TC 29

Addressing the non-motor symptoms in Parkinson‘s disease

WCN 2013 Vienna

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Conflict of interest

I received honoraria for sponsored lectures and councelling from

Novartis, Boehringer-Ingelheim, GSK, UCB, Pharm Allergan, Abbvie, Avanir

I have been investigator in studies sponsored by

Novartis, Boehringer-Ingelheim, UCB, Abbvie, General Electrics

Aims

Summary of non-motor symptoms

Clinical assessment, such as:

- Non-motor symptoms scale for PD
  - Chaudhuri et al. *Mov Disord 2007;22:1901*
- PD sleep scale
  - Chaudhuri et al *J Neurol Neurosurg Psychiatry 2002;73:629*

Clinical context of non-motor symptoms

Therapies and management

References

Non-Motor Symptoms Scale

		Number of items (*frequency, severity)*
1.	Cardiovascular	2
2.	Sleep/fatigue	4
3.	Mood/Apathy	6
4.	Perceptual problems	3
5.	Attention/Memory	3
6.	Gastrointestinal	3
7.	Urinary	3
8.	Sexual function	2
9.	Miscellaneous	4

Chaudhuri et al. *Mov Disord 2007;22:1901*

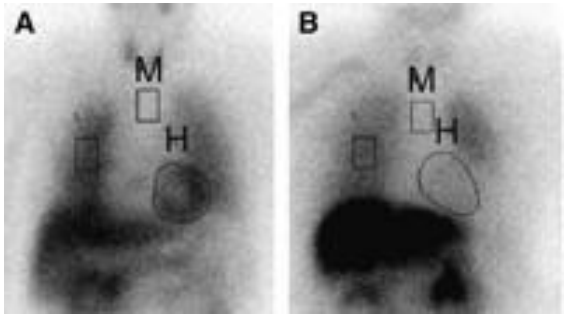
Orthostatic hypotension (OH) – fatigue and syncope

Definition: minus ?20 systol., ?10mm Hg diast. after 3 min. standing position

Often not realised by patient, sometimes severe, early sympt.

Aggravating factors: age, disease duration,
(poly)pharmacological therapy

Delayed fall of blood pressure (>3 min. after onset of standing in upright position)



Tilt test superior to Schellong (? x2)

Degeneration of the peripheral sympathetic
Visualised by MIBG-SPECT (DDx)

Jamnadas-Khoda 2009

Therapies and management of OH

Reduction of medication with blood pressure lowing (side) effect

Fluid and salt

Midodrine	2.5-10mg/d
Dihydroergotamine	2.5-5mg/d
Etilefrine-HCl	7.5-15mg/d
Fludrocortisone	0.1-0.4mg/d
L-threo-DOPS	

Horstink et al 2006
Seppi et al 2011

Impulse control disorders

Voon V et al 2007, Weintraub D et al. *Arch Neurol 2006; 63:969*
Evans AH et al. *JNNP 2006;77:317*

Hypersexuality (including paraphilia, exhibitionism...)
Compulsive eating (binge eating, sweets, chocolate..)
Reckless driving
Compulsive shopping
Pathological gambling
Risky investments et al.

Risk factors:

Dopamine agonists > Levodopa
Young age at disease onset
Male
Impulsive and addictive behavior

Reduction of dopaminergic therapy, antipsychotics….

Dopamin-dysregulation syndrome (hedonistic homeostatic dysregulation)

Giovanoni 2000, Evans and Lees 2004, Katzenschlager 2011
Cilia 2011, 2013

Compulsive medication use

Risk factors:

Levodopa>dopamine agonists
Pos. (family) history of drug abuse
Young age at disease onset
Depression
Impulsivity
Severe offs
Former tobacco, alcohol consumption

Control of intake of dopaminergic drugs

Punding

Lawrence 2007

Complex, purposeless, stereotyped behavior

Risk factors:

Dopamine agonists
Young age at disease onset
impulsivity,

Low QoL.

Reduction of dopaminergic therapy

Hypomania, mania („ADHD like“)

Often related to dopaminergic therapy in fluctuating patients during dyskinesias

Inattention, disorganised cognition, cognitive impulsivity, loss of planning, insight, decorum, hyperactivity

Reduction and stabilization of plasma levels

Further psychiatric complications in PD

Depression, depressive symptoms, anxiety >30%

Psychosis

- Illusions
- Delusions
- Hallucinations, visual>auditory>tacile
- Delirium
- Paranoia

Apathy

Fatigue

Depression und depressive symptoms in PD

Dopamine agonists	**Pramipexole**
Tricyclic antidepressants	**Nortryptiline, Desipramine,**
	Amitryptiline* Miyasaki AAN QS Sub. 2005
SSRI	**Citalopram, Sertraline, Paroxetine,**
	Fluoxetine
MAO-inhibitors	Moclobemide, Selegiline
New antidepressants	Atomoxetine, **Venlafaxien**
Alternative therapies	Omega-3-Fettsäure
Non-pharmacological interventions	**rTMS**, ECT, **cognitive behavior ther.**

Effective **possibly** **probably** effective**;** ***insufficient*** *evidence*

Article

Cognitive-Behavioral Therapy for Depression in Parkinson's Disease: A Randomized, Controlled Trial

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Objective: Despite the negative effects of depression in Parkinson's disease, there is currently no evidence-based standard of care. The purpose of this study was to examine the efficacy of individually administered cognitive-behavioral therapy (CBT), relative to clinical monitoring (with no new treatment), for depression in this medical population.

Method: Eighty depressed (based on DSM-IV criteria) patients with Parkinson's disease participated in a randomized, controlled trial of CBT relative to clinical monitoring (1:1 ratio) in an academic medical center from April 2007 to July 2010. All patients continued to maintain stable medication regimens under the care of their personal physicians. The 17-item Hamilton Depression Rating Scale (HAM-D) total score was the primary outcome. CBT was modified to meet the unique needs of the Parkinson's disease population and provided for 10 weeks. Assessments were completed by blind raters at baseline and 5 (midpoint), 10 (end of treatment), and 14 weeks (follow-up evaluation) postrandomization.

Results: The CBT group reported greater reductions in depression (change in HAM-D score) than the clinical monitoring group. At week 10, the mean HAM-D score change was 7.35 for CBT relative to 0.05 for clinical monitoring. CBT was also superior to clinical monitoring on several secondary outcomes (i.e., Beck Depression Inventory scores, anxiety, quality of life, coping, Parkinson's disease symptom ratings). There were more treatment responders in the CBT group than the clinical monitoring group (56% versus 8%, respectively).

Conclusions: CBT may be a viable approach for the treatment of depression in Parkinson's disease. Further research is needed to replicate and extend these findings.

(Am J Psychiatry 2011; 168:1066–1074)

1x/week for 10 weeks
Cognitive-behavioral therapy
and clinical monitoring
versus clinical monitoring

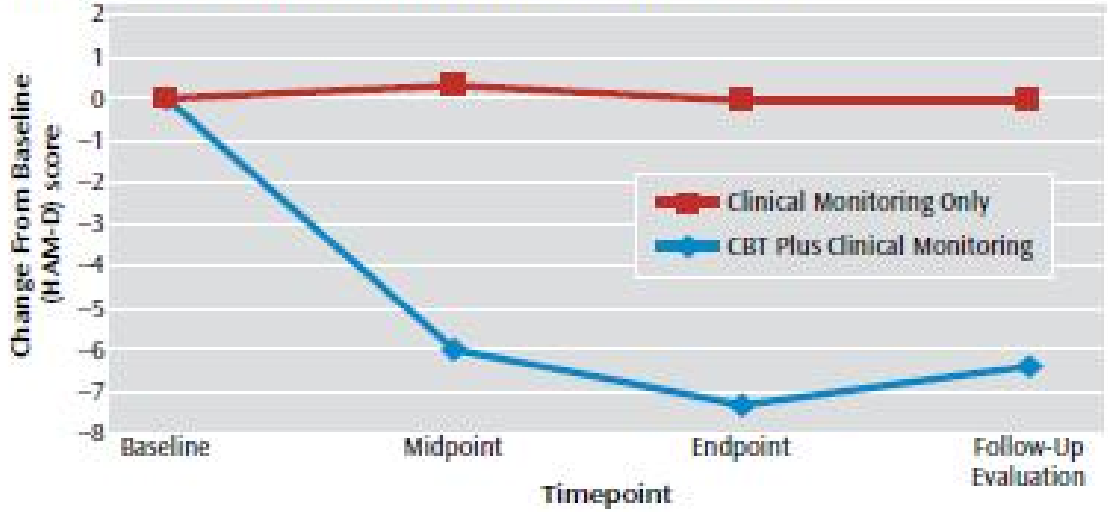
Assessments:
Baseline, wk 5, wk 10
Blinded raters

Dobkin RD 2011

TABLE 1. Baseline Demographic and Clinical Characteristics Among Depressed Parkinson's Disease Patients Randomly Assigned to Receive CBT Plus Clinical Monitoring or Clinical Monitoring Alone

Characteristic	Participants (N=80)		Treatment: CBT Plus Clinical Monitoring (N=41)		Treatment: Clinical Monitoring Only (N=39)		Analysis[a]
	N	%	N	%	N	%	p
Gender							0.86
Male	48	60	25	61	23	59	
Female	32	40	16	39	16	41	
Primary DSM-IV diagnosis							0.74
Major depressive disorder	65	81	33	81	32	82	
Dysthymia	8	10	5	12	3	8	
Depression not otherwise specified	7	9	3	7	4	10	
Comorbid anxiety disorder	45	56.3	26	63	19	49	0.19
Antidepressant use[b]	43	54	22	54	21	54	0.99
Race							0.39
Age (years)	64.56	10.53	63.73	9.89	65.44	11.23	0.47
Parkinson's disease duration (years)	6.34	5.51	6.53	5.53	6.13	5.56	0.74
Age of Parkinson's disease onset (years)	58.21	11.78	57.12	11.22	59.36	12.39	0.40
Depression duration (current episode [years])	2.84	3.06	3.13	3.36	2.54	2.72	0.39
Clinical Global Impression Scale–Severity score	4.41	0.57	4.44	0.63	4.38	0.49	0.67
Hamilton Depression Rating Scale score	20.18	4.27	20.93	4.56	19.38	4.56	0.11
Beck Depression Inventory score	19.30	7.97	19.18	7.47	19.05	7.37	0.90
Hamilton Anxiety Rating Scale score	18.95	4.33	19.32	4.41	18.49	4.35	0.36

FIGURE 1. Hamilton Depression Rating Scale (HAM-D) Change Scores Among Parkinson's Disease Patients Randomly Assigned to Receive CBT Plus Clinical Monitoring or Clinical Monitoring Alone



Management and therapy of psychosis

Treatment of concom. diseases (urinary tract infection etc.)

Reduction of psychotoxic substances
(anticholinergics, amantadine, dopamine agonist, levodopa…..)

Clozapine 12.5-50mg, cave side effects

Quetiapine 25-50mg (?)

Rivastigmine 6-12mg/d

Horstink 2006, Seppi 2011

Mild cognitive impairment in Parkinson‘s disease

Litvan 2012

Cognitive deficits without significant functional impairment

27% in non-demented PD-patients (19-36% of de-novo patients)

Attention and working memory
Executive functions
Language
Memory
Visual spatial cognition

Suggested neuro-psychological tests for MCI-PD

Attention and working memory

TRAIL-B, digit span (WAIS), Stroop word-colour test

Executive functions

Wisconsin card sorting test, Tower of London, word fluency (letters and categories)

Language

Naming (Boston naming test) etc.

Memory

Word list: learning and delayed recall

Visual-spatial functions

Benton line orientation test

Hooper visual organisation test

Clock drawing

?á tests beyond 1-2x negative SD*

*SD standard deviation

Dementia in PD

Prevalence: in up to 80% of patients, 6 fold risk

Deficits

Attention, concentration, memory, visual cognitive functions, frontal executive functions, speed of cognitive processing, behavioral deficits

Cognitive fluctuations!
Similarities to dementia with Lewy bodies

Mainly related to age>disease duration; depression, hallucinosis, apathy, AR-subtype, comorbidities

McKeith 2005, Dubois 2007, Emre 2007

Therapies of dementia in PD

Rivastigmine	(oral) 6-12 mg/d	effect certain
Donepezil	10mg/d	effect uncertain
Memantine	20mg/d	effect uncertain
Levodopa		may stimulate cognition (drive) caveat: overdosage

Treatment/management of (orthostatic) hypotension and other medical problems

Emre 2004, McKeith 2000

Sleep disorders in PD

Peeraully et al. 2012

Systematic review of case-control polysomnographic Studies, N=15

Prevalence	40-90%

	PD	**Co‘s**
Daytime sleepiness*	50-66%	3-12%*
REM-sleep behavior disorder	0-47%	0-1.8%*
Obstructive Sleep apnea	27-60%	13-65%*

* Patient‘s information

Item number	Symptom
1	Overall quality of the night's sleep
2	Difficulty falling asleep
3	Difficulty staying asleep
4	Restlessness of the arms or legs causing disruption of sleep
5	Fidgeting in bed
6	Distressing dreams at night
7	Distressing hallucinations at night
8	Having to get up at night to pass urine
9	Incontinence of urine because of an inability to move due to 'off' symptoms
10	Numbness or tingling of the arms or legs causing waking during the night
11	Painful muscle cramps in the arms or legs whilst sleeping
12	Waking early in the morning with painful posturing of the arms or legs
13	Tremor on waking
14	Feeling tired or sleepy after waking in the morning
15	Unexpectedly falling asleep during the day

Chaudhuri et al
J Neurol Neurosurg Psychiatry 2002;73:629

Factors underlying sleep impairment in PD

Depression, anxiety (nightmares)

(Drenching) sweating

Pain (dystonia, rigidity)

Akinesia, tremor, various sensations

Polyuria

Restless legs, periodic limb movements in sleep

REM-sleep behavior disorder, hallucinations

Medication

Innsbruck REM-Sleep Behavior Disorder (RBD) Questionnaire

Frauscher 2012

1. **Dream contents: violence and aggression**
2. **Vocalisations during sleep (outcries, curses, …)**
3. **Extensive movements during sleep**
4. **Injuries during sleep (oneself, partner)**
5. **Coincidence of sleep and behavior**

Index Nr. of positive answers : nr. of questions answered

? 0.25 indicates RBD Sens. 0.91, Spec. 0.86

Daytime sleepiness, sleep attacks

(Fatigue)

Reduction of dopamine agonists, caffeine, modafinil

Information!

Detrusor hyperactivity, frequency, urge incontinence

Urological examination!

Therapies: Tolterodine, Oxybutinin, Trospium Chloride, fluid restriction, desmopressine,

? STN, levodopa, apomorphine, botulinum toxine (plus catheterism)

Sexual (erectile) dysfunction

Sildenafil Seppi 2011, Horstink 2006

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