MedizincampusTrier

der JG|U UNIVERSITÄTSmedizin. MAINZ

Nicht nur Motorik:

Kognitive Störungen, Depression, Schlafstörungen und Halluzinationen bei Parkinson

Prof. Dr. Matthias Maschke

Brüderkrankenhaus Trier

Interessenskonflikte in den letzten 12 mth

- **Honorare für Vorträge und Advisory Boards sowie Unterstützung für Fortbildungen von**
  - Allergan, Amicus, Bayer, Biogen, Eisai, Daichii Sankyo, Merck, Novartis, Pfizer, Roche, Sanofi, TEVA, USB
- **Teilnahme an Phase III Studien**
  - Daichii, Roche, Novartis
- **Mitglied oder Vorstandsmitglied**
  - Leitlinienkommission DGN, DGNANI, ALNK, DGN, DGKN, AAN, EAN

Fallbeispiel

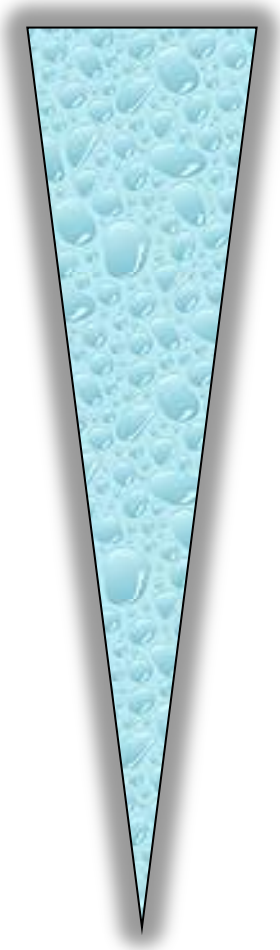
- 76J, männlich
- Aufnahme wegen Halluzinationen, Stürzen, Aggressivität, AZ Minderung
- Vorbekannt:
  - Idiopathischem **Morbus Parkinson** im Stadium IV
  - Charcot-Arthropathie des rechten Fußes
  - CVRF: Arterieller Hypertonus
  - Zustand nach **Stenting der Arteria carotis interna** rechts 2005
  - Chronische sensomotorische Polyneuropathie
  - Diagnosen auf anderem Fachgebiet:
    - Seropositive, CCP- Antikörper positive **rheumatoide Arthritis**
    - aktuell Therapie mit Methotrexat und Prednison
    - **Chronische Niereninsuffizenz**
    - Schwergradige Osteoporose

Fallbeispiel - Medikamentenliste

Clopidogrel 75 mg	0 - 1 - 0
Torasemid 10 mg	1- 0 -0
Citalopram 10 mg	1 - 0 - 0
Kalinor Brausetabletten	0 - 1 - 0
Gabapentin 100 mg	- 1 - 1
Pramipexol 1,05 mg	- 0 - 0
L-Dopa+Carbidopa 100/25 mg	- 0 - 0 - 1
Prednisolon 5 mg (z.B. Decor	1 -0 - 0
L-Dopa+Carb+Entacapon 100/50/200 mg	7 Uhr - 11 Uhr - 17 Uhr - 22
Pantoprazol 40 mg	0 - 0 - 1
Midodrin 2,5 mg	1 - 1 - 1
Methotrexat 7,5 mg	1 x Woche (dienstags) s.c.
Ibandronsäure 3 mg	alle 3 Monate i.v.
Neu: Oxybutynin 5 mg	½-½-½

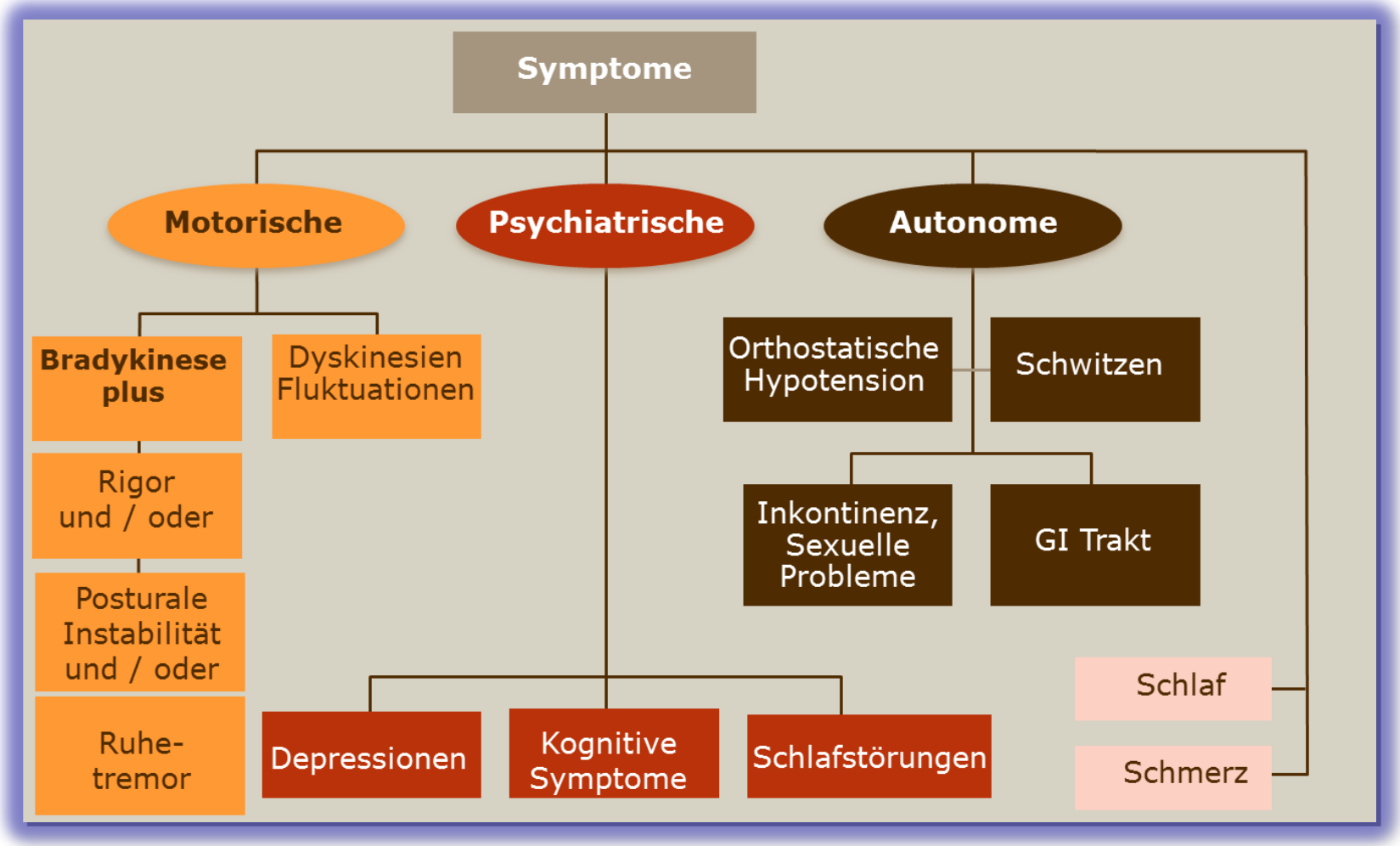
Was belastet Parkinsonpatienten nach >6 Jahren Erkrankungsdauer

- Fluktuationen der Medikamentenwirkung
- **Stimmung**
- Hypersalivation
- **Schlaf**
- Tremor
- Schmerzen
- Obstipation, Inkontinenz
- Stürze
- Appetitlosigkeit, Gewicht



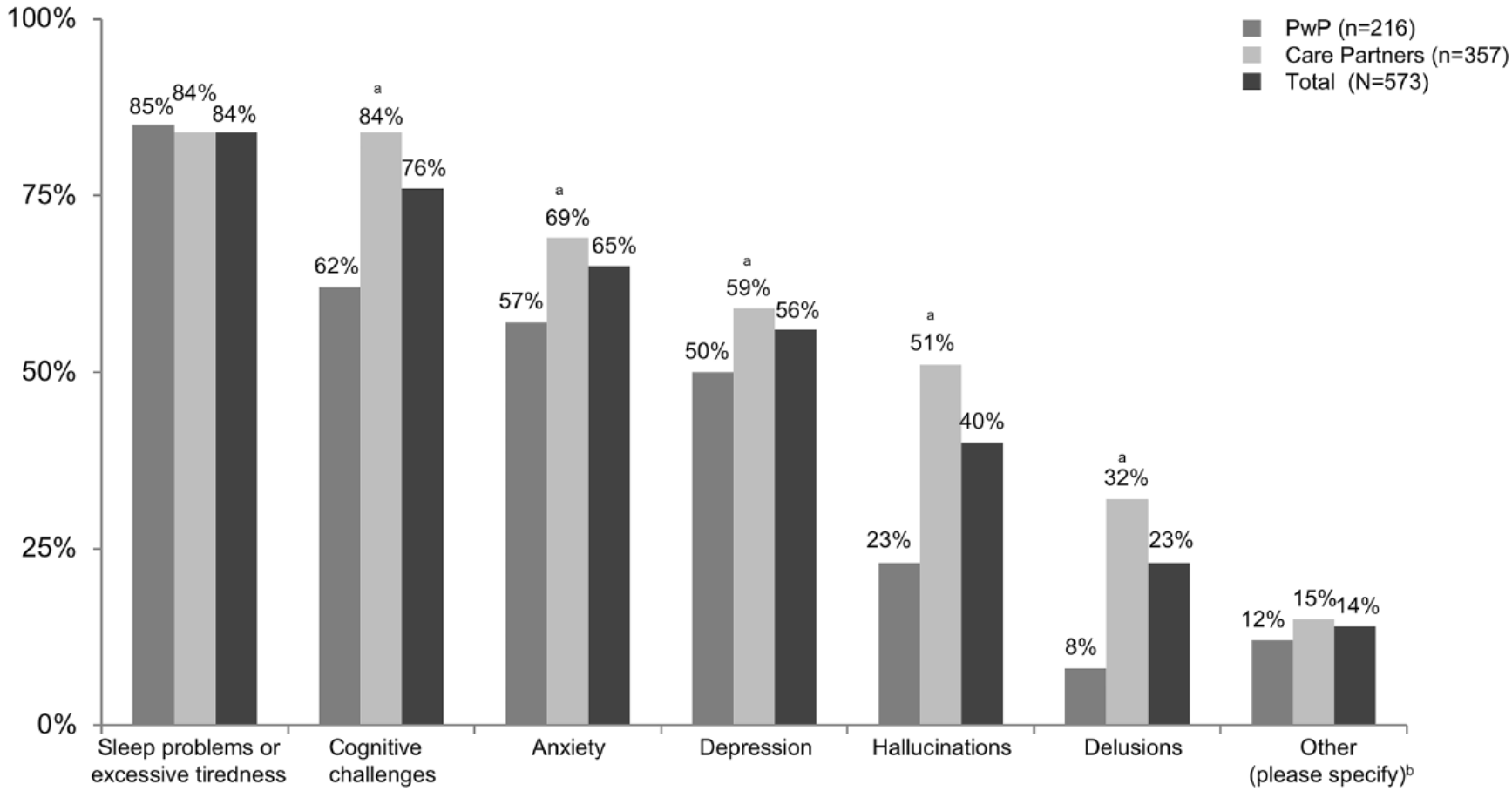
Nach Politis et al. 2010

Nicht motorische Symptome bei Parkinson



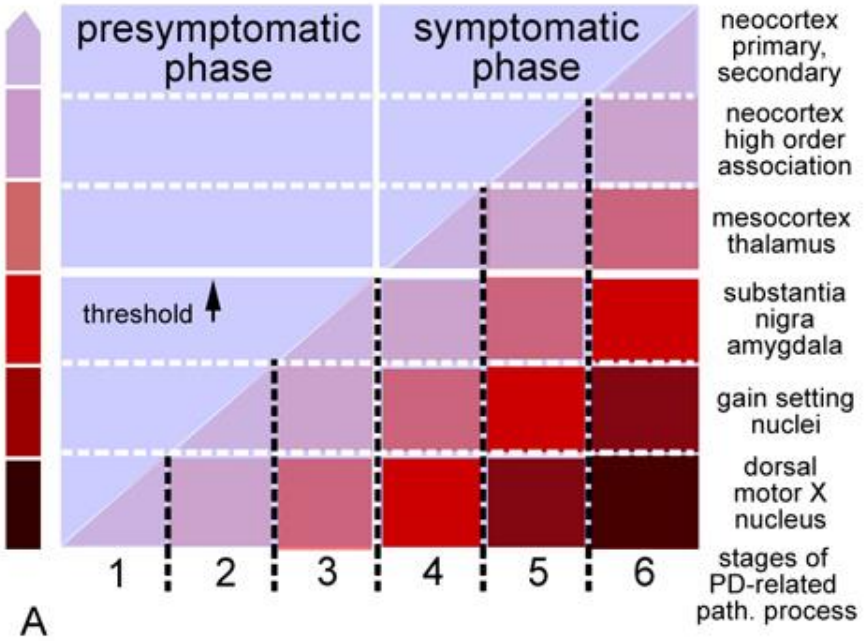
Shulman et al. Mov Dis 2001; Martinez-Martin et al. Mov Dis 2011; DGN Leitlinien 2016

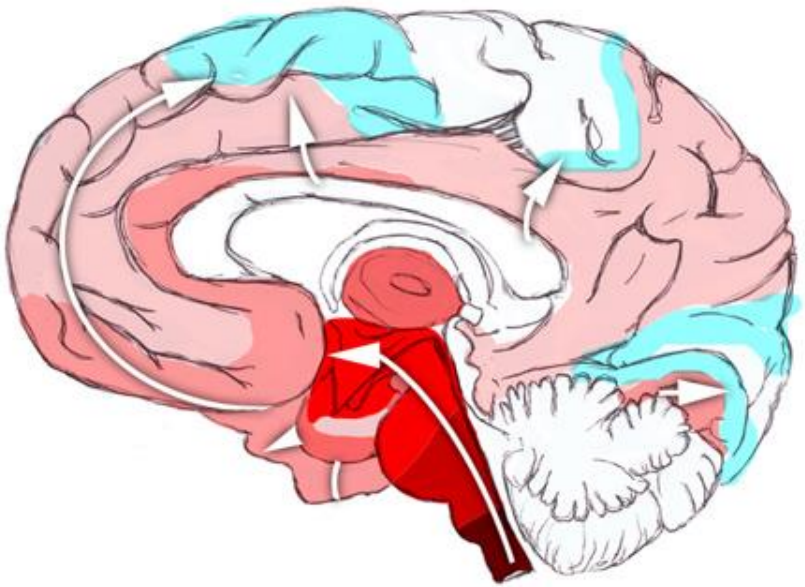
Einfluß der psychischen Symptome auf Lebensqualität



Hermanowicz et al. Neuropsychiatr Dis Treatment 2019

Warum treten nicht-motorische Symptome auf?





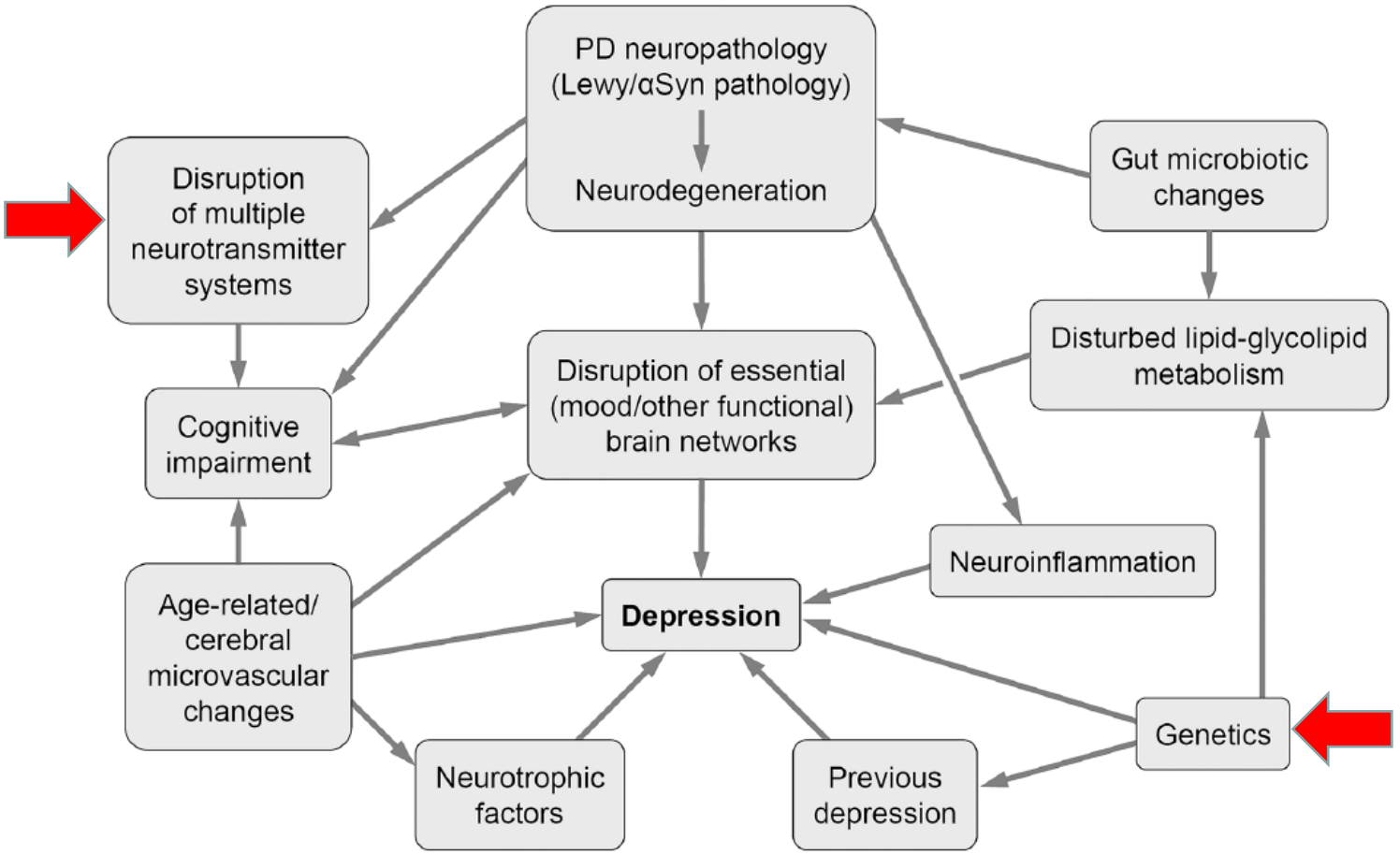
Braak et al. Cell Tissue Res 2004

Depression

Depression und Parkinson

- **40%** der Patient*innen (je nach Studie 10-90%)
- Kann zu **jedem Zeitpunkt** der Erkrankung auftreten
- Teilweise schon **vor Beginn** der motorischen Symptome
- Häufig **nicht diagnostiziert**
  - Ähnlichkeit zu motorischen Symptomen (Antriebsminderung)
  - Vermeintliche Nebenwirkungen von Medikamenten
  - Patient*in berichtet ungern über Symptome
  - Fehlende Krankheitswahrnehmung

Depression und Parkinson: Faktoren

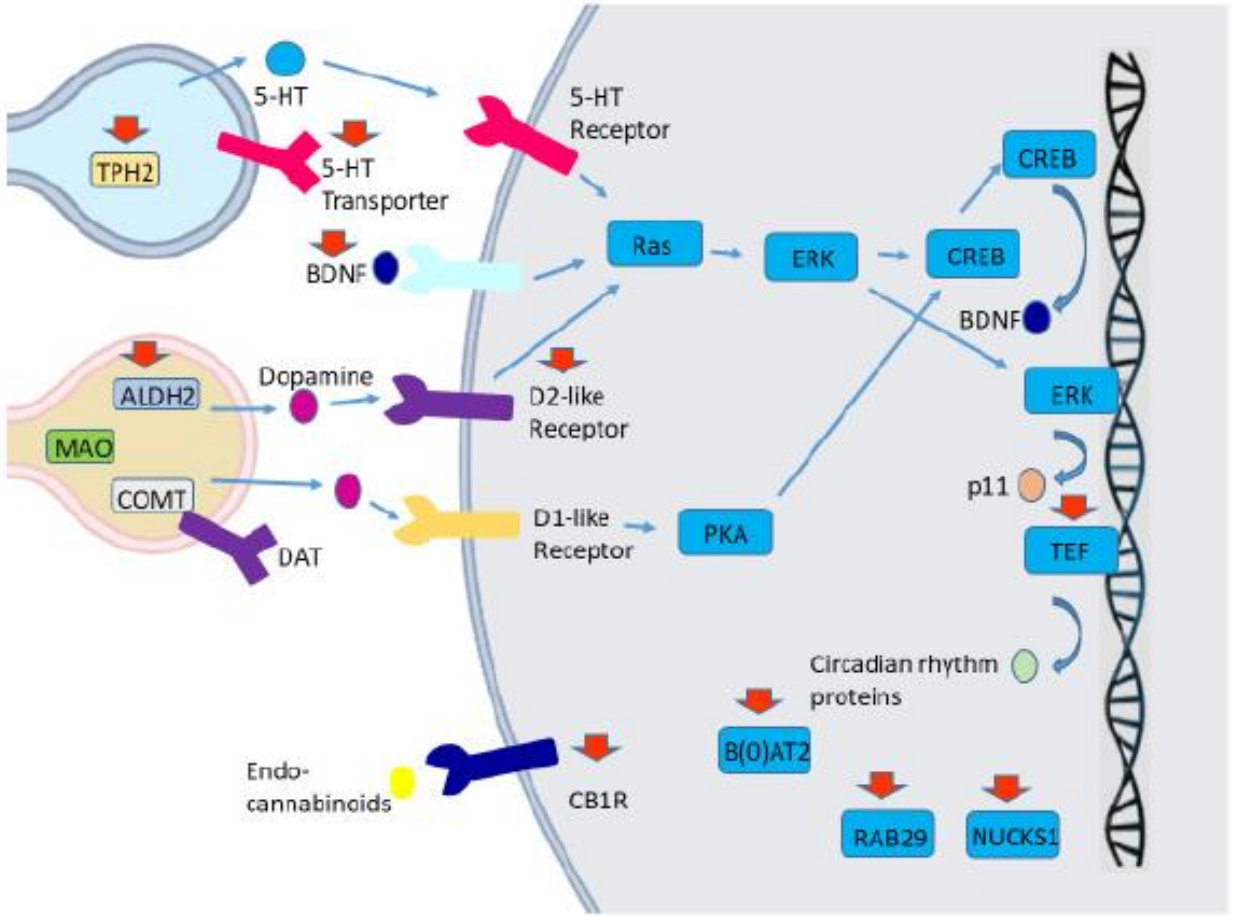


Jellinger. J Neural Transmission 2022

Depression und Parkinson: Pathologie

- Verlust von **Dopamin** v.a. im Nucleus caudatus ist mit Depression assoziiert
- Andere **Neurotransmitter**, die wichtig sind:
  - **Serotonin**
    - Degeneration in den Raphe Kernen
    - Assoziiert mit depressiven Symptomen
  - **Noradrenalin**
    - Degeneration des Locus coeruleus bereits früh bei M. Parkinson
    - Verlust von 70% noradrenerger Stimulation über die Zeit

Depression und Parkinson: Genetik



Jellinger. J Neural Transmission 2022; Angelopoulou et al. Medicina 2023

Depression und Parkinson: Symptome

- **Dysphorie** (niedergedrückte Stimmung)
- Erhöhte **Reizbarkeit**
- **Pessimismus** in Bezug auf Zukunft
- **Müdigkeit**, Energieverlust
- Antriebsmangel
- Lustlosigkeit
- **Appetitminderung**
- **Schlafstörungen** mit frühem Erwachen

Assogna et al. Curr Neuropharmacol 2020

Depression und Parkinson: Therapie

MDS COMMISSIONED REVIEW

CME

Update on Treatments for Nonmotor Symptoms of Parkinson's Disease—An Evidence-Based Medicine Review

Klaus Seppi, MD,[1*] K. Ray Chaudhuri, MD,[2] Miguel Coelho, MD,[3] Susan H. Fox, MRCP (UK), PhD,[4] Regina Katzenschlager, MD,[5] Santiago Perez Lloret, MD,[6] Daniel Weintraub, MD,[7,8] Cristina Sampaio, MD, PhD,[9,10] and the collaborators of the Parkinson's Disease Update on Non-Motor Symptoms Study Group on behalf of the Movement Disorders Society Evidence-Based Medicine Committee

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[4]*Edmond J Safra Program in Parkinson Disease, Movement Disorder Clinic, Toronto Western Hospital, and the University of Toronto Department of Medicine, Toronto, Ontario, Canada*
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Seppi et al. Mov Dis 2019

Depression und Parkinson: Therapie

Drug class/ intervention strategy	Drug/intervention	Efficacy	Safety	Practice implications
Dopamine Agonists	Pramipexole	Efficacious	Acceptable risk without specialized monitoring	Clinically useful
	Pergolide	Insufficient evidence	Acceptable risk with specialized monitoring	Not useful
	Rotigotine	*Unlikely efficacious*	*Acceptable risk without specialized monitoring*	*Investigational*
Monoamine oxidase B (MAO-B) inhibitors	**Rasagiline**	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
	Selegeline	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
	Moclobemide	Insufficient evidence	Acceptable risk with specialized monitoring[a]	Investigational
Tricyclic antidepressants	Nortriptyline	Likely efficacious	Acceptable risk without specialized monitoring[b]	Possibly useful
	Desipramine	Likely efficacious	Acceptable risk without specialized monitoring[b]	Possibly useful
	Amitriptyline	Insufficient evidence	Acceptable risk without specialized monitoring[b]	*Possibly useful*[c]
Selective serotonin reuptake inhibitors/selective serotonin norepinephrine reuptake inhibitors	Citalopram	Insufficient evidence	Acceptable risk without specialized monitoring[e]	*Possibly useful*[d]
	Sertraline	Insufficient evidence	Acceptable risk without specialized monitoring[e]	*Possibly useful*[d]
	Paroxetine	insufficient evidence	Acceptable risk without specialized monitoring[e]	*Possibly useful*[d]
	Fluoxetine	Insufficient evidence	Acceptable risk without specialized monitoring[e]	*Possibly useful*[c]
	Venlafaxine	*Efficacious*	*Acceptable risk without specialized monitoring*[e]	*Clinically useful*
Other antidepressants	Atomoxetine	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
	Nefazodone	Insufficient evidence	Unacceptable risk	Not useful
Alternative therapies	'Ω-3 fatty acids	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Nonpharmacological interventions	**rTMS**	*Insufficient evidence*	*Acceptable risk without specialized monitoring*[f]	*Possibly useful (short term)*
	CBT	*Likely efficacious*	*Insufficient evidence*[g]	*Possibly useful*

Seppi et al. Mov Dis 2019

Depression und Parkinson: Therapie

Schritt 1: Dopaminagonist wie **Pramipexol** oder MAO-B Inhibitor (**Rasagilin**) dazu geben

Schritt 2: Serotonin- oder Serotonin-Noradrenalin Reuptake Inhibitoren wie **Venlafaxin, Sertralin** oder **Paroxetin** dazu geben

Schritt 3: Kognitive Verhaltenstherapie oder Gesprächstherapie

Schritt 4: repetitive transkranielle Magnetstimulation

Seppi et al. Mov Dis 2019

Depr

Venlafaxin 37,5 mg 1-0-0,
langsam erhöhen bis auf 150 mg retard 1-0-0
(Höchstdosis 225 mg)
Paroxetin 10 mg 1-0-0,
erhöhen bis auf 20 mg 1-0-0
(Höchstdosis 40 mg)

Sertralin 25 mg 1-0-0, erhöhen bis auf 100 mg 1-0-0 (bei älteren Menschen und kognitiven Störungen nicht empfohlen)

Cave: nicht mit MAO Inhibitoren kombinieren

Seppi et al. Mov Dis 2019

Kognitive Verhaltenstherapie: auch telefonisch möglich?

ARTICLE OPEN ACCESS CLASS OF EVIDENCE

Telephone-based cognitive behavioral therapy for depression in Parkinson disease

A randomized controlled trial

Roseanne D. Dobkin, PhD, Sarah L. Mann, PhD, Michael A. Gara, PhD, Alejandro Interian, PhD, Kailyn M. Rodriguez, BA, and Matthew Menza, MD

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Neurology® 2020;94:e1764-1773. doi:10.1212/WNL.0000000000009292

Abstract

Objective
To determine whether, for patients with depression and Parkinson disease (PD), telephone-based cognitive-behavioral treatment (T-CBT) alleviates depressive symptoms significantly more than treatment as usual (TAU), we conducted a randomized controlled trial to evaluate the efficacy of a 10-session T-CBT intervention for depression in PD, compared to TAU.

Methods
Seventy-two people with PD (PWP) were randomized to T-CBT + TAU or TAU only. T-CBT tailored to PWPs' unique needs was provided weekly for 3 months, then monthly during 6-month follow-up. CBT targeted negative thoughts (e.g., "I have no control"; "I am helpless") and behaviors (e.g., social withdrawal, excessive worry). It also trained care partners to help PWP practice healthy habits. Blind raters assessed outcomes at baseline, midtreatment, treatment end, and 1 and 6 months post-treatment. Analyses were intent to treat.

Results
T-CBT outperformed TAU on all depression, anxiety, and quality of life measures. The primary outcome (Hamilton Depression Rating Scale score) improved significantly in T-CBT compared to TAU by treatment end. Mean improvement from baseline was 6.53 points for T-CBT and −0.27 points for TAU ($p < 0.0001$); gains persisted over 6-month follow-up ($p < 0.0001$). Improvements were moderated by a reduction in negative thoughts in the T-CBT group only, reflecting treatment target engagement.

Conclusions
T-CBT may be an effective depression intervention that addresses a significant unmet PD treatment need and bypasses access barriers to multidisciplinary, evidence-based care.

RELATED ARTICLE
Editorial
A call for better depression treatment in people with Parkinson disease
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Criteria for rating therapeutic and diagnostic studies
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- N=72
- Kognitive Verhaltenstherapie über Telefon 1 Stunde wöchentlich für 10 Wochen, danach 1xmonatlich für 6 Monate vs. übliche Therapie

	Total (n = 72)	CBT (n = 37)	TAU (n = 35)	*p* Value
Sex				NS
Male	35 (48.61)	17 (23.61)	18 (25.00)	
Female	37 (51.39)	20 (27.78)	17 (23.61)	
Age, y	65.22 ± 9.63	65.62 ± 9.76	64.80 ± 9.62	NS
Age at PD onset, y	59.49 ± 11.08	59.62 ± 11.57)	59.34 ± 10.70	NS
Education, y				NS
High school diploma/some college	23 (31.94)	11 (15.28)	12 (16.66)	
College degree	26 (36.11)	14 (19.44)	12 (16.67)	
Graduate degree	23 (31.95)	12 (16.67)	11 (15.28)	
PD duration, y	6.33 ± 6.34	6.95 ± 7.82	5.65 ± 4.20	NS
Depression duration, y	2.87 ± 1.03	3.10 ± 1.15	2.62 ± 0.83	NS

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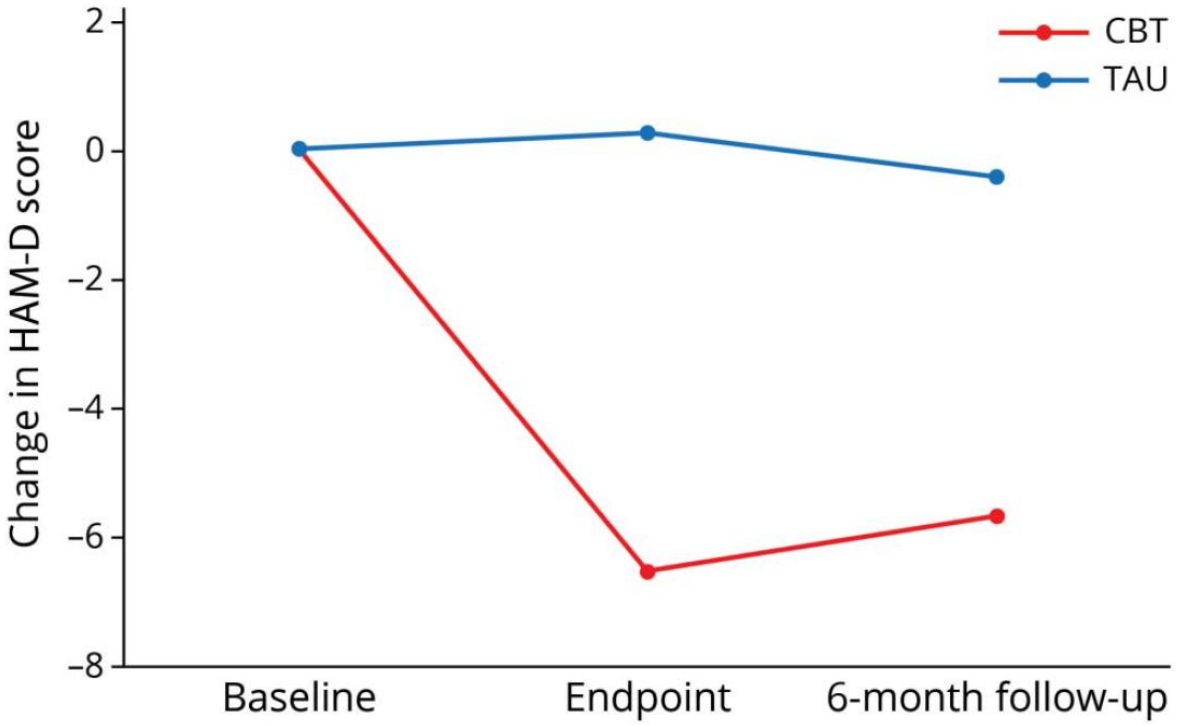
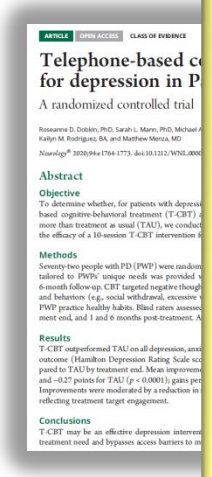


Kognitive Verhaltenstherapie: auch telefonisch möglich?


ARTICLE OPEN ACCESS CLASS OF EVIDENCE

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Abstract

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Gesprächstherapie oder Verhaltenstherapie in Präsenz sinnvoll, Wartezeiten lang

Online Hilfen, die sinnvoll sind:
https://www.deutsche-depressionshilfe.de/depression-infos-und-hilfe/wo-finde-ich-hilfe/selbstmanagement

z.B. **iFightDepression**

Schlafstörungen

Ursachen für Schlafstörungen

- 79% **Nykturie**
- 65% Schwierigkeiten sich **umzudrehen**
- 55% schmerzhafte **Krämpfe**
- 48% lebhafte Träume / **Alpträume**
- 34% **Dystonien**
- 34% **Rückenschmerzen**
- 33% Beinzuckungen
- 17% **visuelle Halluzinationen**

Lees et al. 1988; LL DGN 2016

Krankenhaus der Barmherzigen Brüder Trier

MedizincampusTrier der JGU UNIVERSITÄTSmedizin. MAINZ

Schlaf: der „Hausmeister“ des Gehirn

Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie,[1*] Hongyi Kang,[1*] Qiwu Xu,[1] Michael J. Chen,[1] Yonghong Liao,[1] Meenakshisundaram Thiyagarajan,[1] John O'Donnell,[1] Daniel J. Christensen,[1] Charles Nicholson,[2] Jeffrey J. Iliff,[1] Takahiro Takano,[1] Rashid Deane,[1] Maiken Nedergaard[1]†

The conservation of sleep across all animal species suggests that sleep serves a vital function. We here report that sleep has a critical function in ensuring metabolic homeostasis. Using real-time assessments of tetramethylammonium diffusion and two-photon imaging in live mice, we show that natural sleep or anesthesia are associated with a 60% increase in the interstitial space, resulting in a striking increase in convective exchange of cerebrospinal fluid with interstitial fluid. In turn, convective fluxes of interstitial fluid increased the rate of β-amyloid clearance during sleep. Thus, the restorative function of sleep may be a consequence of the enhanced removal of potentially neurotoxic waste products that accumulate in the awake central nervous system.

Despite decades of effort, one of the greatest mysteries in biology is why sleep is restorative and, conversely, why lack of sleep impairs brain function (*1*, *2*). Sleep deprivation reduces learning, impairs performance in cognitive tests, prolongs reaction time, and is a common cause of seizures (*3*, *4*). In the most extreme case, continuous sleep deprivation kills rodents and flies within a period of days to weeks (*5*, *6*). In humans, fatal familial or sporadic insomnia is a progressively worsening state of sleeplessness that leads to dementia and death within months or years (*7*).

Proteins linked to neurodegenerative diseases, including β-amyloid (Aβ) (*8*), α-synuclein (*9*), and tau (*10*), are present in the interstitial space surrounding cells of the brain. In peripheral tissue, lymph vessels return excess interstitial proteins to the general circulation for degradation in the liver (*11*). Yet despite its high metabolic rate and the fragility of neurons to toxic waste products, the brain lacks a conventional lymphatic system. Instead, cerebrospinal fluid (CSF) recirculates through the brain, interchanging with interstitial fluid (ISF) and removing interstitial proteins, including Aβ (*12*, *13*). The convective exchange of CSF and ISF is organized around the cerebral vasculature, with CSF influx around arteries, whereas ISF exits along veins. These pathways were named the glymphatic system on the basis of their dependence on astrocytic aquaporin-4 (AQP4) water channels and the adoption of functions homologous to peripheral lymphatic removal of interstitial metabolic byproducts (*14*). Deletion of AQP4 channels reduces clearance of exogenous Aβ by 65%, suggesting that convective movement of ISF is a substantial contributor to the removal of interstitial waste products and other products of cellular activity (*12*). The interstitial concentration of Aβ is higher in awake than in sleeping rodents and humans, possibly indicating that wakefulness is associated with increased Aβ production (*15*, *16*). We tested the alternative hypothesis that Aβ clearance is increased during sleep and that the sleep-wake cycle regulates glymphatic clearance.

We used in vivo two-photon imaging to compare CSF influx into the cortex of awake, anesthetized, and sleeping mice. The fluorescent tracers were infused into the subarachnoid CSF via a cannula implanted in the cisterna magna for real-time assessment of CSF tracer movement. Electrocorticography (ECoG) and electromyography (EMG) were recorded in order to continuously monitor the state of brain activity (Fig. 1A and fig. S1). In initial experiments, the volume and rate of tracer infusion were adjusted so as to avoid changes in behavior state or ECoG (fig. S1). Because mice sleep much of the day, a small molecular weight tracer, fluorescein isothiocyanate (FITC)–dextran (3 kD) in aCSF, was infused at midday (12 to 2 p.m.) via the cannula implanted in the cisterna magna. In sleeping mice, a robust influx of the fluorescent CSF tracer was noted along periarterial spaces, in the subpial regions, and in the brain parenchyma similar to previous findings in anesthetized mice (Fig. 1, B and C, and fig. S2) (*12*). ECoG power spectrum analysis depicted a relatively high power of slow waves that is consistent with sleep (Fig. 1D). CSF tracer infusion (Texas red-dextran, 3 kD) was repeated in the same mouse after it was awakened through gentle handling of its tail. Unexpectedly, arousal sharply reduced tracer influx compared with that of the sleeping state. Periarterial and parenchymal tracer influx was reduced by ~95% in awake as compared with sleeping mice during the 30-min imaging session (Fig. 1, B and C, and fig. S2). ECoG showed a reduction in the relative prevalence of slow (delta) waves concomitant with a significant increase in the power of fast activity, confirming that the animals were awake ($n = 6$ mice, $P < 0.05$, paired t test) (Fig. 1D). To investigate whether the state of brain activity indeed controlled CSF influx, we repeated the experiments in a new cohort of mice in which all experiments were performed when the animals were awake (8 to 10 p.m.). Because mice normally do not sleep at this time of day, we first evaluated CSF tracer influx in the awake state by means of intracisternal infusion of FITC-dextran. CSF tracer influx into the brain was largely absent and only slowly gained access to the superficial cortical layers (Fig. 1, E and F, and fig. S2). After 30 min imaging of CSF tracer in the awake state, the animals were anesthetized with intraperitoneal administration of ketamine/xylazine (KX). Texas red-dextran was administered 15 min later, when a stable increase in slow wave activity was noted (Fig. 1, E and F). Texas red-dextran rapidly flushed in along periarterial spaces and entered the brain parenchyma at a rate comparable with that of naturally sleeping mice (Fig. 1, B and E). Ketamine/xylazine anesthesia significantly increased influx of CSF tracer in all mice analyzed [$n = 6$ mice, $P < 0.05$, two-way analysis of variance (ANOVA) with Bonferroni test], which was concomitant with a significant increase in the power of slow wave activity ($n = 6$ mice, $P < 0.05$, paired t test) (Fig. 1, G and F). Thus, glymphatic CSF influx is sharply suppressed in conscious alert mice as compared with naturally sleeping or anesthetized littermates.

Influx of CSF is in part driven by arterial pulse waves that propel the movement of CSF inward along periarterial spaces (*12*). It is unlikely that diurnal fluctuations in arterial pulsation are responsible for the marked suppression of convective CSF fluxes during wakefulness because arterial blood pressure is higher during physical activity. An alternative possibility is that the awake brain state is linked to a reduction in the volume of the interstitial space because a constricted interstitial space would increase resistance to convective fluid movement and suppress CSF influx. To assess the volume and tortuosity of the interstitial space in awake versus sleeping mice, we used the real-time iontophoretic tetramethylammonium (TMA) method in head-fixed mice (Fig. 2A and fig. S3) (*17*, *18*). TMA recordings in cortex of sleeping mice collected at midday (12 to 2 p.m.) confirmed that the interstitial space volume fraction (α) averaged 23.4 ± 1.9% ($n = 6$ mice) (*19*). However, the interstitial volume fraction was only 14.1 ± 1.8% in awake mice recorded at 8 to 10 p.m. ($n = 4$ mice, $P < 0.01$, t test) (Fig. 2B). Analysis of cortical ECoG recorded by the TMA reference electrode confirmed that the power of slow wave activity was higher in sleeping than in awake mice, which is concurrent with a lower power of high-frequency activity (Fig. 2C).

To further validate that the volume of the interstitial space differed in awake versus sleeping mice, we also obtained TMA recordings in awake mice in the late evening (8 to 10 p.m.) and repeated the recordings in the same mice after administration of ketamine/xylazine. This approach,

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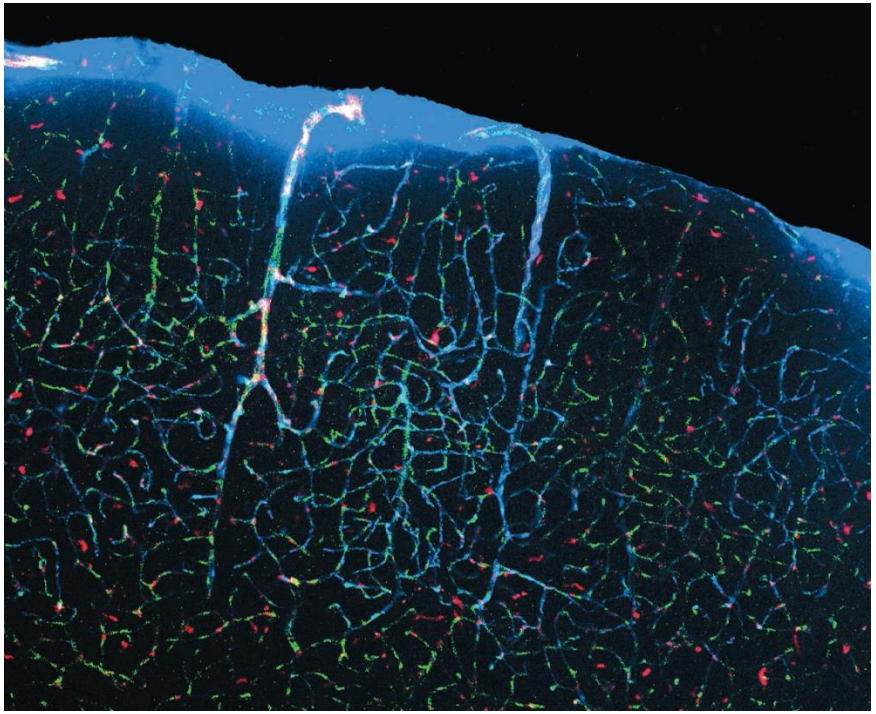

- Xie et al. Science 2013

Paroxysmales komplexes nächtliches Verhalten bei Parkinson

- **REM Schlaf Verhaltensstörung (87%):**
  - Komplexe Bewegungen während des REM Schlafes
  - Treten, Schlagen, Boxen
  - Kombiniert mit Vokalisationen oder auch mit verständlichem Sprechen
  - Zumeist im Kontext eines imaginären Kampfes während des REM Schlafes
- **Aufwachen aus dem NREM Schlaf** mit komplexen Bewegungen (13%)

- **Klinische Charakteristika:**
  - Männer > Frauen
  - Längere Krankheitsdauer
  - Mehr Levodopa
  - Höherer UPDRS III
  - Häufiger Halluzinationen

Manni et al. Mov Dis 2010; 2020

REM Schlafstörungen – Therapie

- **Modifikation Verhalten/Pharmaka:**
  - Kein Kaffee, Alkohol zur Nacht
  - Keine späten Mahlzeiten
- wenig randomisierte Studien
- **Fallsammlungen:**
  - **Clonazepam** in 89% wirksam (N=57)
- **Randomisierte Studien:**
  - **Memantine 20 mg:** signifikant weniger Aktivität während des Schlafes
  - **Melatonin 3 mg:** weniger REM Störungen

Kunz et al. J Sleep Res 2010; LL DGN 2016; Seppi et al. Mov Dis 2019

LL Empfehlungen zur Therapie der Schlafstörung

Empfehlung 84:
Die nächtliche Akinese und frühmorgendliche Dystonie sollte mit transdermalem Rotigotin oder retardiertem Ropinirol behandelt werden.

(1+)

Empfehlung 85:
Die Therapie der Insomnie mit Durchschlafstörung sollte mit Zopiclon versucht werden.

B (1+)

Hypnotics	Eszopiclone	Insufficient evidence	Acceptable risk without specialized monitoring[1]	*Possibly useful*[a]
Melatonin	3-5 mg	Insufficient evidence	Acceptable risk without specialized monitoring	*Possibly useful*[b]
	50 mg	Insufficient evidence	Insufficient evidence	Investigational
Nonpharmacological interventions	**Continuous positive airway pressure**[c]	*Likely efficacious*	*Acceptable risk without specialized monitoring*	*Possibly useful*

Kunz et al. J Sleep Res 2010; LL DGN 2016; Seppi et al. Mov Dis 2019

Rotigotin bei Schlaf (RECOVER Studie)

RESEARCH ARTICLE

Rotigotine Effects on Early Morning Motor Function and Sleep in Parkinson's Disease: A Double-Blind, Randomized, Placebo-Controlled Study (RECOVER)

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[14]Neurology Service, Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Hospital Clínic, IDIBAPS, Universitat de Barcelona, Spain
[15]Department of Neurology, Medical University Innsbruck, Innsbruck, Austria
[16]UCB Pharma GmbH, Monheim, Germany
[17]Schwarz Biosciences Inc, a member of the UCB Group, Raleigh, NC, USA
[18]NIHR Centre of Excellence, Kings College Hospital and University Hospital Lewisham, Kings College and Institute of Psychiatry, London, United Kingdom

ABSTRACT: In a multinational, double-blind, placebo-controlled trial (NCT00474058), 287 subjects with Parkinson's disease (PD) and unsatisfactory early-morning motor symptom control were randomized 2:1 to receive rotigotine (2–16 mg/24 hr [n = 190]) or placebo (n = 97). Treatment was titrated to optimal dose over 1–8 weeks with subsequent dose maintenance for 4 weeks. Early-morning motor function and nocturnal sleep disturbance were assessed as coprimary efficacy endpoints using the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (Motor Examination) measured in the early morning prior to any medication intake and the modified Parkinson's Disease Sleep Scale (PDSS-2) (mean change from baseline to end of maintenance [EOM], last observation carried forward). At EOM, mean UPDRS Part III score had decreased by −7.0 points with rotigotine from a baseline of 29.6 [standard deviation (SD) 12.3] and by −3.9 points with placebo (baseline 32.0 [13.3]). Mean PDSS-2 total score had decreased by −5.9 points with rotigotine (from a baseline of 19.3 [SD 9.3]) and by −1.9 points with placebo (baseline 20.5 [10.4]). This represented a significantly greater improvement with rotigotine compared with placebo on both the UPDRS Part III (treatment difference:

Additional Supporting Information may be found in the online version of this article.

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Relevant conflicts of interest: All investigators received grant payments from Schwarz Biosciences GmbH, a member of the UCB group of companies, for enrolling patients into the study.
Members of the "RECOVER Study Group" are listed as an Appendix.
Full financial disclosures and author roles may be found in the online version of this article.
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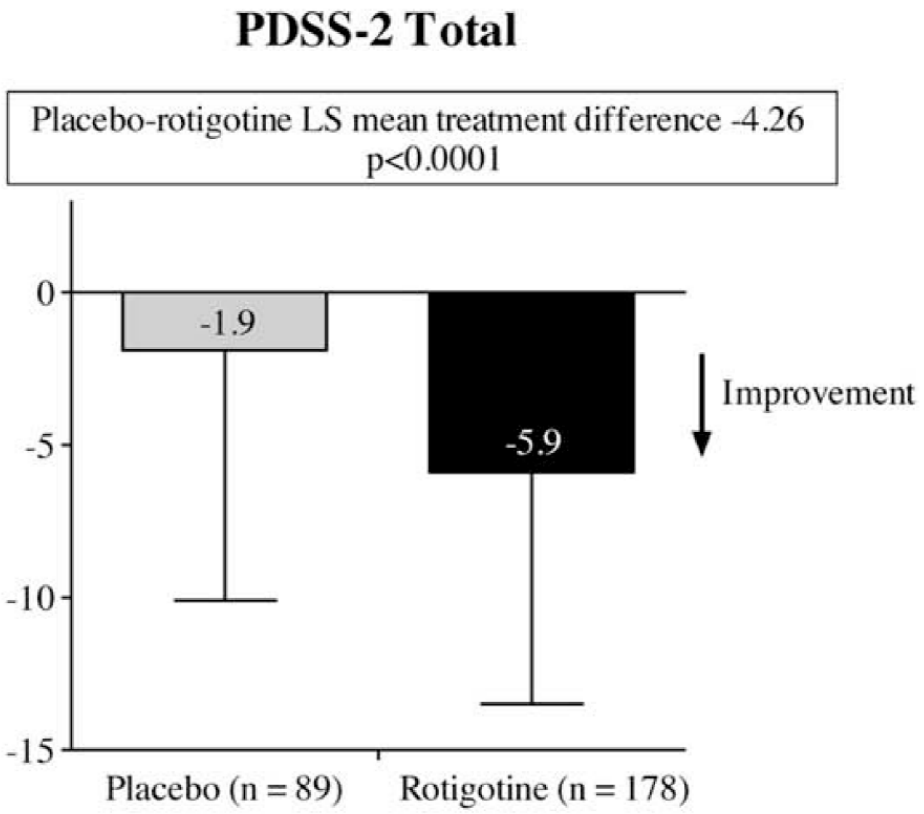
Published online 18 November 2010 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23441



Schlafstörungen und Parkinson: Therapie

Schritt 1: **Levodopa retard** z.N.

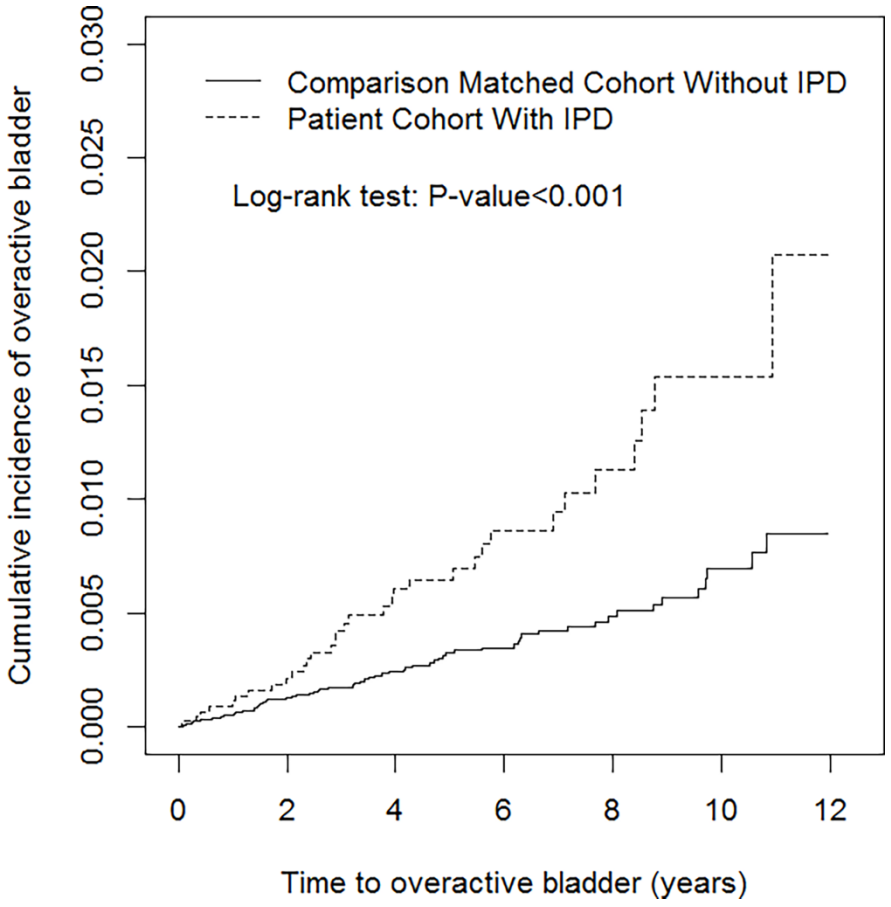
Schritt 2: retardiert Dopaminagonist wie **Ropinirol** oder **Pramipexol z.N.** oder **Rotigotin** dazu geben

Schritt 3: **Melatonin** 3 mg z.N., wenn nicht ausreichend wirksam **Zopiclon** 3.75-7.5 mg z.N.

Schritt 4: Schlaflabor zum Ausschluss **obstruktives Schlafapnoesyndrom**

Seppi et al. Mov Dis 2019

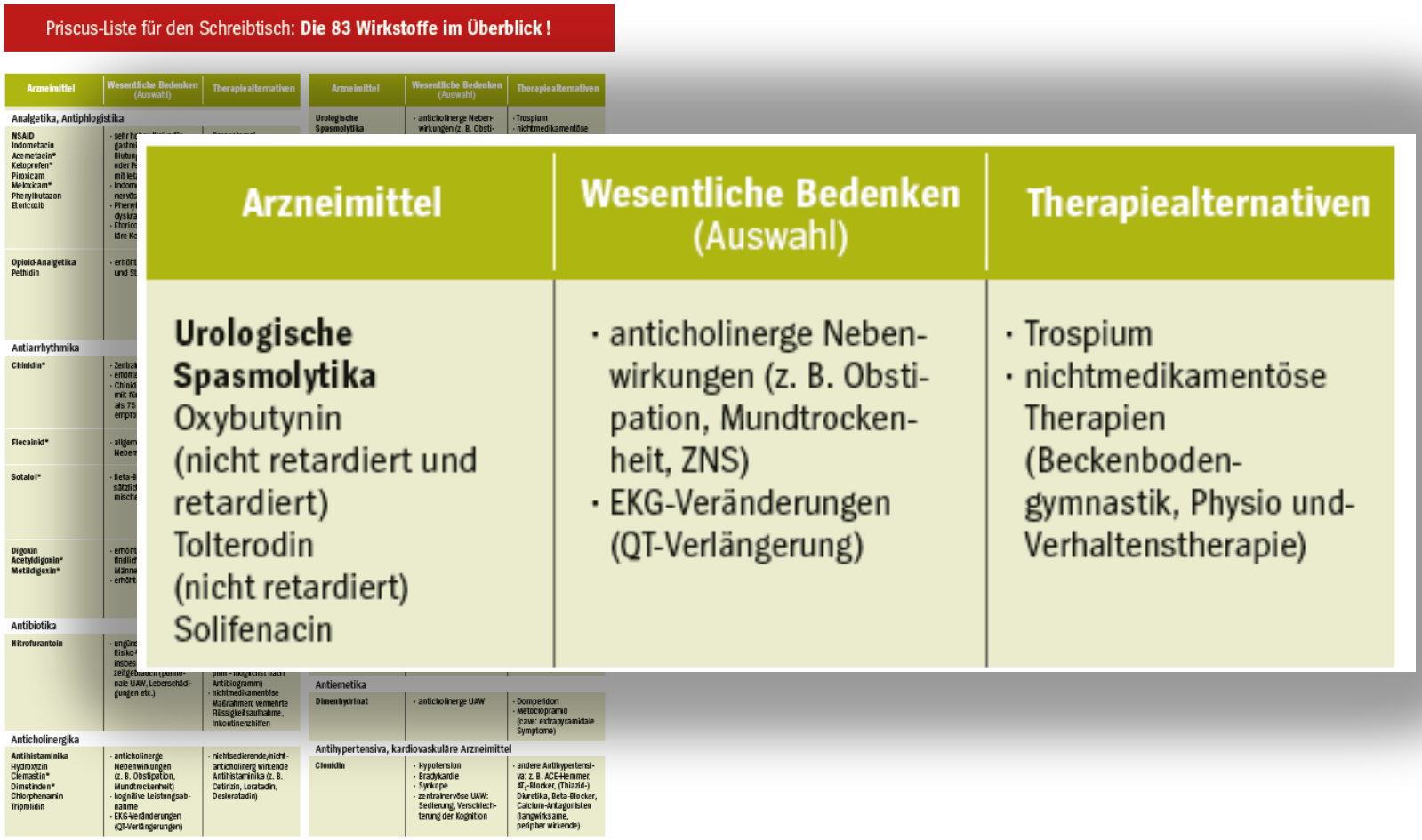
Blasenstörungen bei M. Parkinson: wie häufig ist das?



- 14.5 vs. 6.37 per 10,000 person-years
- OR 2.34

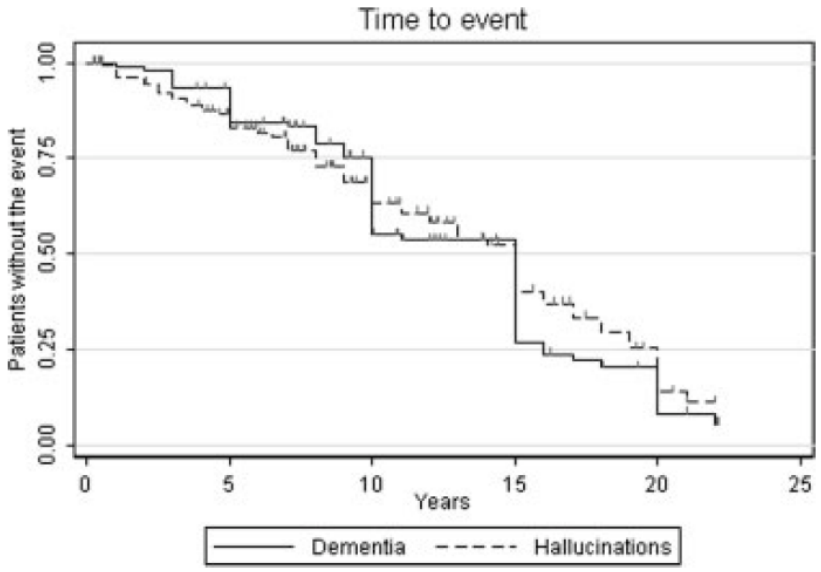
Lee et al. PLOS 2018

Problematische Medikamente: PRISCUS Liste (*www.priscus.net*)



Kognitive Störungen

Wie häufig sind kognitive Störungen im Verlauf?



- **Nach 20 Jahren**
  - 74% Halluzinationen
  - 83% Demenz
  - 50% Depression
- **DLB:** 71.5 Jahre
- **PDD:** 72.6 Jahre
- Medianer Follow-up bis Demenz diagnostiziert wurde: 11 Jahre

Hely et al. Mov Dis 2008

Welche kognitiven Störungen treten auf?

- Bereits bei frühen Stadien 20-30%, assoziiert mit Hyposmie und stärker reduziertem DATScan
- **Kognitive Defizite:**
  - **Exekutivfunktion**
  - Arbeitsgedächtnis
  - Merkfähigkeit
  - **Psychomotorische Geschwindigkeit**
  - Aufmerksamkeit
  - Visuoräumliche Fähigkeiten

Weintraub et al. Mov Dis 2017

Was sind Störungen der Exekutivfunktion?

- **kognitive Flexibilität:** Die Fähigkeit, Gedanken und Verhaltensweisen an neue Situationen anzupassen.
- **Inhibition:** Die Fähigkeit, impulsive und automatische Antworten zu kontrollieren.
- **Planung:** Die Fähigkeit, über zukünftige Ereignisse nachzudenken und den richtigen Weg vorherzusehen, um eine Aufgabe auszuführen
- **Entscheidungsfindung:** Die Fähigkeit, eine Option aus verschiedenen Alternativen zu wählen.
- **Problemlösung:** Die Fähigkeit, einen logischen Schluss zu ziehen, wenn über etwas Unbekanntes nachgedacht wird.

Was kann man machen?

Medikamentöse Therapie: Acetylcholinesterase-inhibitoren

Kognitives Training

Bewegungstraining

Ernährung
Soziale Aktivitäten
Therapie
Komorbiditäten

Medikamentöse Therapie: Rivastigmin

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivastigmine for Dementia Associated with Parkinson's Disease

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ABSTRACT

BACKGROUND

Cholinergic deficits are prominent in patients who have dementia associated with Parkinson's disease. We investigated the effects of the dual cholinesterase inhibitor rivastigmine in such patients.

METHODS

Patients in whom mild-to-moderate dementia developed at least 2 years after they received a clinical diagnosis of Parkinson's disease were randomly assigned to receive placebo or 3 to 12 mg of rivastigmine per day for 24 weeks. Primary efficacy variables were the scores for the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and Alzheimer's Disease Cooperative Study–Clinician's Global Impression of Change (ADCS-CGIC). Secondary clinical outcomes were the scores for the Alzheimer's Disease Cooperative Study–Activities of Daily Living, the 10-item Neuropsychiatric Inventory, the Mini–Mental State Examination, Cognitive Drug Research power of attention tests, the Verbal Fluency test, and the Ten Point Clock-Drawing test.

RESULTS

A total of 541 patients were enrolled, and 410 completed the study. The outcomes were better among patients treated with rivastigmine than among those who received placebo; however, the differences between these two groups were moderate and similar to those reported in trials of rivastigmine for Alzheimer's disease. Rivastigmine-treated patients had a mean improvement of 2.1 points in the score for the 70-point ADAS-cog, from a baseline score of 23.8, as compared with a 0.7-point worsening in the placebo group, from a baseline score of 24.3 (P<0.001). Clinically meaningful improvements in the scores for the ADCS-CGIC were observed in 19.8 percent of patients in the rivastigmine group and 14.5 percent of those in the placebo group, and clinically meaningful worsening was observed in 13.0 percent and 23.1 percent, respectively (mean score at 24 weeks, 3.8 and 4.3, respectively; P=0.007). Significantly better outcomes were seen with rivastigmine with respect to all secondary efficacy variables. The most frequent adverse events were nausea (affecting 29.0 percent of patients in the rivastigmine group and 11.2 percent of those in the placebo group, P<0.001), vomiting (16.6 and 1.7 percent, P<0.001), and tremor (10.2 and 3.9 percent, P=0.01).

CONCLUSIONS

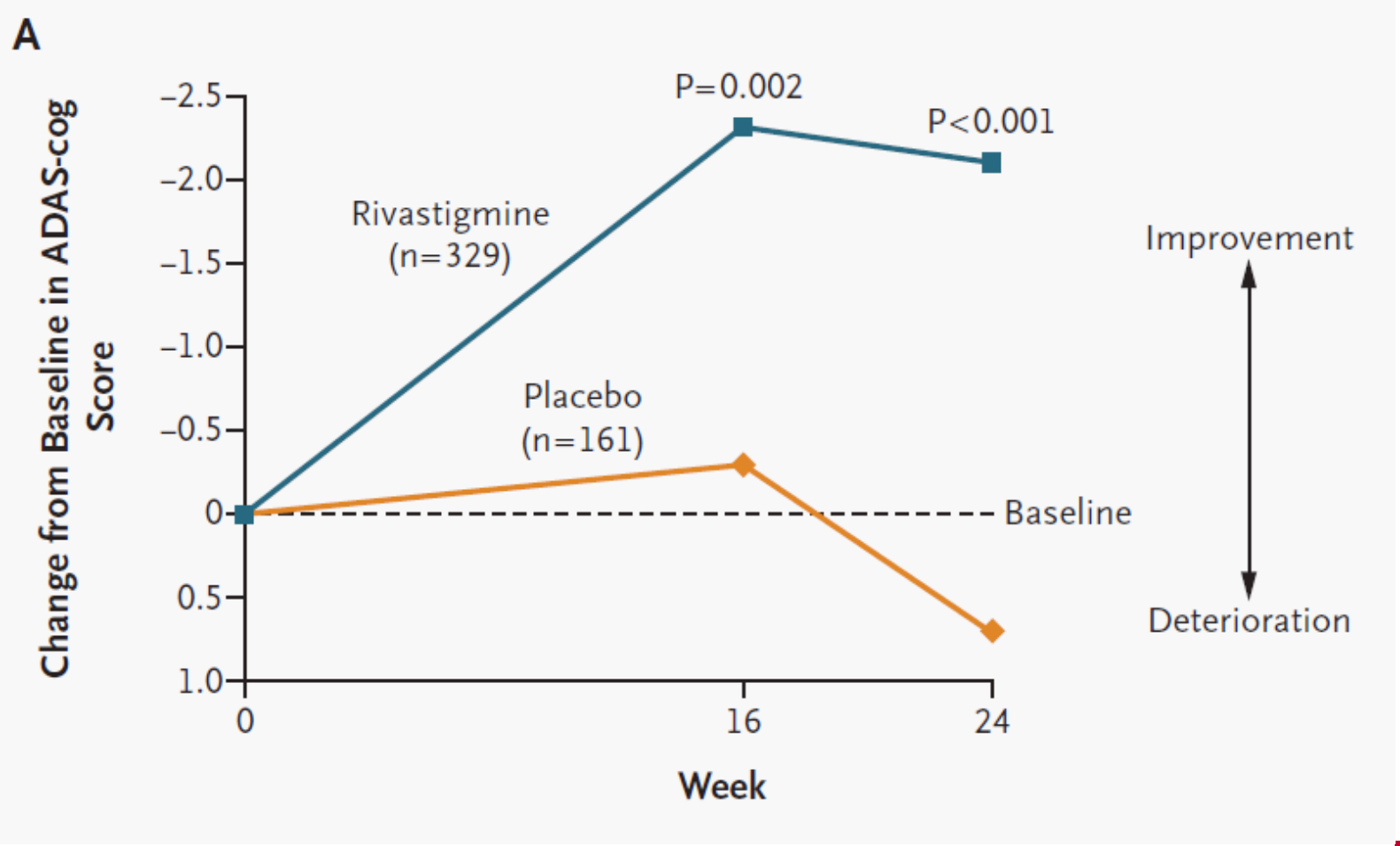
In this placebo-controlled study, rivastigmine was associated with moderate improvements in dementia associated with Parkinson's disease but also with higher rates of nausea, vomiting, and tremor.

From the Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey (M.E.); Rogaland Central Hospital, Stavanger, Norway (D.A.); the School of Medicine, University of Bergen, Bergen, Norway (D.A.); Istituto Nazionale Neurologico Carlo Besta and Università Cattolica, Milan, Italy (A.A.); the University of Manchester, Manchester, United Kingdom (E.J.B.); Christian-Albrechts-Universität Kiel, Kiel, Germany (G.D.); Middelheim Hospital, Zeikenhuis Netwerk Antwerpen, and the Born–Bunge Foundation, University of Antwerp, Wilrijk-Antwerp, Belgium (P.P.D.); Centre Hospitalier Universitaire Clermont-Ferrand, Clermont-Ferrand, France (F.D.); Sant Pau Hospital, Barcelona, Spain (J.K.); Groningen University Hospital, Groningen, the Netherlands (T.L.); the Reta Lila Weston Institute for Neurological Studies, University College London, London (A.L.); Innsbruck Medical University, Innsbruck, Austria (W.P.); Hôpital Maisonneuve-Rosemont, Montreal (A.R.); Hospital de Santa Maria, Lisbon, Portugal (M.M.R.); the Research Institute for Neurosciences, Vrije Universiteit Medical Center, Amsterdam (E.W.); Novartis Pharma, Basel, Switzerland (P.Q.); and Novartis Pharmaceuticals, East Hanover, N.J. (S.T., R.L.). Address reprint requests to Dr. Emre at Istanbul Tip Fakültesi, Nöroloji Anabilim Dali, 34390 Capa, Istanbul, Turkey, or at muratemre@superonline.com.

N Engl J Med 2004;351:2509-18.

- **Rivastigmin** vs. Plazebo 3-12 mg/d für 24 Wochen
- N=410
- Alter 72.8 Jahre +/- 6.7
- Milde bis moderate Parkinsondemenz
- MMSE 19.4 +/-3.8

Medikamentöse Therapie: Rivastigmin



Emre et al. NEJM 2004

Medikamentöse Therapie: Rivastigmin

Adverse Event	Rivastigmine Group (N=362)	Placebo Group (N=179)	P Value
	no. (%)		
Any	303 (83.7)	127 (70.9)	<0.001
Nausea	105 (29.0)	20 (11.2)	<0.001
Vomiting	60 (16.6)	3 (1.7)	<0.001
Tremor	37 (10.2)	7 (3.9)	0.01
Diarrhea	26 (7.2)	8 (4.5)	0.26
Anorexia	22 (6.1)	5 (2.8)	0.14
Falls	21 (5.8)	11 (6.1)	0.85
Dizziness	21 (5.8)	2 (1.1)	0.01
Hypotension	19 (5.2)	14 (7.8)	0.25
Constipation	17 (4.7)	12 (6.7)	0.32
Hallucinations	17 (4.7)	17 (9.5)	0.04
Confusion	13 (3.6)	10 (5.6)	0.36
Orthostatic hypotension	6 (1.7)	9 (5.0)	0.05

Emre et al. NEJM 2004

Medikamentöse Therapie: andere Medikamente

- **Andere Acetylcholinesteraseinhibitoren:**
  - Donepezil (EDON Studie, off-label)
- **Antidepressiva:**
  - **Atomoxetin 40 mg**: positiver Effekt auf Kognition
  - Venlafaxin: unklar
- **Neuere Studien:**
  - 5-HT_6 Rezeptor Antagonisten (Piperazin Derivate)

Arten des körperlichen Trainings

Aerobe Ausdauer

- Walken, Ballspiele

Koordinationstraining

- Balancetraining, Ballspiele

Krafttraining (Resistance)

- Isometrisches Training; Gerätetraining

Dual Task Aufgaben

- Kognitive und motorische Aufgaben gleichzeitig; 2 motorische Aufgaben

Musik/Tanztherapie

- Gruppentherapien mit Singen

Dual task Aufgaben

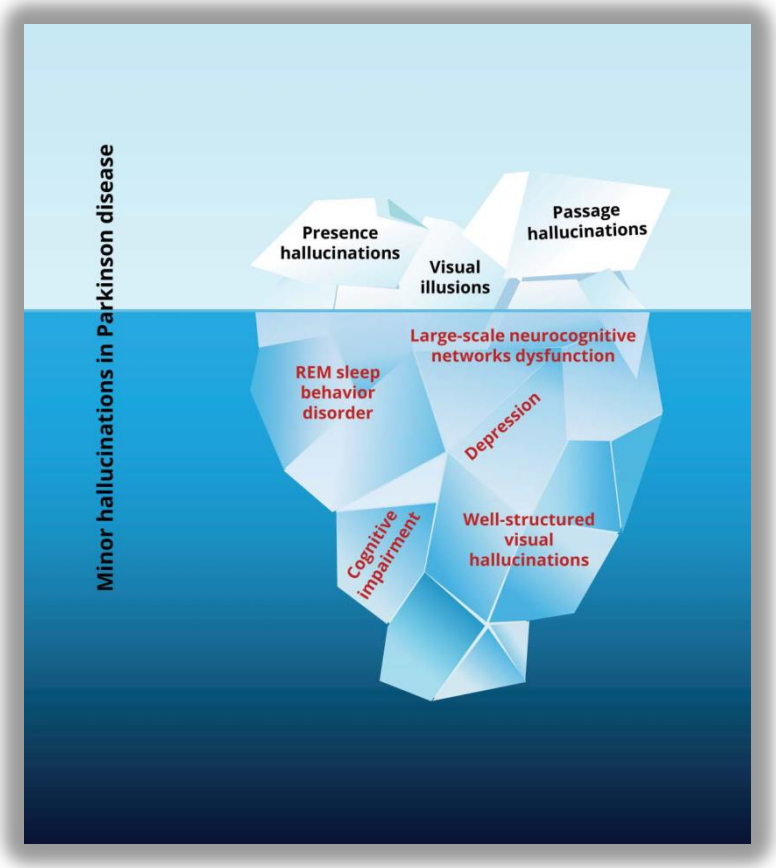
Backes, Maschke, Wihr. Reinhardt Ernst Verlag 2018

Halluzinationen und Psychose

Halluzinationen und Psychose

- Je nach Studie **bis zu einem Drittel** der Parkinson Patient*innen weisen mindestens ein Symptom auf
- Folgende Faktoren **erhöhen das Risiko**:
  - Vorhandensein anderer **nicht-motorischer** Symptome
  - **REM Schlafverhaltensstörungen**
  - **Depression**
  - **Polypharmazie**
  - **Anticholinergika**> MAO-B Hemmer > Amantadin > Dopaminagonisten > COMT-Hemmer
  - **Visusminderung, Hörminderung**

Halluzinationen als Spitze des Eisbergs



- **Morphologische Veränderungen** in bestimmten Hirnregionen:
  - Visuelles System
  - Hippocampus
  - Lcus coereleus
- Assoziiert mit **cholinergen Defiziten**

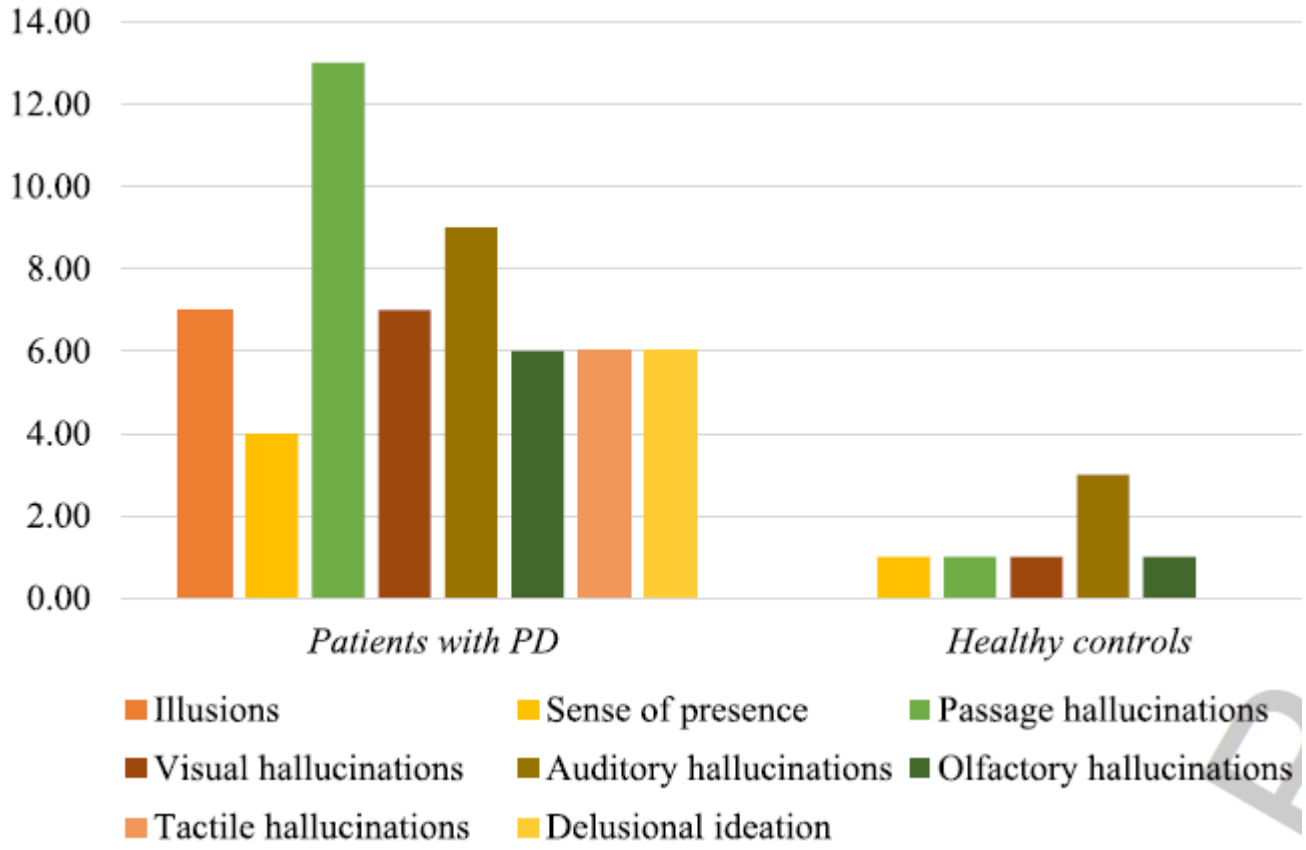
Lenka et al. Neurology 2019

Illusion, Delusional ideation und passage Halluzinationen

- **Illusion:**
  - falsche Deutung von tatsächlichen Sinneswahrnehmungen
- **Passage Halluzinations:**
  - Fragliche Gestalten/Formen beim Vorbeigehen
- **Delusional ideation (wahnhafte Ideen):**
  - Grandiose delusions: besonders reich oder talentiert
  - Paranoid delusions: jemand möchte etwas böses
  - Somatic delusions: irgend etwas stimmt nicht mit dem Körper

Pachi et al. JPD 2023 (in press)

Welche Formen der Halluzinationen treten wie häufig auf?



Pachi et al. JPD 2023 (in press)

Sinnvolle Strategien

- **Risiko-Nutzen Analyse kritisch für jedes Medikament in der Liste**
- **Reduktion der Polypharmazie**
- **Möglichst einfache Verordnungspraktiken**
  - Präparate mit möglicher Einmalgabe
  - Sind transdermale Applikationen möglich?
- **Start-low and go-slow**
  - Viele Medikamente sind bei >80 jährigen Menschen nicht geprüft

Medikamente beim alten Menschen: PRISCUS Liste (*www.priscus.net*)

Priscus-Liste für den Schreibtisch: **Die 83 Wirkstoffe im Überblick !**

Arzneimittel	Wesentliche Bedenken (Auswahl)	Therapiealternativen
Analgetika, Antiphlogistika		
NSAID Indometacin Acemetacin* Ketoprofen* Piroxicam Meloxicam* Phenylbutazon Etoricoxib	· sehr hohes Risiko für gastrointestinale Blutungen, Ulzerationen oder Perforationen, auch mit letalem Ausgang · Indometacin: Zentralnervöse Störungen · Phenylbutazon: Blutdyskrasie · Etoricoxib: Kardiovaskuläre Kontraindikationen	· Paracetamol · (schwach wirksame) Opioide (Tramadol, Codein) · ggf. schwächere NSAID (z. B. Ibuprofen)
Opioid-Analgetika Pethidin	· erhöhtes Risiko für Delir und Stürze	· Paracetamol · andere Opioide (mit geringerem Delirrisiko, z. B. Tilidin/Naloxon, Morphin, Oxycodon, Buprenorphin, Hydromorphon) · ggf. schwächere NSAID (z. B. Ibuprofen)
Antiarrhythmika		
Chinidin*	· Zentralnervöse UAW · erhöhte Mortalitätsrate · Chinidin plus Verapamil: für Patienten älter als 75 Jahre nicht empfohlen	· Beta-Blocker · Verapamil · Diltiazem · Amiodaron · Defibrillator-Implantation
Flecainid*	· allgemein höhere Nebenwirkungsrate	· Beta-Blocker · Amiodaron
Sotalol*	· Beta-Blocker mit zusätzlich antiarrhythmischer Wirkung	· Kardioselektive Beta-Blocker (z. B. Metoprolol, Bisoprolol, Carvedilol) · Amiodaron · Propafenon (je nach Art der Arrhythmie)
Digoxin **Acetyldigoxin*** **Metildigoxin***	· erhöhte Glykosid-Empfindlichkeit (Frauen > Männer) · erhöhtes Toxizitätsrisiko	· bei Tachykardie/Vorhofflimmern: Beta-Blocker · bei Herzinsuffizienz: Diuretika, ACE-Hemmer etc. · Digitoxin besitzt möglicherweise geringere Toxizitätsrate
Antibiotika		
Nitrofurantoin	· ungünstiges Nutzen-Risiko-Verhältnis, insbesondere bei Langzeitgebrauch (pulmonale UAW, Leberschädigungen etc.)	· andere Antibiotika (z. B. Cephalosporine, Cotrimoxazol, Trimethoprim - möglichst nach Antibiogramm) · nichtmedikamentöse Maßnahmen: vermehrte Flüssigkeitszufuhr, Inkontinenzhilfen
Anticholinergika		
Antihistaminika Hydroxyzin Clemastin* Dimetinden* Chlorphenamin Tripelidin	· anticholinerge Nebenwirkungen (z. B. Obstipation, Mundtrockenheit) · kognitive Leistungsabnahme · EKG-Veränderungen (QT-Verlängerungen)	· nichtsedierende/nicht-anticholinerg wirkende Antihistaminika (z. B. Cetirizin, Loratadin, Desloratadin)
Urologische Spasmolytika Oxybutynin (nicht retardiert und retardiert) Tolterodin (nicht retardiert) Solifenacin	· anticholinerge Nebenwirkungen (z. B. Obstipation, Mundtrockenheit, ZNS) · EKG-Veränderungen (QT-Verlängerung)	· Trospium · nichtmedikamentöse Therapien (Beckenbodengymnastik, Physio und Verhaltenstherapie)
Antikoagulantien, Thrombozytenaggregationshemmer		
Ticlopidin	Blutbildveränderungen	· ASS · Clopidogrel
Prasugrel*	ungünstiges Nutzen-Risiko-Verhältnis insbesondere für Patienten ≥ 75 Jahren	· ASS · Clopidogrel
Antidepressiva		
Klassische Antidepressiva Amitriptylin Doxepin Imipramin Clomipramin Maprotilin Trimipramin	· periphere anticholinerge UAW (z. B. Obstipation, Mundtrockenheit, orthostatische Dysregulation, kardiale Arrhythmien) · zentrale anticholinerge UAW (Benommenheit, innere Unruhe, Verwirrtheitszustände und andere delirante Syndrome) · kognitive Defizite · erhöhtes Sturzrisiko	· SSRI (z. B. Sertralin, Citalopram, max. 20 mg, cave: Natriumspiegel kontrollieren) · Mirtazapin · nichtmedikamentöse Therapien (ggf. verhaltenstherapeutische Verfahren)
SSRI Fluoxetin	· Zentralnervöse UAW (Übelkeit, Schlafstörungen, Schwindel, Verwirrtheit) · Hyponatriämie	· andere SSRI (z. B. Sertralin, Citalopram, max. 20 mg, cave: Natriumspiegel kontrollieren) · Trazodone · Mirtazapin · nichtmedikamentöse Therapien (z. B. verhaltenstherapeutische Verfahren)
MAO-Hemmer Tranylcypromin*	· irreversibler MAO-Hemmer: Blutdruckkrisen, Hirnblutungen · maligne Hyperthermie	· SSRI (außer Fluoxetin) · nichtmedikamentöse Therapien (z. B. verhaltenstherapeutische Verfahren)
Antiemetika		
Dimenhydrinat	· anticholinerge UAW	· Domperidon · Metoclopramid (cave: extrapyramidale Symptome)
Antihypertensiva, kardiovaskuläre Arzneimittel		
Clonidin	· Hypotension · Bradykardie · Synkope · zentralnervöse UAW: Sedierung, Verschlechterung der Kognition	· andere Antihypertensiva: z. B. ACE-Hemmer, AT_1-Blocker, (Thiazid-) Diuretika, Beta-Blocker, Calcium-Antagonisten (langwirksame, peripher wirkende)

Therapie bei M. Parkinson

- **Nicht jede Halluzination bedarf einer Behandlung!**
- **Medikamentöse Maßnahmen:**
  - **Absetzen** von **Anticholinergika**>**MAO-B-Hemmer>Amantadin>Dopaminagonisten**>COMT-Hemmer.
  - Reduktion von **L-Dopa** auf die **niedrigstmögliche Dosierung**
  - Ggf. Eindosierung von **Clozapin** oder **Quetiapin**

Therapie bei M. Parkinson

Nicht-medikamentös:

Ausreichende **Trinkmenge** und Ernährung

Gleichförmiger **Tagesablauf** (Routinen)

Vermeiden langer **Mittagsruhen** (>1 Stunde)

Validation (unbedingte Wertschätzung)

Vermeiden von Krankenhausaufenthalten, wenn doch **rooming-in** möglich?

Quetiapin und Clozapin

- **Clozapin (zugelassen für M. Parkinson):**
  - antipsychotische und sedierende Wirkung
  - Beginn **mit 6.25-12.5 mg z.N. (1/4-1/2 Tbl),** langsames einschleichen und aufdosieren bis maximal 50 mg/d
  - **NW:** Schläfrigkeit, Sedierung, Schwindel, Pulsbeschleunigung, Verstopfung, übermäßiger Speichelfluss, Verminderung der Anzahl weißer Blutkörperchen, Gewichtszunahme, Sprachstörungen, Krampfanfälle, Muskelzuckungen, Störungen der unbewussten Bewegungsabläufe mit Zittern und evtl. Fallneigung, u.v.m.

Quetiapin und Clozapin

- **Quetiapin (nicht speziell zugelassen):**
  - antipsychotische und sedierende Wirkung
  - Beginn **mit 25 mg z.N.,** langsames einschleichen und aufdosieren bis maximal 200 mg/d
  - **NW:** verringerter Hämoglobinwert, Anstieg der Blutfettwerte (Cholesterin, Serumtriglyceride), , Gewichtszunahme, Schwindel, Schläfrigkeit, Kopfschmerzen, Störungen der unbewussten Bewegungsabläufe mit Zittern, evtl. Fallneigung, Mundtrockenheit, Absetzsymptome beim Beenden der Behandlung u.v.m.

Quetiapin und Clozapin

- **Quetiapin (nicht speziell zugelassen):**

Blutbildkontrollen vor und während der Therapie
EKG Kontrollen vor und während der Therapie
So niedrig wie möglich, nach Besserung
Reduktion und Absetzen erwägen

nd

Kopfschmerzen, Störungen der unbewussten Bewegungsabläufe mit Zittern, evtl. Fallneigung, Mundtrockenheit, Absetzsymptome beim Beenden der Behandlung u.v.m.

Fallbeispiel - Medikamentenliste

- Clopidogrel 75 mg — 0 - 1 - 0
- Torasemid 10 mg — 1- 0 -0
- ~~Citalopram 10 mg — 1 - 0 - 0~~
- Kalinor Brausetabletten — 0 - 1 - 0
- Gabapentin 100 mg — 1 - 1 - 1
- ~~Pramipexol 1,05 mg — 2 - 0 - 0~~
- L-Dopa+Carbidopa 100/25 mg — 0 - 0 - 0 - 1
- Prednisolon 5 mg (z.B. Decortin H) — 1 -0 - 0
- L-Dopa+Carb+Entacapon 100/50/200 mg — 7 Uhr - 11 Uhr - 17 Uhr - ~~22~~
- Pantoprazol 40 mg — 0 - 0 - 1
- Midodrin 2,5 mg — 1 - 1 - 1
- Methotrexat 7,5 mg — 1 x Woche (dienstags) s.c.
- ~~Ibandronsäure 3 mg — alle 3 Monate i.v.~~
- ~~Oxybutynin 5 mg~~
- NEU: Melperon 25 mg z.N., Clonazepam 0.25 mg b.Bed. Z.N.

Zusammenfassung

- Psychiatrische Symptome **sehr häufig** im Verlauf
- Ausprägung und Progression **sehr variabel**
- Sowohl für betroffene Menschen mit Parkinson wie Angehörige sehr störend
- **Therapie medikamentös und nicht medikamentös:**
  - Bei Halluzinationen und Psychose Medikation verschlanken
  - Vermeiden von Over the Counter Medikation
  - Konsequentes Behandeln der Depression und kognitiver Symptome

Vielen Dank für die Aufmerksamkeit!

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