



”Den trötta Parkinson-patienten: sömn, dagtrötthet och fatigue”

Adjmal Nahimi, Neurolog, PhD,
Neurologiska kliniken, Lund, SUS.
Minneskliniken, Malmö, SUS. Neurologens
Forskningsenhet, Lund, SUS. Restorative
Parkinson Unit, LU.

1

Översikt

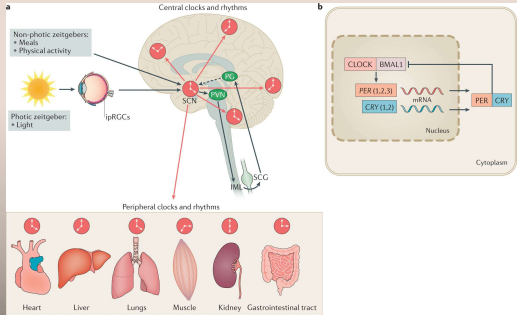
- Sömnfysiologi
- Diagnostik och behandling av sömnstörning vid Parkinsons sjukdom

Insomni
Dagtrötthet (Excessive Daytime Sleepiness), fatigue.
REM-sömnstörning



2

Cirkadianske rytm (dygnsrytm)



Central clocks and rhythms

Nonphotic zeitgeber:
• Meals
• Physical activity

Photic zeitgeber:
• Light

ipRGCs

SCN, PVN, MCH, VL

SCG, ML

Peripheral clocks and rhythms

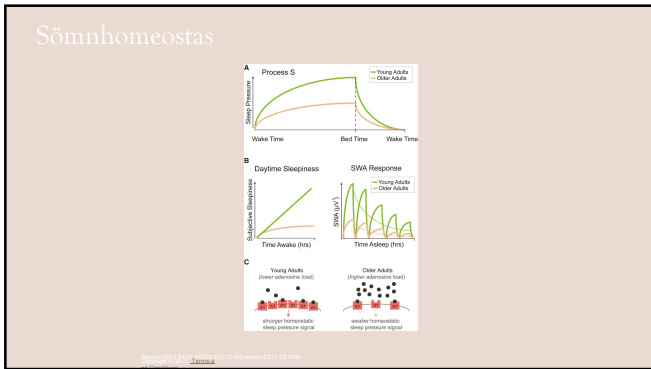
Heart, Liver, Lungs, Muscle, Kidney, Gastrointestinal tract

Molecular mechanism:

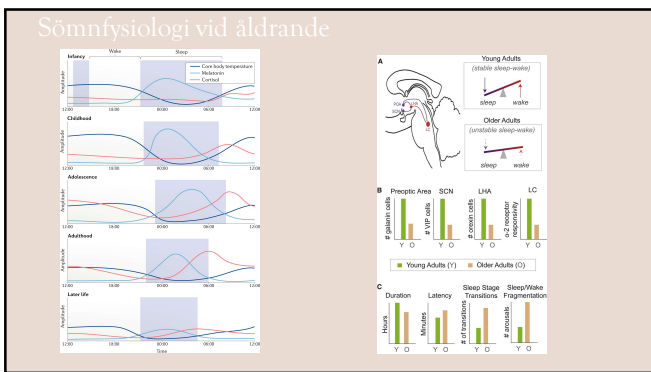
CLOCK, BMAL1 → PER (12,2), CRY (1,2) → mRNA → PER, CRY

Nucleus, Cytoplasm

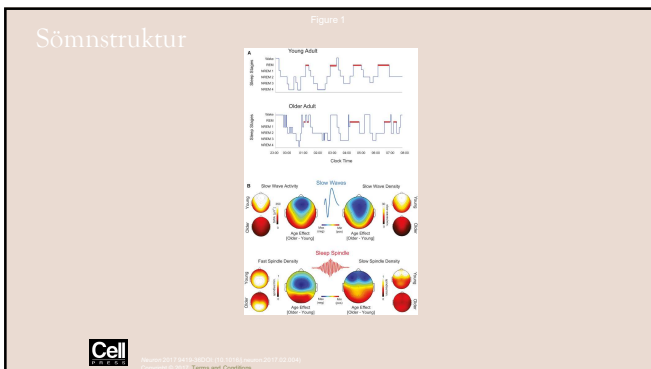
3



4

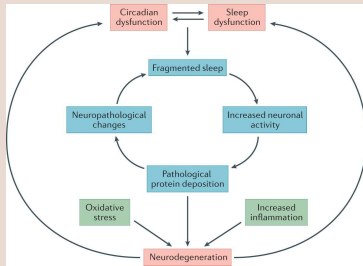


5



6

Sömndysfunktion vid neurodegenerative sjukdomar



7

Table 1 Prevalence of sleep disorders in neurodegenerative diseases

Sleep-wake disorder	Insomnia		Parasomnia		SDB	RLS
	EDS	REM parasomnia	RBD	Nightmares		
PD	33%–44% [84–242]	21%–70% [27, 243]	39%–69% [142, 243]	17.2%–30% [241, 244]	Sleep: 8.8% [149–188], 15.8% [152, 244] Night terror: 3.9% [241] NREM arousal: 1.8% [245] RBD disorder: 10.3% [245]	14% [27]
MSA	19% [247]	28% [248]	88% [248]	–	Obstructive: 30%–70% [254–156], 15% [250]	4.7%–28% [251]
DLB	36%–79% [252]	11%–100% [252]	76% [112]	83% [152]	–	–
POC	72% [252]	83% [252]	17% [252]	78% [252]	–	–
FTD	48% [254]	64% [254]	Rare [254]	Rare [255]	–	–
CRD	Rare [256, 257]	–	14.3% [258]	–	–	–
PSP	60% [249]	60% [260]	11.4%–38% [258, 261]	–	–	–
AD	40% [48]	43% [264]	Rare [265]	–	–	–
HD	25%–41% [266, 267]	35.4%–68% [268, 269]	12%–35.8% [269, 270]	22.5% [269]	–	–

EDS excessive daytime sleepiness; RBD rapid eye movement (REM) sleep behavior disorder; NREM non-REM; SDB sleep-disordered breathing; RLS restless leg syndrome; PD Parkinson's disease; MSA multiple system atrophy; DLB dementia with Lewy bodies; FTD frontotemporal dementia; CDD corticobasal degeneration; PSP progressive supranuclear palsy; AD Alzheimer's disease; HD Huntington's disease; OSA obstructive sleep apnea

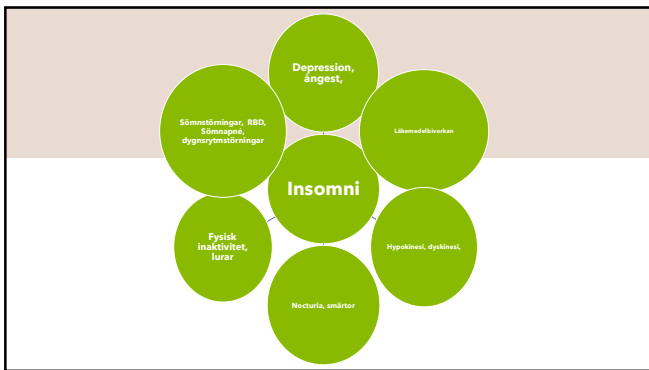
8

9

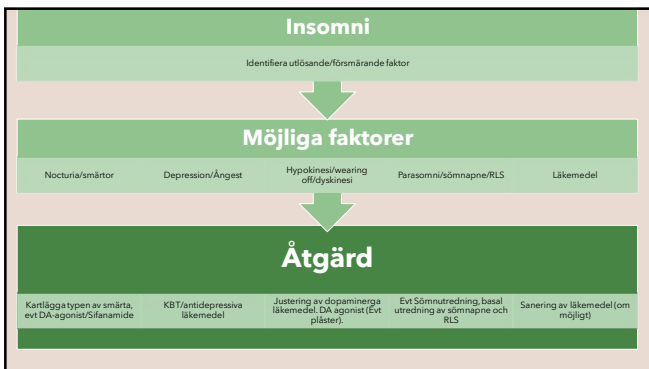


Insomningsproblem (difficulty initiating sleep).
 Flera uppvaknanden (difficulty maintaining sleep).
 Tidig uppvaknanden (early morning awakenings).

10



11



12

Behandling av insomni vid tidig Parkinsons sjukdom

Icke farmakologisk behandling

- Sömnhygiejn
- Dagljusterapi eller träning
- KBT

Farmakologisk behandling

- Melatonin
- Zopiclone
- Mirtazapin
- I enskilda fall → Quetiapine/Clozapine
- Ängest/depression → Venlafaxine, TCA

13

Study ID	Device	Exposure distance	Interventional protocol	Investigated parameters	
				EXP	CON
Videnovic 2017	Sun Ray Sunbox SB-SS8	86.4 cm	60 min/day morning-evening (2-week, follow-up 2-week)	White light (10,000 lux)	Dim red light (200 lux)
Ruffen 2016-2019	Light box (Braxi, Lumix, Cambridge UK)		30 min/day morning-evening (3-month, follow-up 6-month)	White light (10,000 lux)	Dim light (200 lux)
Ruffen 2019	Spectramax light therapy device		60 min/day, evening (6-month, follow-up 1-month)	Blue/green light (100 lux)	Polychromatic light (100 lux)
Willis 2018	Light source containing fluorescent tubes	0.9-1 m	60 min/day, evening (2-week)	Polychromatic light (3,000 lux)	Dim red light (200 lux)
Raymackers 2019	A portable head-mounted device (Luminether®, Lucimed SA, Villiers-le-Bouillet, Belgium)		45 min/day, morning (1-month, 2-week washout, 1-month)	Blue light	Orange light (175 lux)


Modifierad från MDS konferens 2023, Dr Srinagan J

14

Outcomes	Study ID/number of participants (N/control)					Difference from pre to post (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Videnovic 2017	Ruffen 2016-2019	Ruffen 2019	Raymackers 2019	Willis 2018			
Motor function	UPDRS III	UPDRS III	UPDRS III		UPDRS III	-4.68 lower (0.25 to -9.12 lower)	209 (4 studies)	High
Depression	BDI	HDRS	BDI	HADS (depression)	BDI	0.27 standard deviations lower (0.52 to 0.02 lower)	234 (5 studies)	High
Daytime sleepiness	ESS	SCOPA (daytime sleepiness)	ESS	ESS	ESS	0.14 standard deviations lower (0.39 lower to 0.11 higher)	241 (5 studies)	High
Sleep	POSS		POSS			3.43 standard deviations higher (0.12 to 6.78 higher)	122 (2 studies)	High
Adverse events						88 1.73 (1.19 to 2.52)	231 (5 studies)	High

Modifierad från MDS konferens 2023, Dr Srinagan J

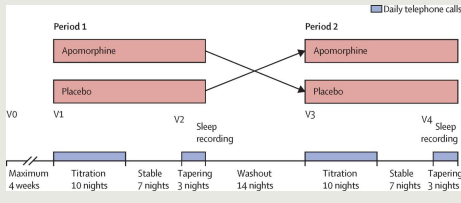
15



Behandling av insomni vid avancerad Parkinsons sjukdom

16

Subkutan apomorfin



17



	Apomorphine (n=64)	Placebo (n=44)	Treatment effect (95% CI)	P value
Primary outcomes				
PDSS change	15.18 (24.34)	5.23 (21.52)	9.95 (0.88 to 19.02)	0.041
Secondary outcomes				
Subjective nocturnal awakenings	16.62 (9.72)	10.26 (9.06)	-6.36 (-3.82 to -8.90)	0.011
CGG score	6.32 (2.62)	4.92 (2.11)	1.40 (0.02 to 2.78)	0.007
ESS score	11.16 (5.72)	11.15 (5.64)	-0.01 (-1.42 to 1.42)	0.98
Subjective sleepiness (ESS score ×10)	24 (22%)	24 (22%)	1.04 (-0.27 to 2.3)	0.59
Parkinson Severity Scale	38.64 (12.24)	38.9 (12.22)	-0.46 (-0.67 to -0.25)	0.001
Revised Apgar syndrome	20 (44%)	21 (46%)	2.44 (0.05 to 4.82)	0.20
IRISMS score	22.15 (9.28)	22.19 (9.11)	-0.03 (-1.18 to 1.12)	0.94
Clinical Global Impression-behavior disorder	17 (27%)	15 (22%)	2.0 (0.08 to 3.9)	0.77
Clinical symptoms of obstructive sleep apnea	20 (42%)	22 (48%)	1.63 (0.37 to 2.9)	0.02
UPDRS-part 1	10.71 (4.84)	12.07 (4.00)	-1.34 (-2.44 to -0.24)	0.004
MDS-UPDRS-part 1	16.21 (7.02)	16.43 (7.26)	-0.22 (-1.01 to 0.48)	0.47
Motor condition on morning awakening	1.24 (1.02)	1.01 (1.22)	-0.07 (-0.08 to -0.10)	0.02
Levit score	1.95 (1.16)	1.29 (1.15)	-0.26 (-0.38 to -0.14)	0.00
DUARF score	10.42 (10.66)	10.01 (10.26)	2.04 (-0.08 to 4.16)	0.21
Stages-High-Intensity Inventory score	38.61 (12.16)	43.72 (12.16)	-5.11 (-0.67 to 9.50)	0.10
Beck Depression Inventory score	10.62 (7.76)	12.76 (8.50)	-1.78 (-3.42 to -0.26)	0.11
BDQSD item score	8.92 (4.67)	8.02 (4.60)	0.90 (0.43 to 1.46)	0.00
ICQOL VAS score	59.01 (10.39)	51.26 (10.44)	7.75 (4.08 to 11.50)	0.011


18

Effects of Levodopa-Carbidopa Intestinal Gel on Dyskinesia and Non-Motor Symptoms Including Sleep: Results from a Meta-Analysis with 24-Month Follow-Up

Outcome	Measure	Range	PDY Number	Control Number	IG-ICG Number	IG-ICG Number	IG-ICG Number
Dyskinesia	LSDYD-FC (0-64)	NA	n=89	n=422	n=343	n=146, n=189	n=146, n=189
	UPDRS-III (0-34)	NA	n=89	n=422	n=343	n=146, n=189	n=146, n=189
LSDYD-FC (0-64)	NA	0 (0-64)	n=89	n=422	n=343	n=146, n=189	n=146, n=189
	UPDRS-III (0-34)	NA	n=89	n=422	n=343	n=146, n=189	n=146, n=189
UPDRS-III (0-34)	NA	0 (0-34)	n=89	n=422	n=343	n=146, n=189	n=146, n=189
	UPDRS-III (0-34)	NA	n=89	n=422	n=343	n=146, n=189	n=146, n=189
Non-motor symptoms	NMS-UCS (0-100)	NA	n=89	n=422	n=343	n=146, n=189	n=146, n=189
	NMS-UCS (0-100)	NA	n=89	n=422	n=343	n=146, n=189	n=146, n=189
Mood	UHDRS-10 (0-100)	NA	n=89	n=422	n=343	n=146, n=189	n=146, n=189
	UHDRS-10 (0-100)	NA	n=89	n=422	n=343	n=146, n=189	n=146, n=189
Sleep	PSQI score (0-30)	NA	n=89	n=422	n=343	n=146, n=189	n=146, n=189
	PSQI score (0-30)	NA	n=89	n=422	n=343	n=146, n=189	n=146, n=189

Chaudhuri et al.,

19



Dagröttthet (excessive daytime sleepiness).

20

Definition: Dagröttthet

- Något förmåga att vara vaken och uppmärksam under dagen med eller utan sömnapptaker.
- 20-60% av patienter har EDS och svårigheten av konsekvenser med andra icke-motoriska symtom samt duration av sjukdomen.
- Mer frekvent hos män och patienter som har DA-avancerad behandling.
- Möjlig orsaker beror på sjukdomens svårighetsgrad och daglig livskvalitet för patienter.



21

Diagnos

ANAMNES OCH FRÅGAFÖRMULÄR

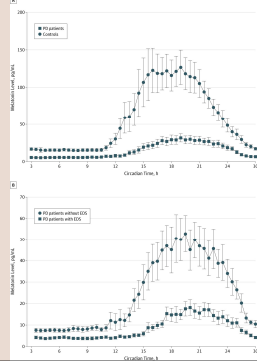
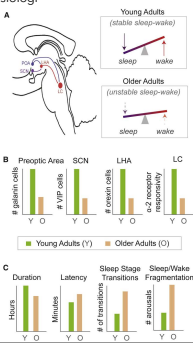
- Epworth Sleepiness Scale (ESS) >12 (10)
- Parkinson's Disease Sleep Scale version 2 (PDSS-2)
- Scale for Outcomes in Parkinson's disease Sleep (SCOPA-S)

OBJEKTIVT

- Multiple sleep latency test
- Maintenance of wakefulness test
- Polysomnography för att utesluta andra sömnsjukdomar (RBD, sömnapné)
- Actigrafi

22

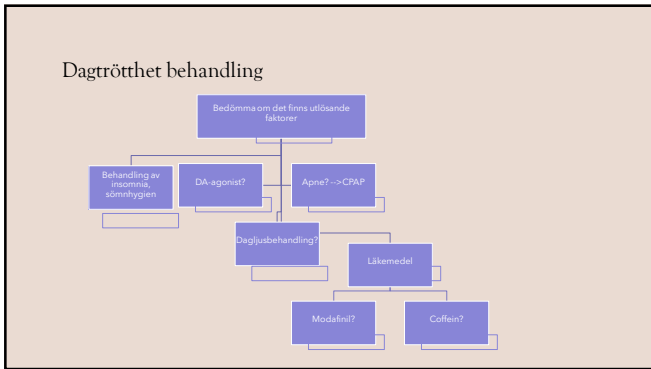
Patofysiologi



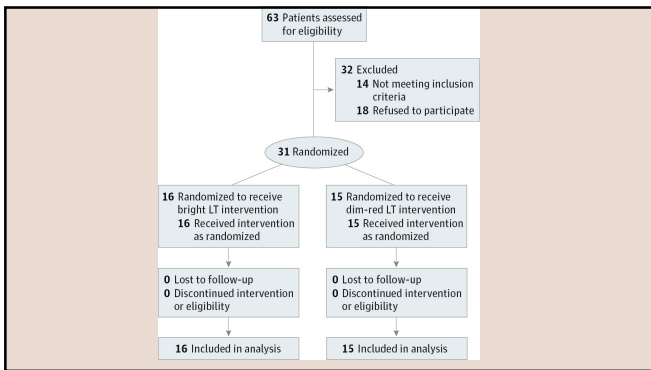
23

Dagtrötthet	Fatigue	Wearing off	Autonom dysfunktion
Nedsatt förmåga att hålla sig vakna. Sömnattaker.	Subjektiv känsla av nedsatt energi till att utföra göromål. Nedsatt motivation och önska om vila.	Non-motor off	Yrsel, sömnlighet,
Nedsatt koncentration Nedsatt förmåga att hålla ögon öppna	Co-morbid ångest, depression. Nedsatt koncentration.	Förbättras med ökad dopaminerg behandling och fluktuerar.	Kalla händer och fötter. Episoder med svimning vid blodtrycksfall (ändring av kroppställning) eller postprandialt.

24



25



26



Dagljus terapi

- Frigör dopamin vid stimulering av retinala celler och stabiliserar den biologiska dygnsrytm
- Mindre studier visade att sömnfragmentering, och den subjektive upplevelse av sömnkvalitet samt rörlighet under dagen förbättrades

27



28

Table 1 Prevalence of sleep disorders in neurodegenerative diseases

Sleep-wake disorder	EDS		Parasomnia		SDB	RLS
	Insomnia	EDS	REM parasomnia	NREM parasomnia		
PD	33%–44% [81–242]	21%–70% [27, 243]	39%–69% [142, 248]	17.2%–30% [241, 244]	Sleep apnea: 27.6%–48% [189–191] [158, 172, 246] Night terror: 3.9% [241] NREM arousal: 10.3% [245]	14% [27]
MSA	19% [247]	28% [248]	88% [248]	–	Obstructive: 30%–70% [251] OSA: 15%–17% [251]	4.7%–28% [251]
DLB	36%–79% [252]	11%–100% [252]	76% [112]	83% [152]	–	–
POC	72% [252]	83% [252]	17% [252]	78% [252]	–	–
FTD	48% [254]	64% [254]	Rate [254]	Rate [253]	–	–
CRD	Rate [256, 257]	–	14.3% [258]	–	–	Rate [259]
PPS	60% [260]	60% [260]	11.4%–38% [258, 261]	–	–	Rate [259]
AD	40% [48]	43% [264]	Rate [265]	–	–	Rate [259]
HD	25%–41% [266, 267]	35.4%–68% [268, 269]	12%–35.8% [269, 272]	22.5% [269]	–	13.4% & one family case [202] [60, 271]

EDS excessive daytime sleepiness; RBD rapid eye movement (REM) sleep behavior disorder; NREM non-REM; SDB sleep-disordered breathing; RLS restless leg syndrome; PD Parkinson's disease; MSA multiple system atrophy; DLB dementia with body fluid; POC progressive olivary degeneration; CRD corticobasal degeneration; PPS progressive supranuclear palsy; AD Alzheimer's disease; HD Huntington's disease; OSA obstructive sleep apnea

29



Diagnostik

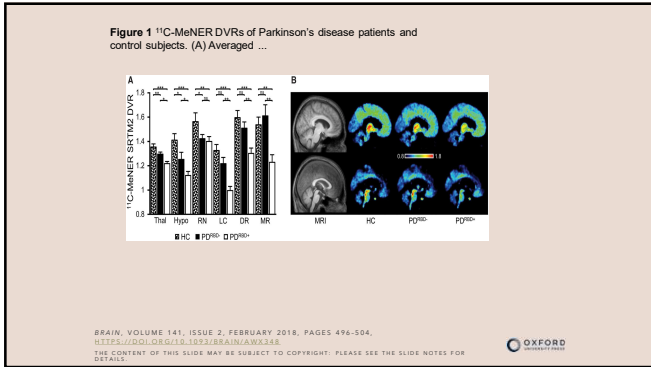
ICSD-3:

Repeated episodes of sleep-related vocalization and/or complex motor behaviors.

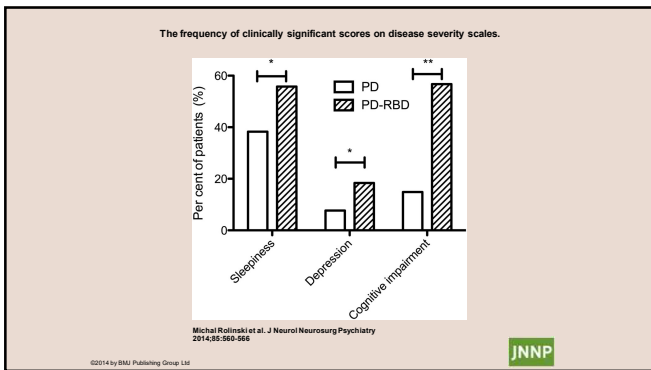
These behaviors are documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep.

Polysomnographic recording demonstrates REM sleep without atonia (RWA).

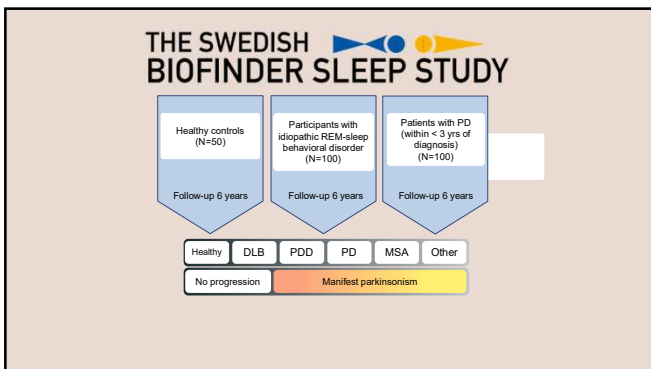
30



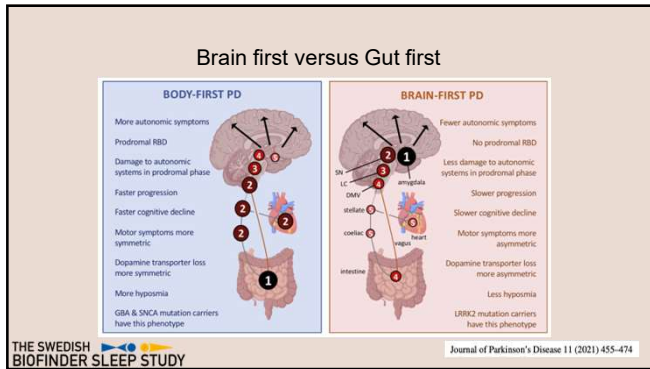
31



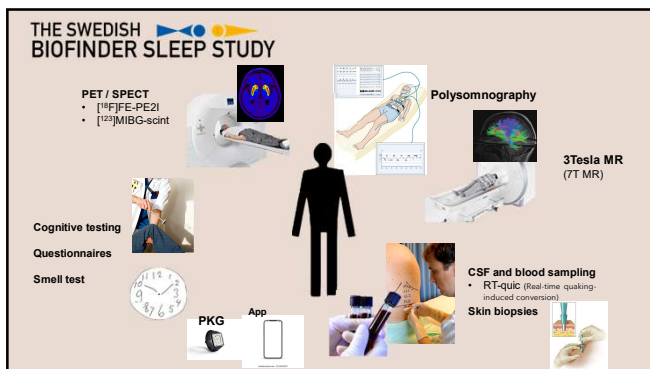
32



33



34



35

Sammanfattning

Sömnstörningar som inkluderar insomni, dagtrötthet, och REM-sömnstörning förekommer mycket ofta vid Parkinsons sjukdom. Stor negativ effekt på livskvalitet. Identifiera orsaken och riktiga behandlingen på utlösande orsak. Försök med icke-farmakologiska metoder initialt.

36



37
