5mg x5/day - not well tolerated
    - Entacapone = better on, but GI upset, decreased appetite & more dyskinesia
    - Safinamide increased
    - Added in neupro patch overnight
        - ‘Brain fog’
        - Some increase in postural symptoms
    - ??opicapone switch

Moved to Apomorphine

- Commenced as inpatient following domperidone prep, normal ECG
- Adjusted in the community
  - Mild postural drop
  - Still on sinemet 125mg x5 & CR
  - Madopar disp 125mg on waking
  - No off periods, ‘lifesaver’ – back playing tennis, early retirement, travelling
- Issues: Increasing dyskinesia with increasing dose, requiring more boluses & developed CAS
- **Now for DBS work up**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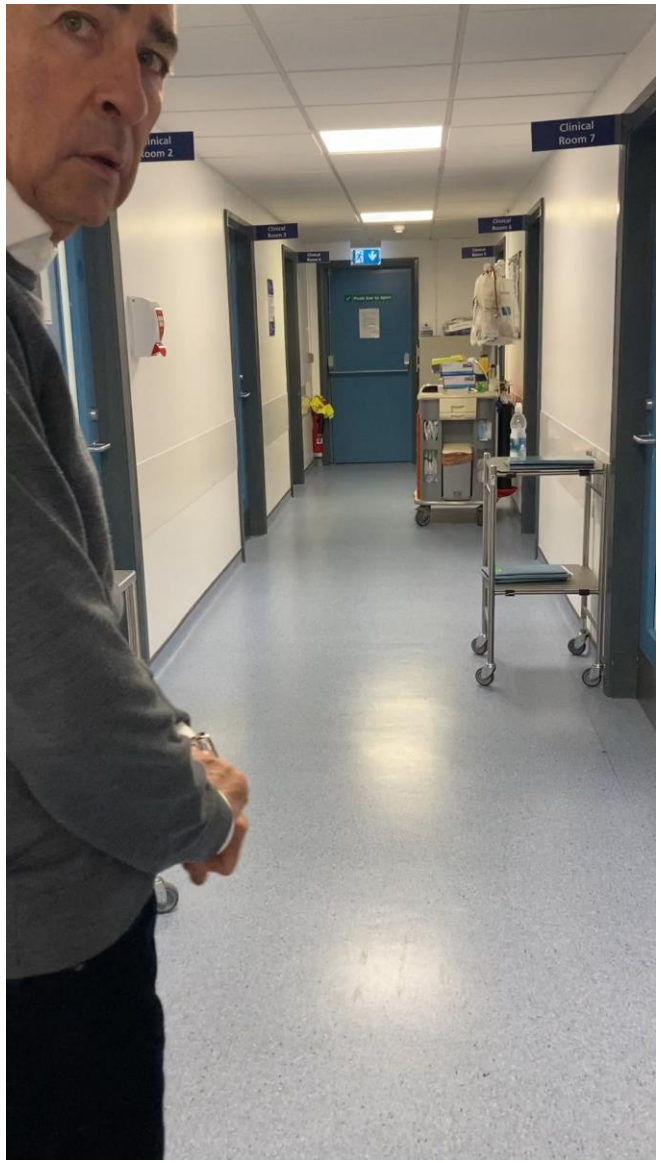
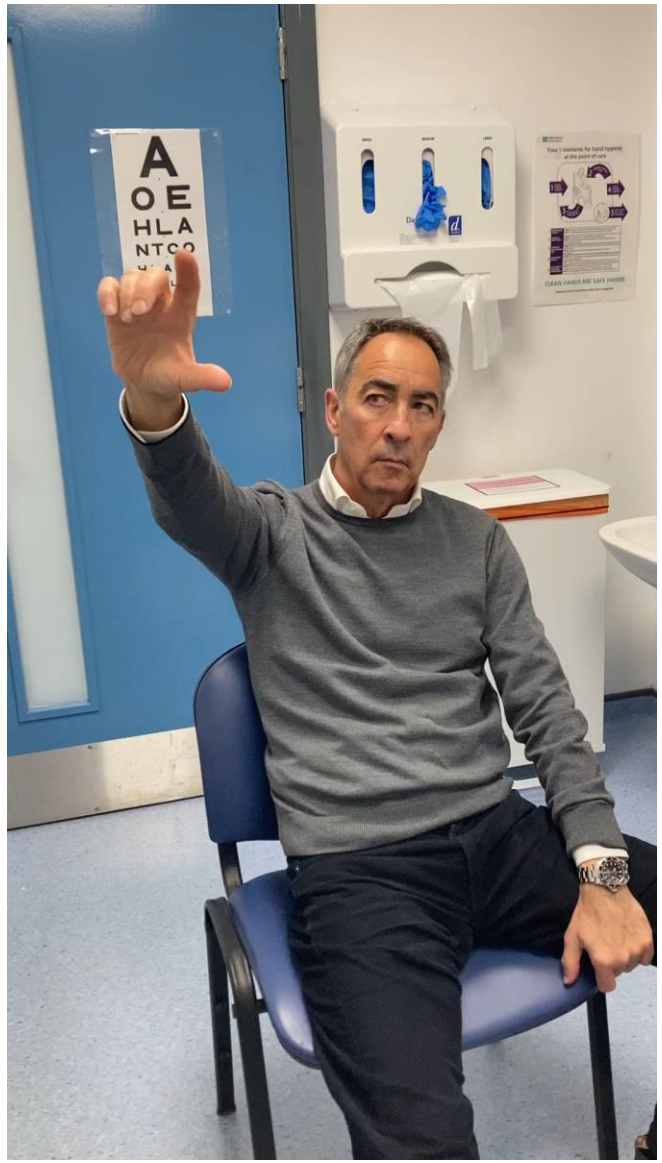
Clinical
Room 2
Clinical
Room 7


Clinical
Room 7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Delirium & Psychosis in PD

Hallucinations & psychosis occurring 2 common scenarios (with or without PD-D):

1. Dopaminergic drugs
2. Systemic illness – incl. dehydration, constipation, metabolic derangement

- **Drug rationalisation:** typically, 'last in, first out approach'
  - Anticholinergics
  - Amantadine
  - Dopamine agonists
  - MAOIs
  - COMTs
  - L-dopa

- Involve psychiatry early ??clozapine

<u>Commence on:</u>
Quetiapine (12.5mg – 75mg)
Rivastigmine for hallucinations*
*less effective if underlying PD-D is not felt to be the cause

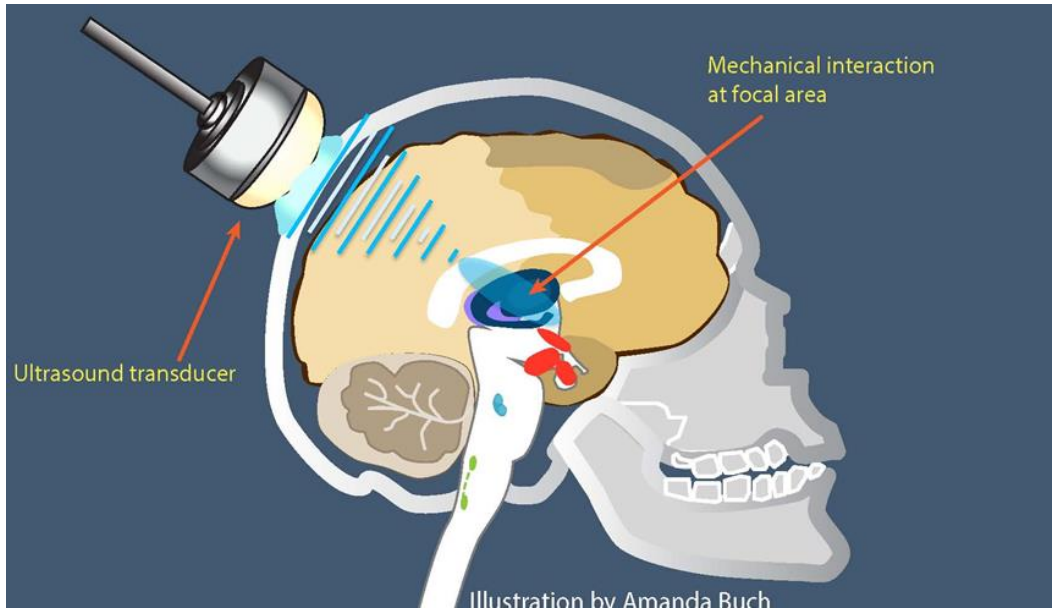
Nil by mouth

- **NG TUBE**
- Local guidelines
  - NG Tube
  - Only commence rotigiotine patch if no other option
  - Be wary in patient who are elderly, showing evidence of emerging PD-D, Hx of ICBs or dopamine dysregulation
  - Be wary of 'dose calculators' – often discrepancy
    - Patient on Sinemet 125mg QDS
    - PDMed cal: 2mg patch
    - Optimal: 10mg patch (6mg if patient has delirium)
  - Always go for a lower dose if delirium present & then increase if necessary
  - Always contact their neurologist/movement disorder specialist

Both on Parkinson's UK website

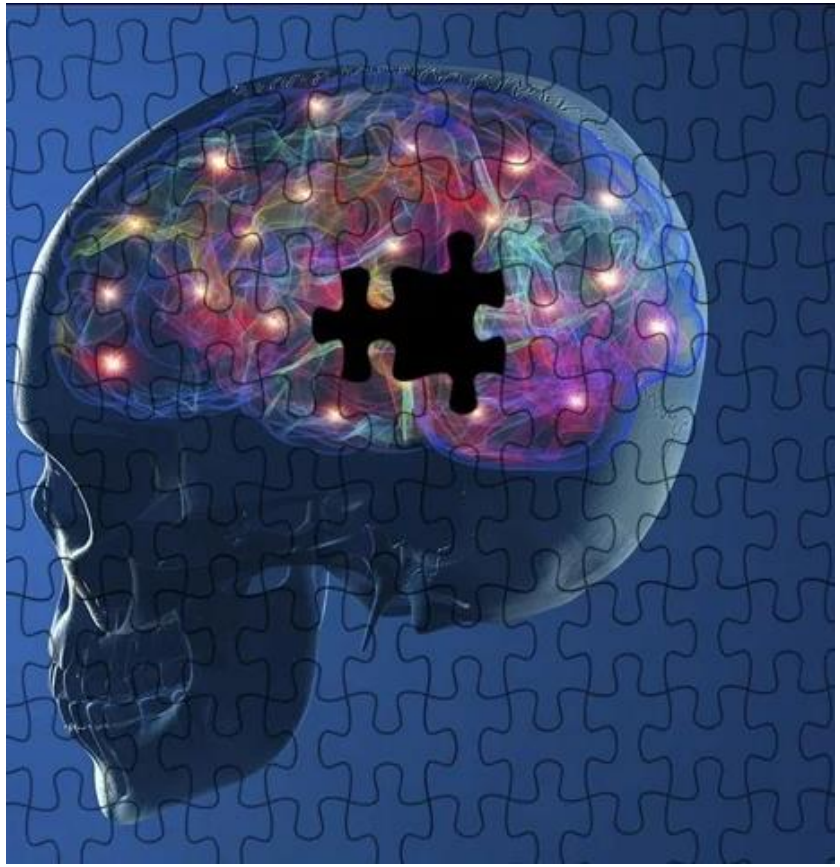
What's new?

- **Produodopa**
- **MRgFUS** ?
- Crexont (extended release L-dopa)
- Lexicon

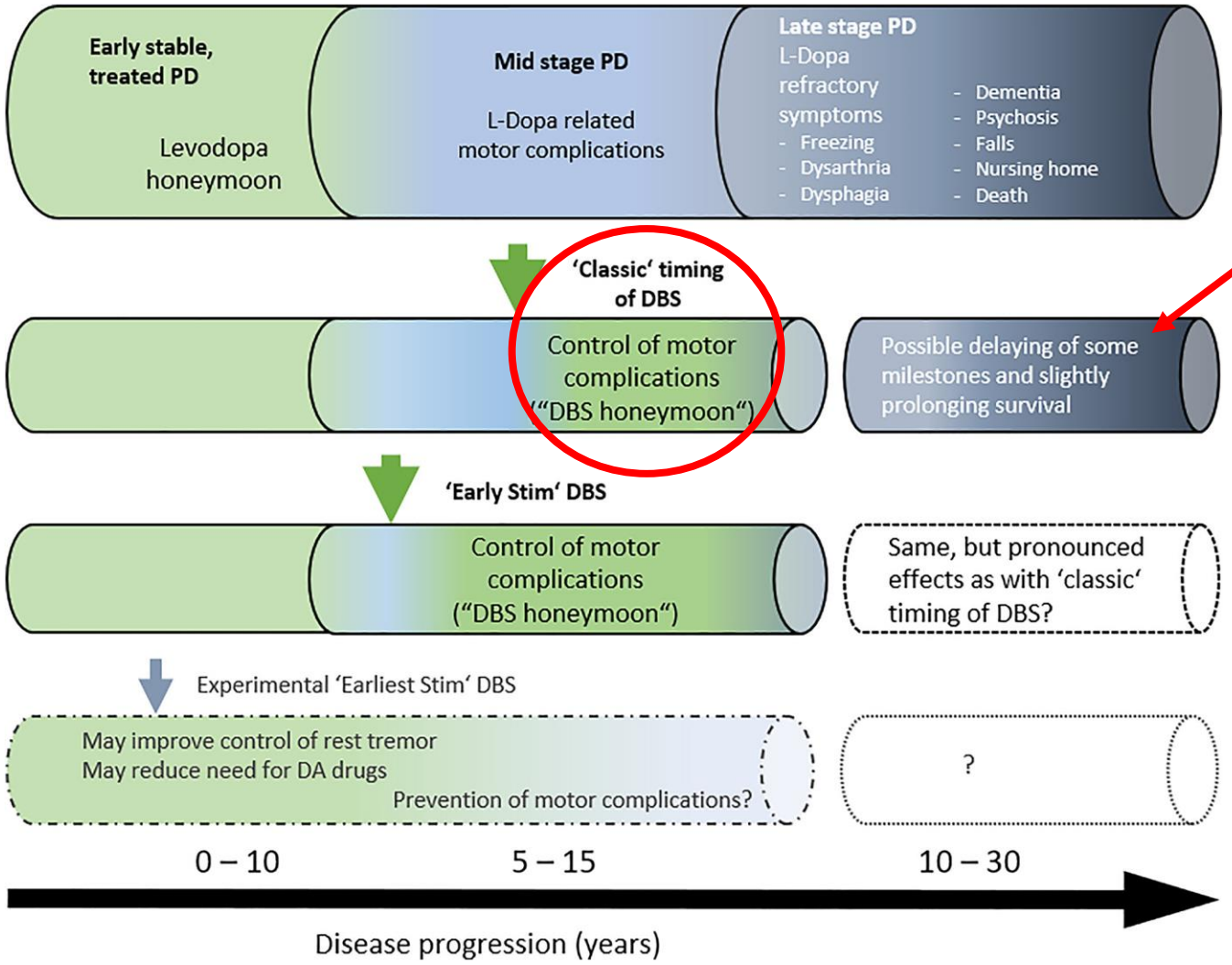


Future perspectives

- **Controlled trials comparing efficacies of non-oral therapies are difficult**
  - **INVEST (INfusion VErsus STimulation) trial** is a head-to-head comparison of CLI & DBS looking at costs & effectiveness
  - Prospective, open label multicentre RCT
- **Important knowledge gaps**
  - Differential effect of advanced therapies on NM features, criteria for discontinuation (e.g. severe dementia) & predictors of LT complications
- **Utility of early use of advanced therapies**
  - EARLY-STIM – **not when, but whom**
  - EARLY-PUMP (ongoing for apomorphine)
- **DBS techniques continuing to evolve** – adaptive neurostimulation (Dec 2024)
- Focused Ultrasound therapy (MRgFUS)
- **Development of easier delivery methods for infusional therapies**
- **Potential for gene therapy, cell-based therapy & disease modifying therapies to alter the course of the disease**
  - HER-096 – collaboration between Parkinson's UK & MJFF looking at Cerebral Dopamine Neurotrophic Factor (CDNF)



When should we offer DBS?



Reduction in severity & functional impact of motor & non-motor symptoms, exerting beneficial effects on progression of disability

5-year outcomes (Neurology, 2020) Class II evidence that DBS implanted in early-stage PD decreases the risk of disease progression and polypharmacy compared to optimal medical therapy alone

Mahlknect *et al. Movement Disorders* 2022

Target	Therapy	
	Preclinical studies	Clinical studies
SNCA 	Beta-2 adrenergic receptor, siRNA, non-steroidal anti-inflammatory drugs, antistreptolysin O	Thiazolidinedione (glitazones)
Misfolded α-synuclein fibrils 	Anti-LAG3 antibody, small molecule inhibitors, CLR01, KYP	Active or passive immunotherapy (eg, BIIB065), nilotinib, deferiprone
Autophagy lysosomal pathway 	LTI-291, AT3375	Ambroxol, glucosylceramide synthase inhibitors
Calcium ion homoeostasis 	Calcium ion channel blockers	Calcium ion channel blockers (eg, isradipine)
Mitochondria dysfunction  Parkin pathway	Ursocholanic acid, mitochondrial division inhibitor 1, MIRO reduction, sirolimus	11-dehydrosinularoiolide, MitoQ, exenatide, LRRK2 small molecule kinase inhibitors
Neurotrophic factors 	Brain-derived neurotrophic factors, vascular endothelial growth factor	Cerebral dopamine neurotropic factor, glial cell line-derived neurotrophic factor, neurturin
Inflammation 	Anti-inflammatory (eg, non-steroidal anti-inflammatory drugs)	Sargramostim, exenatide, liraglutide, lixisenatide, AZD3241
Oxidative stress 	DJ-1 chaperones	Deferiprone, inosine, coenzyme Q10, caffeine, nicotine, creatine
Therapies under investigation		
⏭ Vaccines, neuroinflammatory therapies, diets and microbiome, cannabinoids, novel druggable targets, gene therapy, and next generation adaptive deep brain stimulation		
Emerging future therapies		

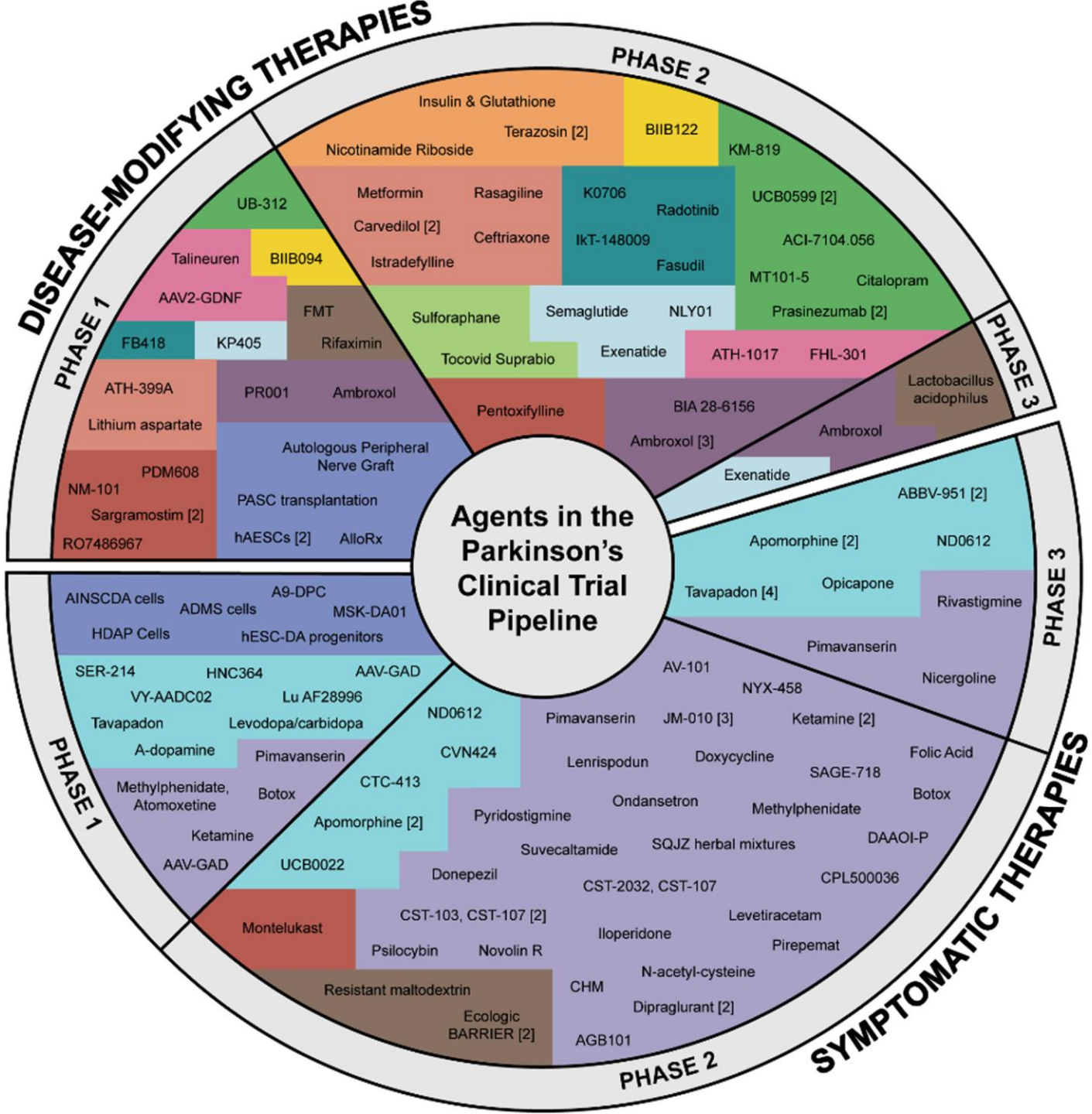
Bloem *et al. Lancet*, 2021

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Need reliable biomarkers for early diagnosis of PD, specifically in the prodromal phase;

In 2023:

- Alpha-synuclein seeding assay in CSF
- Blood-based mitochondrial damage assay which may allow monitoring of biological impact of drugs targeting LRRK2



McFarthing K, *et al; J Parkinson's Dis,* 2024

Thank you!
Any questions?