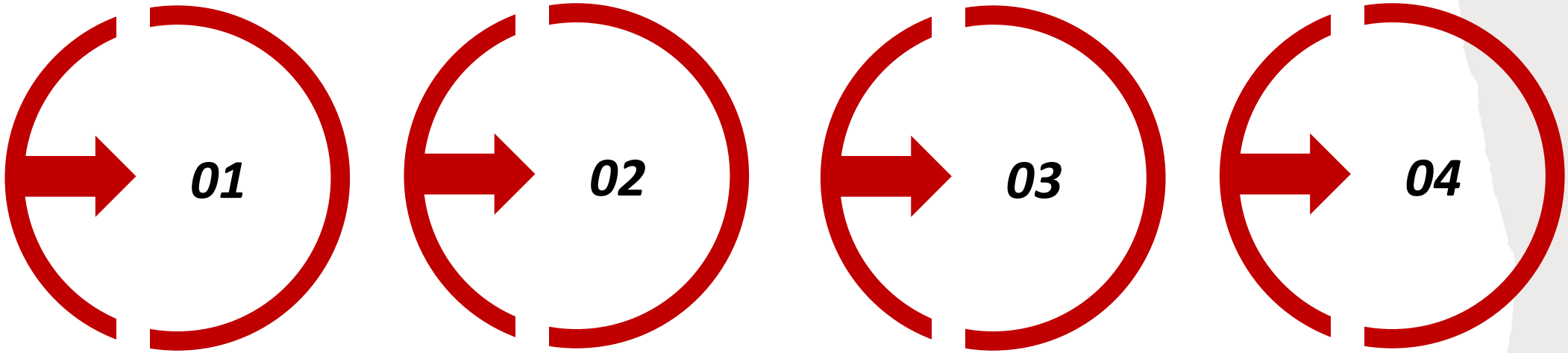
LA DISAUTONOMIA NELLA MALATTIA DI PARKINSON E PARKINSONISMI

UNIVERSITÀ DI TORINO

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

OUTLINE



Introduction

Predictive role

Impact on QoL/caregiver

Gastrointestinal

Main clinical features

Treatment

Urinary / Sexual

Main clinical features

Treatment

Cardiovascular

Pathophysiology and treatment implicaitions

New insights

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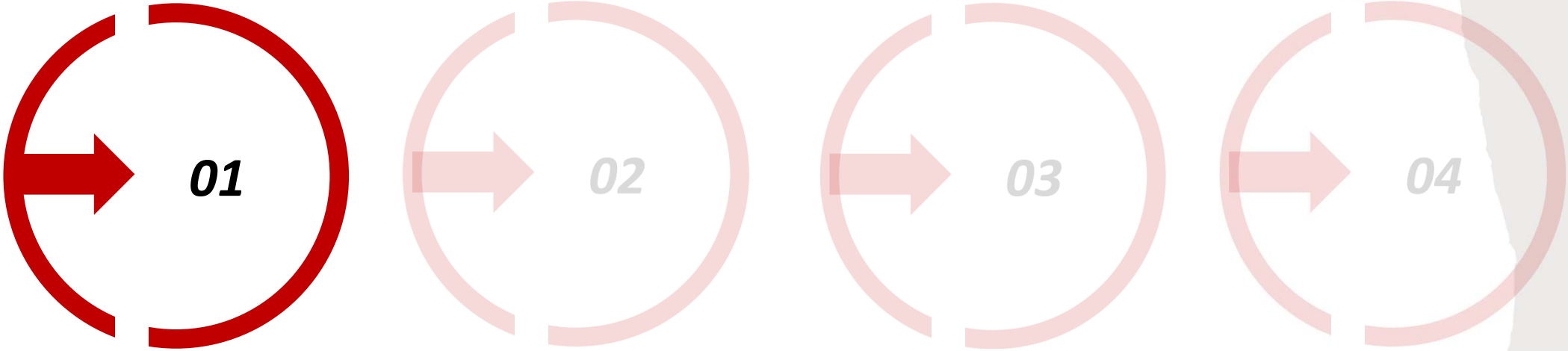

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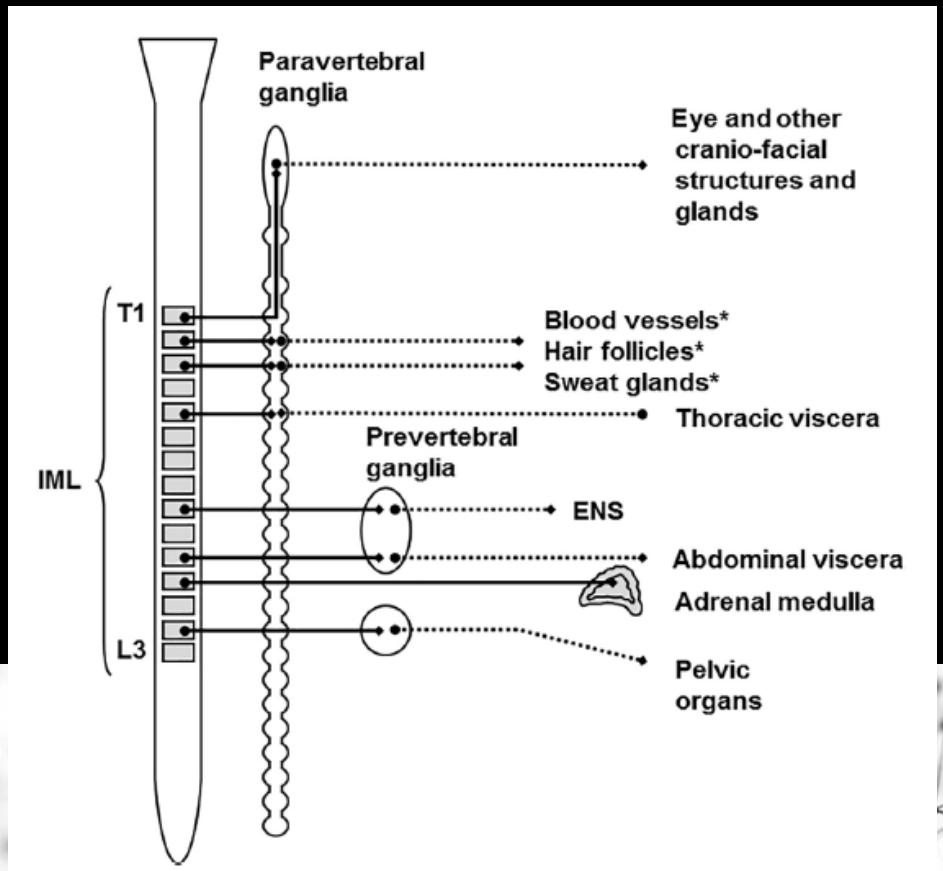
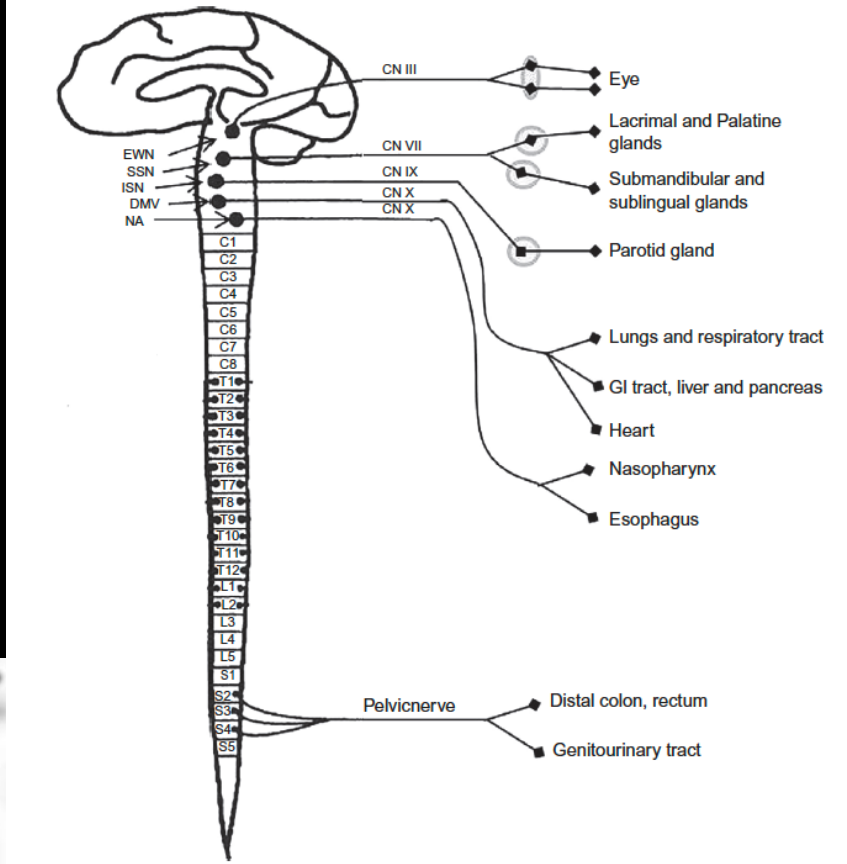
Anatomy of Autonomic Nervous System



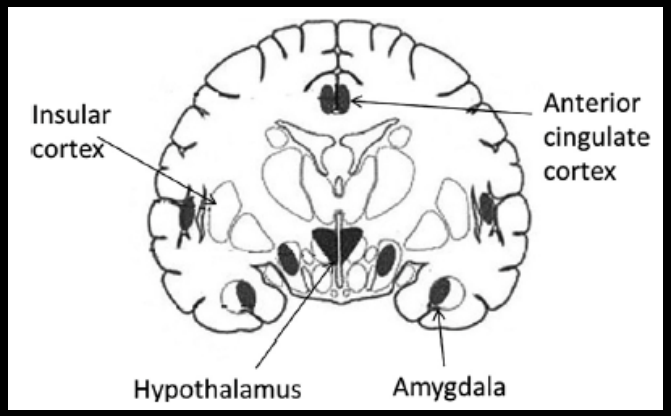
Ach (nicotinic R)



Post-ganglionic: NE
Sweat glands: Ach (muscarinic R)
Kidney: DA

Post-ganglionic: Ach (muscarinic R)

Anatomy of Autonomic Nervous System



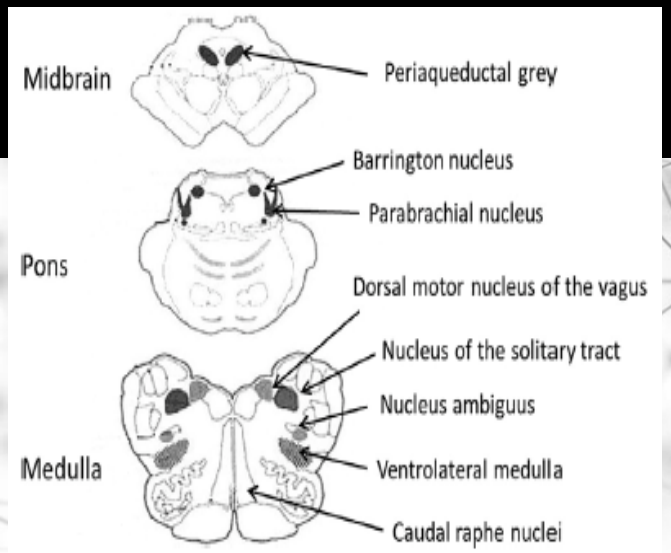
Integration of internal and external stimuli

Insula

ACC

Amygdala

Hypothalamus



Fundamental structures for autonomic control

PG

PBN: visceral, nociceptive, and thermoregulatory inputs from the spinal cord that project to the hypothalamus, amygdala, and thalamus. Control of the GI, respiratory, and CV functions

BN: micturition reflex; control of lower GI and sexual function

NTS: relay center for taste, visceral sensation, cardiac and baroreflex function, carotid chemoreflex and pulmonary mechanoreceptor reflex function, and GI motility

VLM (rostral/caudal): baroreflex, chemoreflex, and cardiopulmonary reflexes

DMNV and NA: control vagal output to the heart, respiratory tract, ENS, liver, pancreas

RN: mediator of thermoregulation, pain, and respiration; vasoconstrictive responses to cold

Autonomic dysfunction can occur early in PD: role for prodromal PD biomarker?

Autonomic dysfunction in subjects at high risk for Parkinson's disease

J Neurol (2015) 262:2643–2652

Inga Liepelt-Scarfone[1,2] · Andrea Pilotto[1,3] · Katharina Müller[1,2] · Christian Bormann[1,2] · Katharina Gauss[1,2] · Isabel Wurster[1,2] · Johannes Streffer[4] · Daniela Berg[1,2]

Pre-Motor PD (n= 40):

Compared to:

a) Healthy Controls (n= 50)

b) PD patients (n= 113; 71 early, 42 advanced)

Autonomic dysfunction can occur early in PD: role for prodromal PD biomarker?

Autonomic dysfunction in subjects at high risk for Parkinson's disease

J Neurol (2015) 262:2643–2652

	Healthy Controls	Pre-Motor PD	Early PD	Advanced PD
Urinary Dysfunction	12%	45%	45.2%	62%
Bowel Dysfunction	8%	27.5%	47.9%	57.1%
Sexual Dysfunction	24%	37.5%	49.3%	59.5%
OH	0%	7.5%	28.1%	28.5%

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Autonomic dysfunction can occur early in PD: role for prodromal PD biomarker?

Update of the MDS Research Criteria for Prodromal Parkinson's Disease

Sebastian Heinzel, PhD,[1*] Daniela Berg, MD,[1,2] Thomas Gasser, MD,[2] Honglei Chen, MD, PhD,[3] Chun Yao, MSc,[4] Ronald B. Postuma, MD, MSc,[4*] and the MDS Task Force on the Definition of Parkinson's Disease

MDS Research Criteria for Prodromal Parkinson's Disease

Daniela Berg, MD,[1*] Ronald B. Postuma, MD, MSc,[2*] Charles H. Adler, MD, PhD,[3] Bastiaan R. Bloem, MD, PhD,[4] Piu Chan, MD, PhD,[5] Bruno Dubois, MD, PhD,[6] Thomas Gasser, MD,[1] Christopher G. Goetz, MD,[7] Glenda Halliday, PhD,[8] Lawrence Joseph, PhD,[9] Anthony E. Lang, OC, MD, FRCPC,[10] Inga Liepelt-Scarfone, PhD,[1] Irene Litvan, MD,[11] Kenneth Marek, MD,[12] José Obeso, MD, PhD,[13] Wolfgang Oertel, MD,[14] C. Warren Olanow, MD, FRCPC,[15] Werner Poewe, MD,[16] Matthew Stern, MD,[17] and Günther Deuschl, MD[18]

Prodromal markers	PSG-proven RBD	130
	Possible RBD (questionnaire)	2.8
	Dopaminergic PET/SPECT clearly abnormal (eg, <65% normal, 2 SDs below mean)	43.3
	Subthreshold parkinsonism (UPDRS-III >3 excluding action tremor or MDS-UPDRS-III >6 excluding postural and action tremor)	9.6
	or	
	Abnormal quantitative motor testing	3.5
	Olfactory loss	6.4
	Constipation	2.5
	Excessive daytime somnolence	2.7
	Orthostatic hypotension (OH) — neurogenic OH	18.5
	Symptomatic OH	3.2
	Erectile dysfunction	3.4 (in men)
	Urinary dysfunction	2.0

Autonomic dysfunction reduce quality of life

Prevalence and Burden of Dysautonomia in Advanced Parkinson's Disease

Aristide Merola, MD, PhD,[1]* Alberto Romagnolo, MD,[2] Cristoforo Comi, MD,[3] Michela Rosso, MD,[1] Carlo Alberto Artusi, MD,[2] Maurizio Zibetti, MD, PhD,[2] Michele Lanotte, MD,[2] Andrew P. Duker, MD,[1] Simona Maule, MD,[4] Leonardo Lopiano, MD, PhD,[2] and Alberto J. Espay, MD, MSc[1]

Movement Disorders, Vol. 32, No. 5, 2017

RESEARCH ARTICLE

Autonomic Dysfunction in Parkinson's Disease: A Prospective Cohort Study

Aristide Merola, MD, PhD,[1]* Alberto Romagnolo, MD,[2] Michela Rosso, MD,[1] Ritika Suri, MD,[1] Zoe Berndt, MD,[1] Simona Maule, MD,[3] Leonardo Lopiano, MD, PhD,[2] and Alberto J. Espay, MD, MSc[1]

[redacted]

[redacted] reported dysautonomia

($P = 0.796$). Adjusted analysis showed that dysautonomia was independently associated with a threefold impairment in ADL/iADL (OR, 2.850; 95% CI, 1.044-10.326; $P = 0.042$). There was a robust correlation between autonomic symptoms (SCOPA-AUT) and quality-of-life impairment ($P < 0.001$). The strongest correlation was for gastrointestinal ($P < 0.001$), urinary/sexual ($P = 0.01$), and cardiovascular ($P = 0.017$) domains.

Autonomic Symptoms Worsening	ADL Deterioration OR (95% CI)	*P* Value	HRQoL Deterioration OR (95% CI)	*P* Value
SCOPA-AUT total score	2.097 (1.171-5.084)	0.021	2.998 (1.143-8.445)	0.025
Gastrointestinal domain	2.235 (1.081-5.144)	0.034	2.909 (1.164-7.269)	0.022
Urinary-sexual domain	1.828 (0.795-4.202)	0.155	2.542 (1.005-6.435)	0.049
Cardiovascular domain	2.340 (1.021-6.067)	0.041	3.516 (1.342-9.215)	0.011
Thermoregulatory domain	2.151 (0.926-4.998)	0.075	3.487 (1.546-8.777)	0.005
Pupillomotor domain	2.201 (0.496-8.760)	0.299	2.098 (0.943-3.201)	0.147

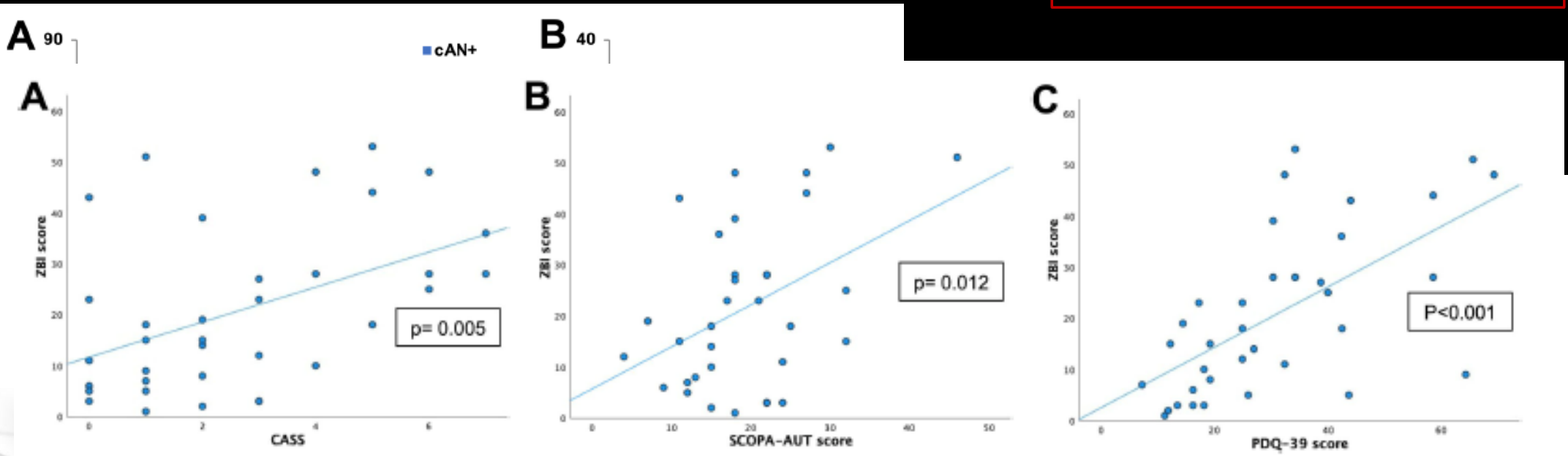
Autonomic dysfunction increase caregiving burden

Clinical Autonomic Research (2022) 32:455–461
https://doi.org/10.1007/s10286-022-00888-9

RESEARCH ARTICLE

Burden of caregiving for cardiovascular dysautonomia in Parkinson's disease

Claudia Ledda[1,2] · Elisa Montanaro[1,2] · Gabriele Imbalzano[1,2] · Aristide Merola[3] · Ilaria Bruno[1] · Carlo Alberto Artusi[1,2] · Maurizio Zibetti[1,2] · Mario Giorgio Rizzone[1,2] · Marco Bozzali[1,2] · Gabriele Sobrero[4] · Fabrizio Vallelonga[4] · Simona Maule[4] · Leonardo Lopiano[1,2] · Alberto Romagnolo[1,2]



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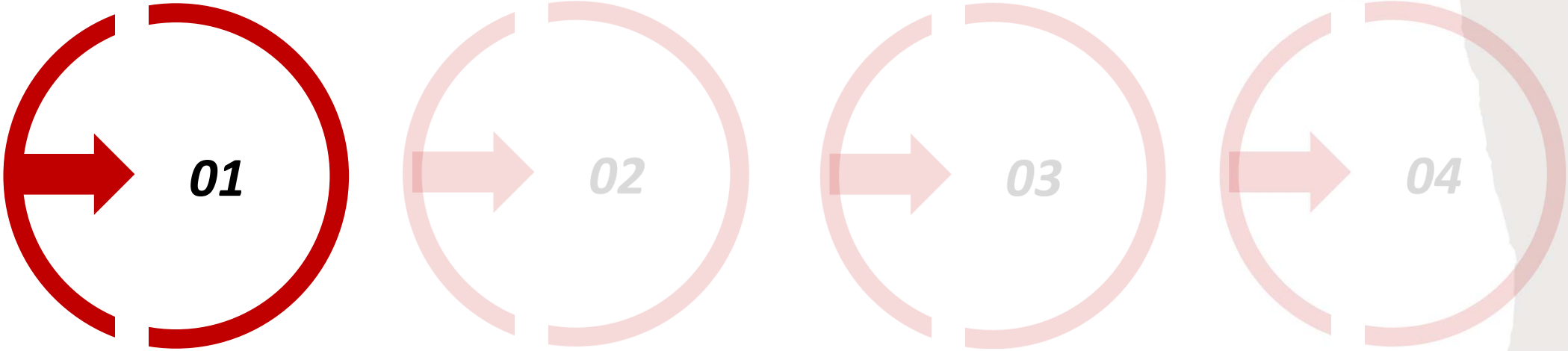

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Predictive role

Impact on QoL/caregiver

Gastrointestinal

Main clinical features

Treatment

Urinary / Sexual

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Cardiovascular

Pathophysiology and treatment implicaitions

New insights

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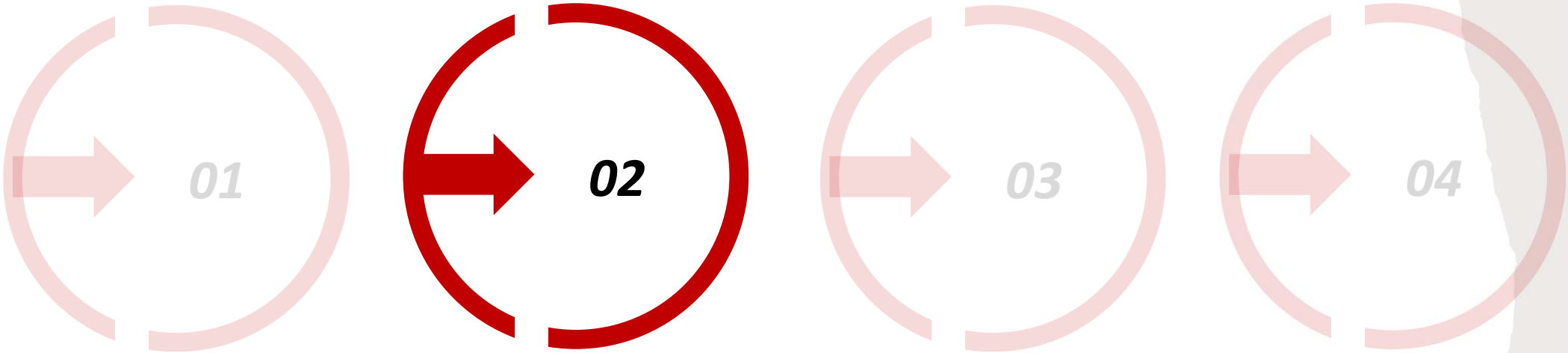

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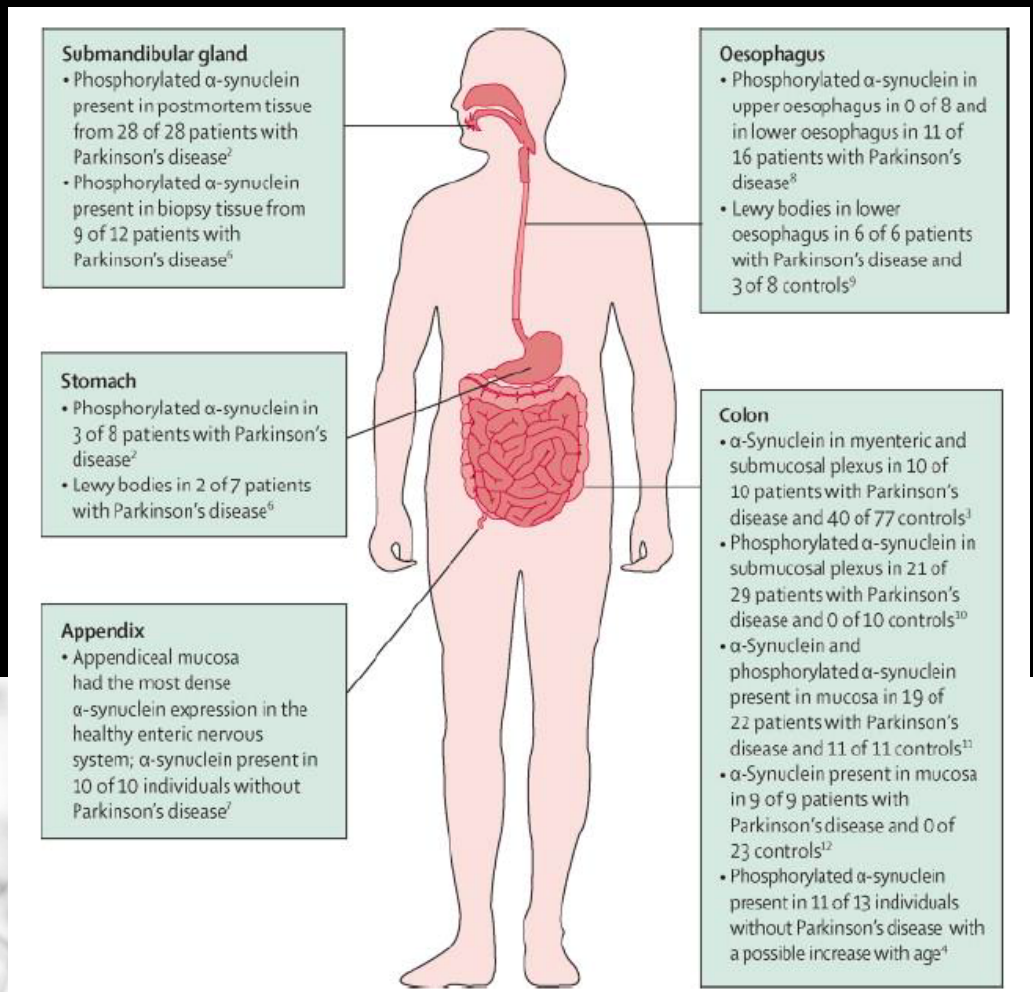
Main clinical features of GI dysautonomia

- Correlation with **alpha-syn** deposition and neuronal loss



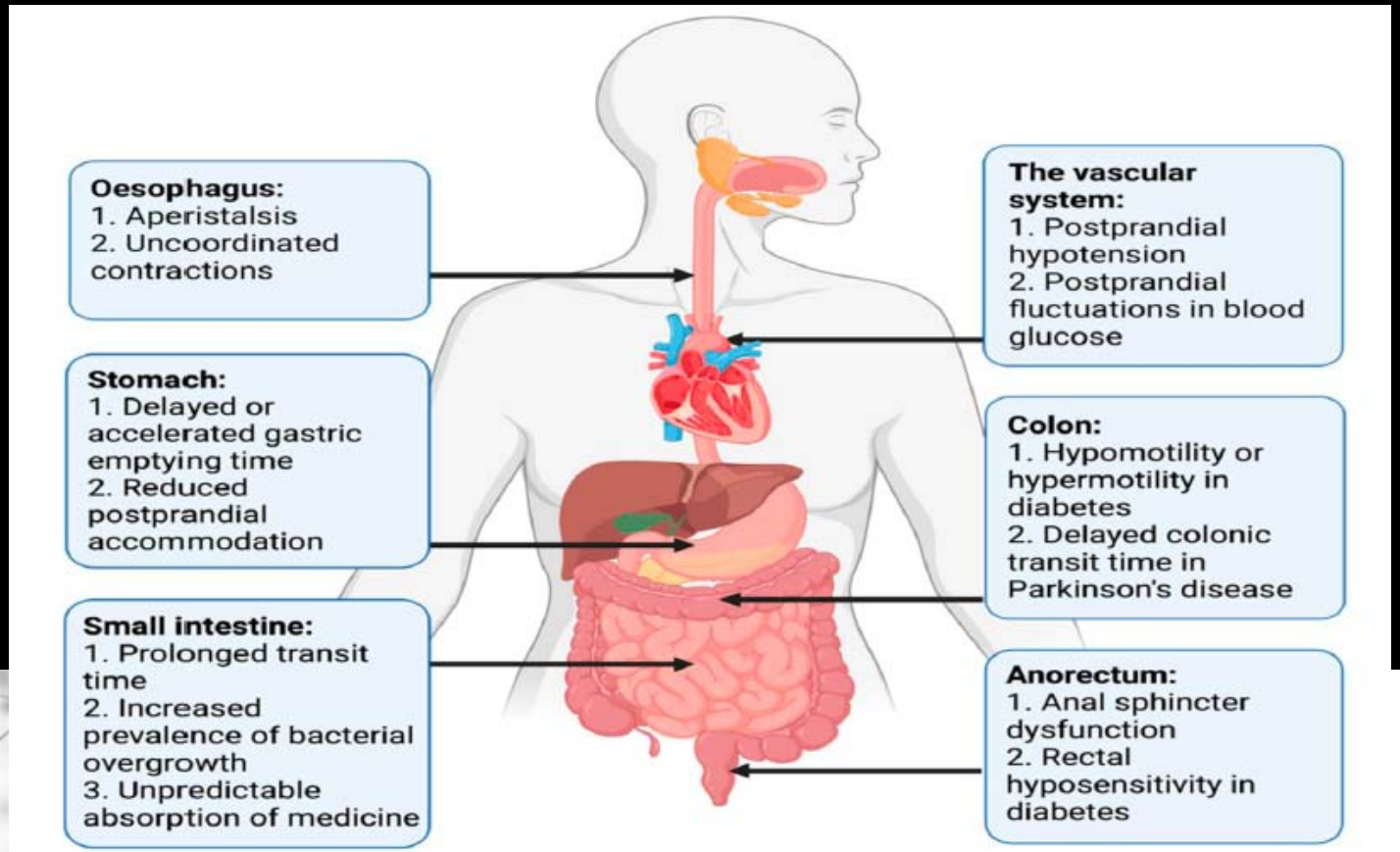
Main clinical features of GI dysautonomia

dysphagia

LOWER TRACT

- **Stool transit time** is **prolonged** due to abnormal intrinsic (ENS) and extrinsic (vagal) innervation
- **PD and DLB:** early enteric sympathetic denervation with αSyn pathology along the entire GI tract
- **MSA:** neurodegeneration of brainstem nuclei (including the dorsal motor nucleus of the vagus) and the intermediolateral cell column in the spinal cord

Main clinical features of GI dysautonomia



Almost all a-syn pts
Delayed gastric emptying→ nausea, early satiety, abdominal distension.

Constipation
Single most common autonomic symptom: 90% in PD, 80% in MSA; Pre-motor PD, DLB, MSA
Colonic volvulus, intestinal pseudo-obstruction, megacolon, fecal impaction, overflow diarrhea

Treatment of GI symptoms

Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies

Mov Disord. 2018 March ; 33(3): 372–390.

Jose-Alberto Palma, MD, PhD and **Horacio Kaufmann, MD**

- Gastrostomy

Sialorrhea/Drooling:

- Oral glycopyrrolate (very short term); Ipratropium bromide (investigational)
- Botulinum toxin injections into the salivary glands
- Amitriptyline rinses?

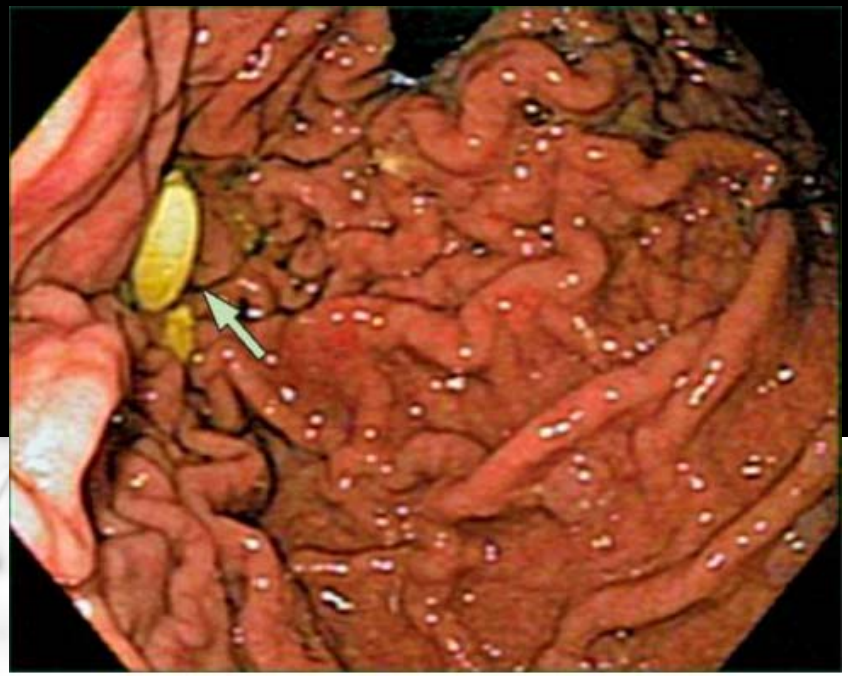
Treatment of GI symptoms

Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies

Mov Disord. 2018 March ; 33(3): 372–390.

Jose-Alberto Palma, MD, PhD and **Horacio Kaufmann, MD**

correction of malnutrition, and improvement of therapy absorption
- Low-fat diet with small frequent meals and liquid nutrients



Treatment of GI symptoms

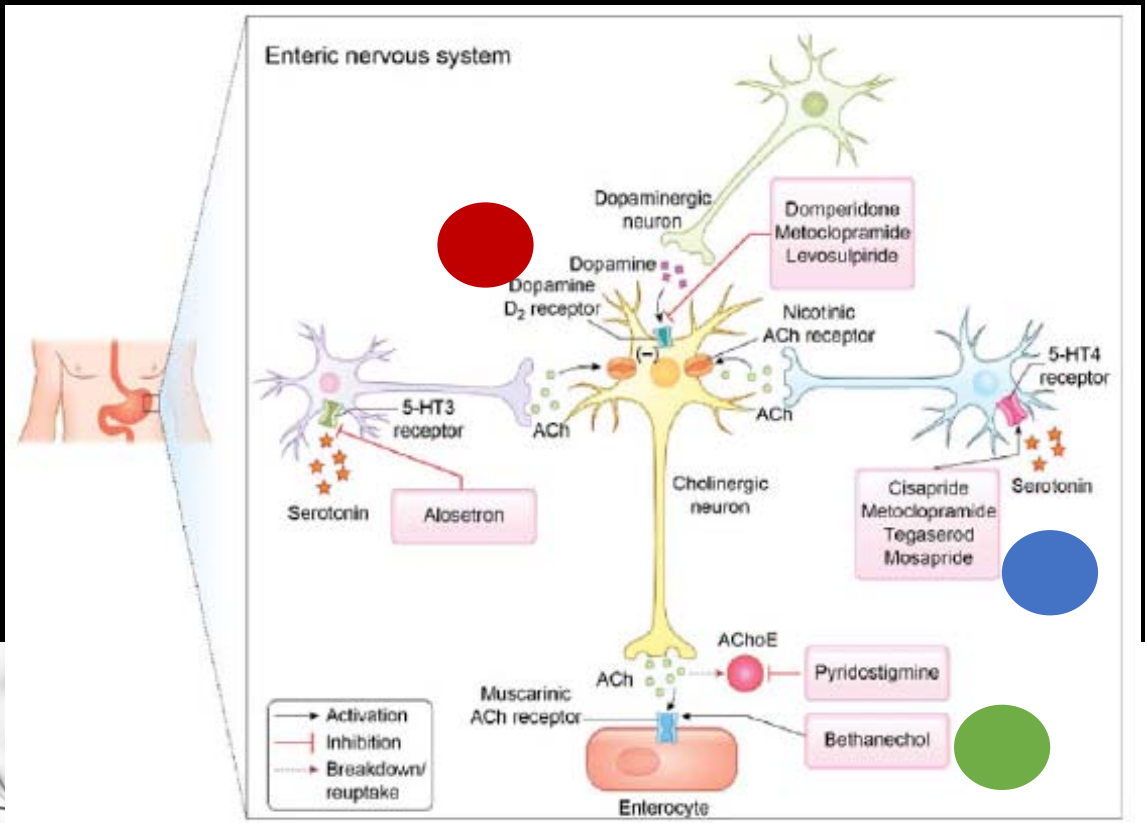
Dopamine receptor blockers

Serotonin agonists

- cisapride and tegaserod → NO
- mosapride/prucalopride?

Others

- muscarinic agonists
- Ach-esterase inhibitors



- Endoscopic pyloric botulinum toxin?
- STN-DBS?

Treatment of GI symptoms

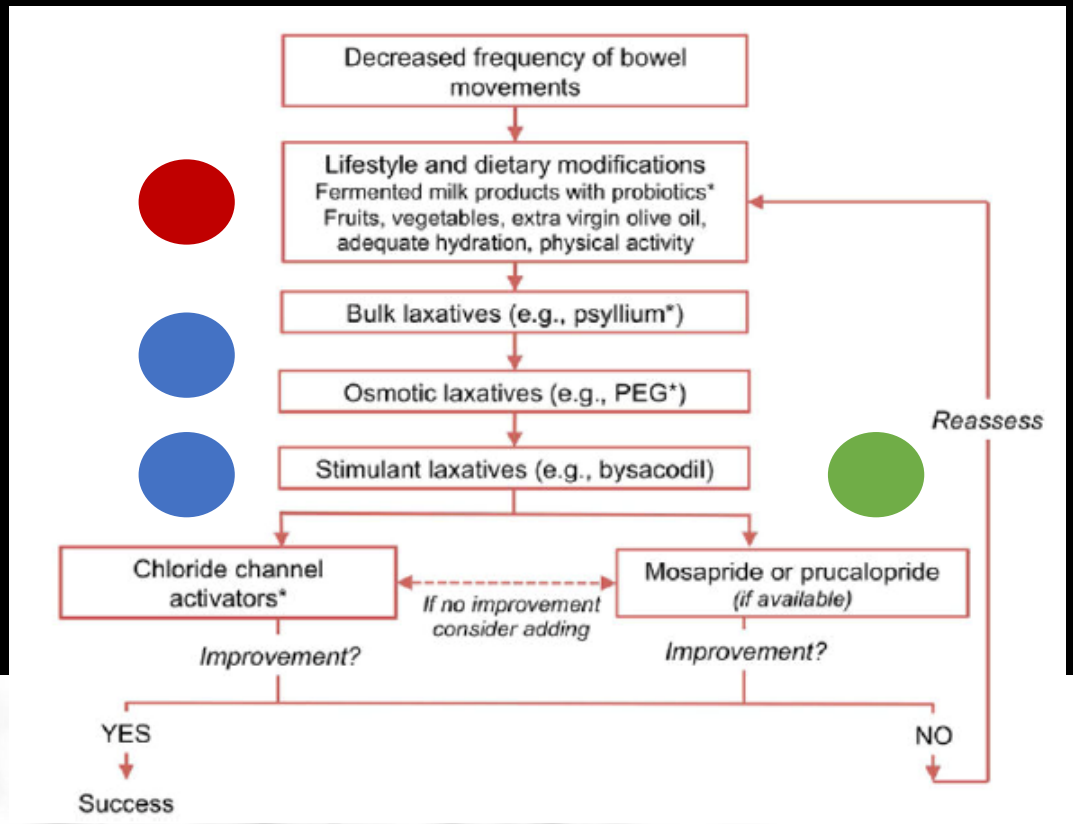
Non-pharmacological measures

Pharmacological measures

- Bulk laxative (*psyllium; methylcellulose*)
- Osmotic laxative (*polyethylene glycol → macrogol; lactulose*)

+ ADEQUATE HYDRATION

- Stimulant laxative (senna)?
- Chloride channel activators (lubiprostone)



- Serotonin agonists (mosapride)
- Ghrelin receptor agonist (ongoing trials)
- Anal sphincter botulinum toxin in dyssynergic defecation

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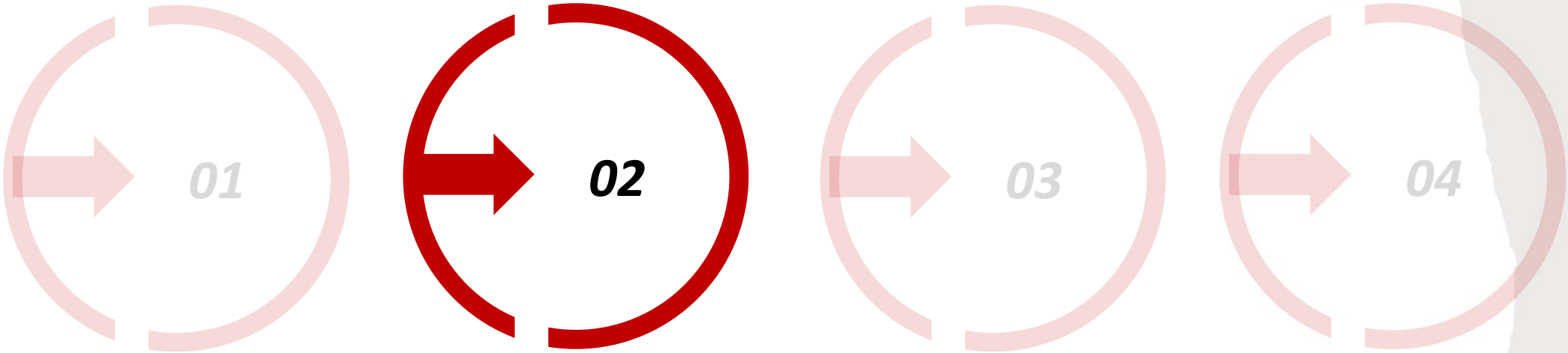

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Treatment

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Main clinical features

Treatment

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Pathophysiology and treatment implicaitions

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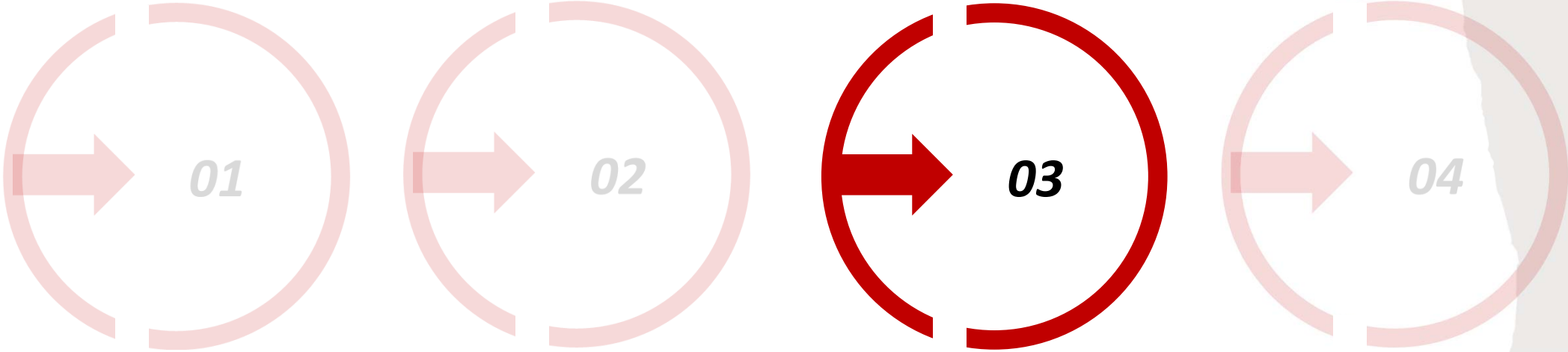

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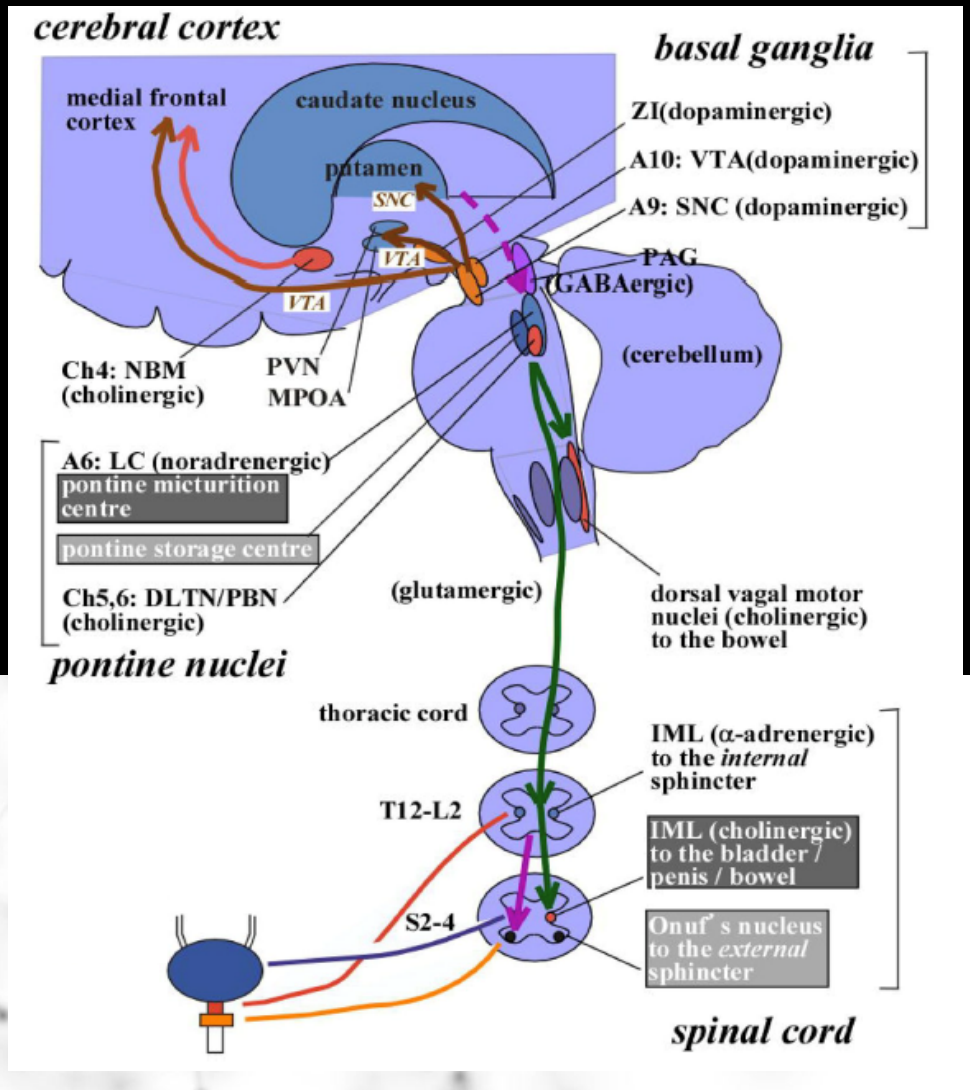
Main clinical features of urinary dysautonomia

- alpha-Syn-mediated disruption of central and peripheral genitourinary autonomic pathways and basal ganglia dysfunction
  (+ Onuf nucleus degeneration in MSA)
- Poor management of bladder dysfunction can increase the risk of urosepsis and death



Main clinical features of urinary dysautonomia

Urological dysfunction in synucleinopathies: epidemiology, pathophysiology and management

Clin Auton Res (2018) 28:83–101

Ryuji Sakakibara[1] · Fuyuki Tateno[1] · Tatsuya Yamamoto[2] · Tomoyuki Uchiyama[3] · Tomonori Yamanishi[3]

McDonald C, Winge K, Burn DJ. Lower urinary tract symptoms in Parkinson's disease: Prevalence, aetiology and management. Parkinsonism & related disorders. 2017; 35:8–16. [PubMed: 27865667]

Sakakibara R, Ito T, Uchiyama T, et al. Lower urinary tract function in dementia of Lewy body type. Journal of neurology, neurosurgery, and psychiatry. 2005; 76(5):729–732.

Tateno F, Sakakibara R, Ogata T, et al. Lower urinary tract function in dementia with Lewy bodies (DLB). Movement disorders : official journal of the Movement Disorder Society. 2015; 30(3): 411–415. [PubMed: 25356960]

Ogawa T, Sakakibara R, Kuno S, Ishizuka O, Kitta T, Yoshimura N. Prevalence and treatment of LUTS in patients with Parkinson disease or multiple system atrophy. Nat Rev Urol. 2017; 14(2): 79–89. [PubMed: 27958390]

- Extremely frequent in MSA (70-80%)
- Less frequent in PD/DLB (40%)
- **Difficulty in initiating urination** (40% PD/DLB and 73% MSA)
- **Poor stream** (70% (men) and 81%)
- **Straining** (28% and 55%)
- **High post-void residual volume** (10% and 70%)

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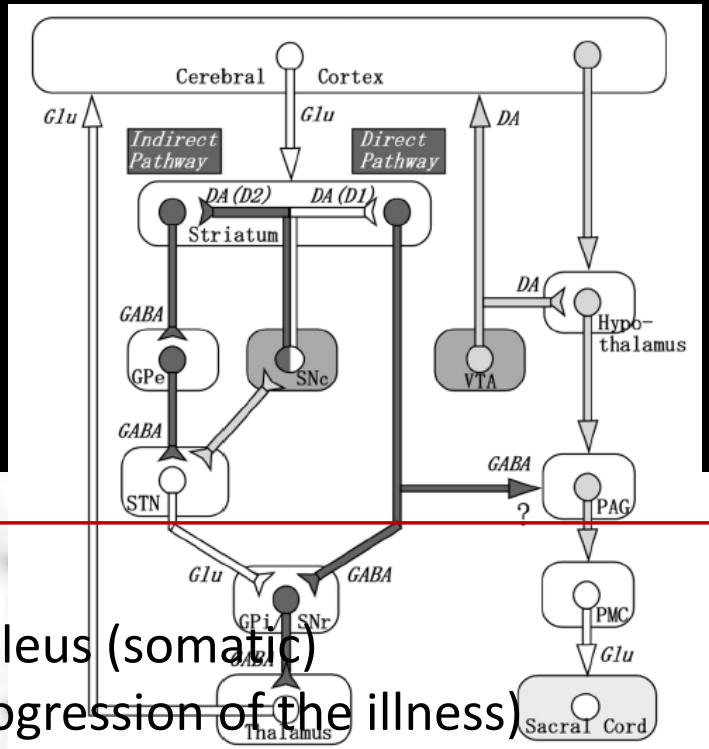
Ryuji Sakakibara[1] · Fuyuki Tateno[1] · Tatsuya Yamamoto[2] · Tomoyuki Uchiyama[3] · Tomonori Yamanishi[3]



Rare high post-void residual (PVR) volume

MSA

- More **widespread** central degeneration, including **Onuf** nucleus (somatic)
- Wide range of urodynamic abnormalities (changing with progression of the illness)
- Bladder overactivity + open bladder neck + uninhibited external sphincter relaxation + bladder underactivity + detrusor-sphincter dyssynergia → **Urge-incontinence** + **high PVR**

Treatment of urinary symptoms

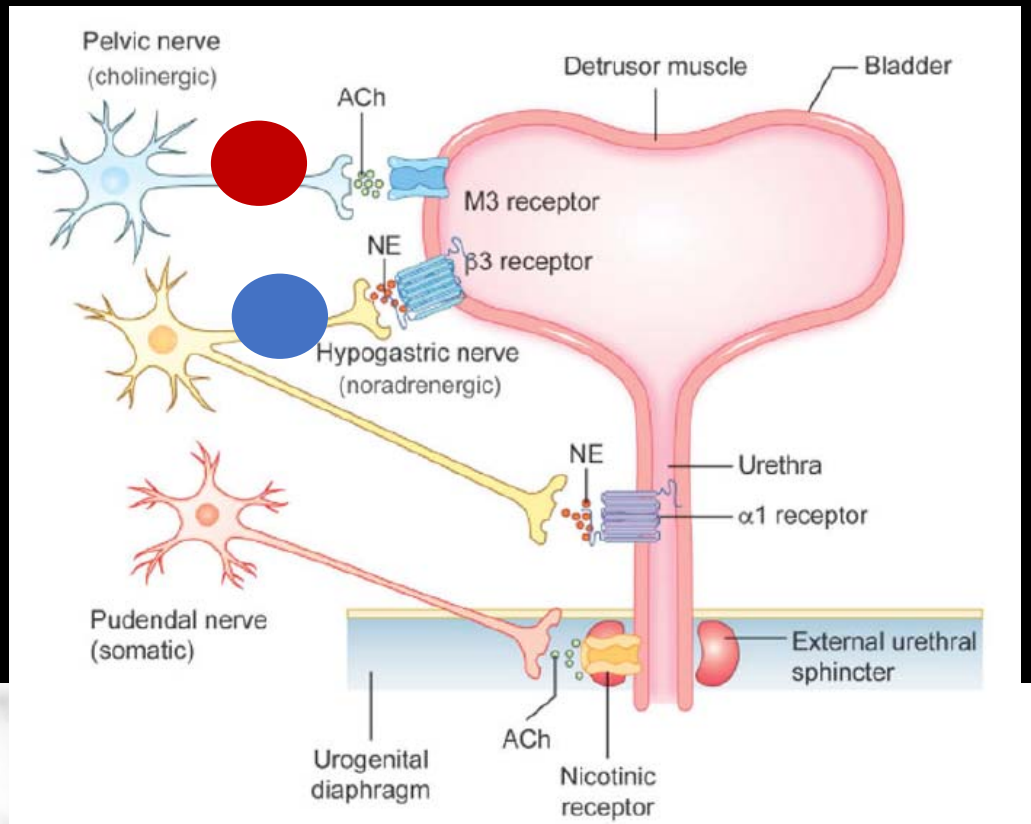
Antimuscarinic agents

cognitive impairment

β3-adrenergic agonist → Mirabegron

Detrusor relaxation → > bladder capacity

Retention, abdominal pain, hypertension



- Intramural botulinum toxin
- Sacral neuromodulation
- STN-DBS?

Treatment of urinary symptoms

Treatment	Recommended dosing regimen	Adverse events	Receptor selectivity	CNS penetration
Anticholinergic agents				
Darifenacin	7.5 or 15 mg/day	Constipation, dry mouth, urinary retention	M_3 selective	Low
Trospium	20 mg twice a day 60 mg/day (extended release form)	Constipation, dry mouth, dry eyes, headache, urinary retention	Non-selective	Low
Solifenacin	5 or 10 mg/day	Constipation, dry mouth, blurred vision, nausea, dyspepsia, urinary retention	M_3 and M_1 selective	Moderate
Oxybutinin	5 mg up to 4 times/day 5-30 mg/day (extended release form) 3 pumps once a day (gel) 1 patch every 3-4 days (patch)	Constipation, dry mouth, blurred vision, nausea, dyspepsia, urinary retention	M_3 and M_1 selective	Moderate
Tolterodine	2 mg twice a day 2 or 4 mg/day (long acting form)	Constipation, dry mouth, dyspepsia, dizziness, blurry vision, urinary retention	Non-selective	Moderate
Fesoterodine	4 or 8 mg	Constipation, dry mouth, dyspepsia, dizziness, blurry vision, urinary retention	Non-selective	Moderate
β_3-adrenergic agonists				
Mirabegron	25 or 50 mg/day	Hypertension, irregular heart rate, abdominal or pelvic pain, worsening dyskinesias in PD (one case report)	β_3-selective	Low

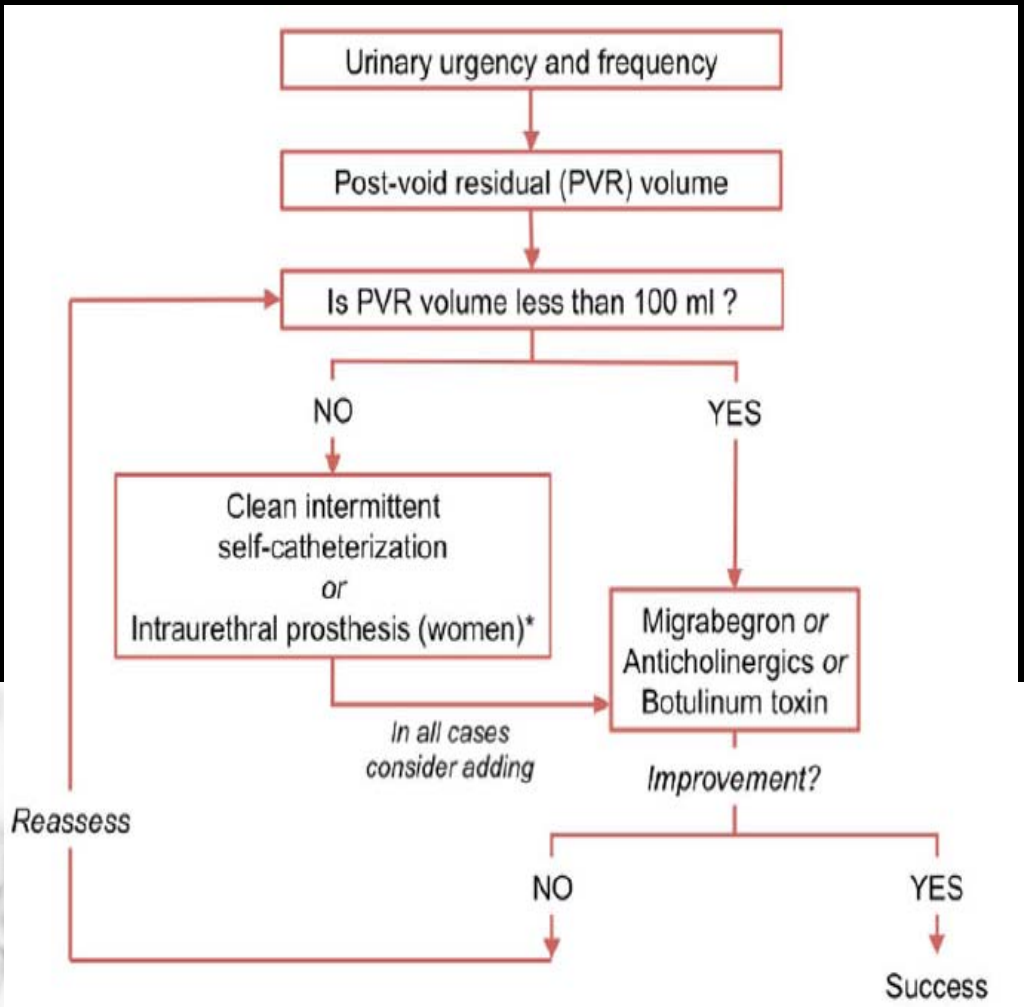
Treatment of urinary symptoms

Clean intermittent self-catheterization

Alpha-adrenergic blockers

Tamsulosin, silodosin (OH !!!)

Scarce benefit (no action on bladder underactivity)



Main clinical features of sexual dysfunction

biomakers of synucleinopathies

- Women reporting **vaginal dryness**, decreased **libido**, and difficulties reaching **orgasm**:
  PD/MSA: up to 75%

Treatment of sexual dysfunction

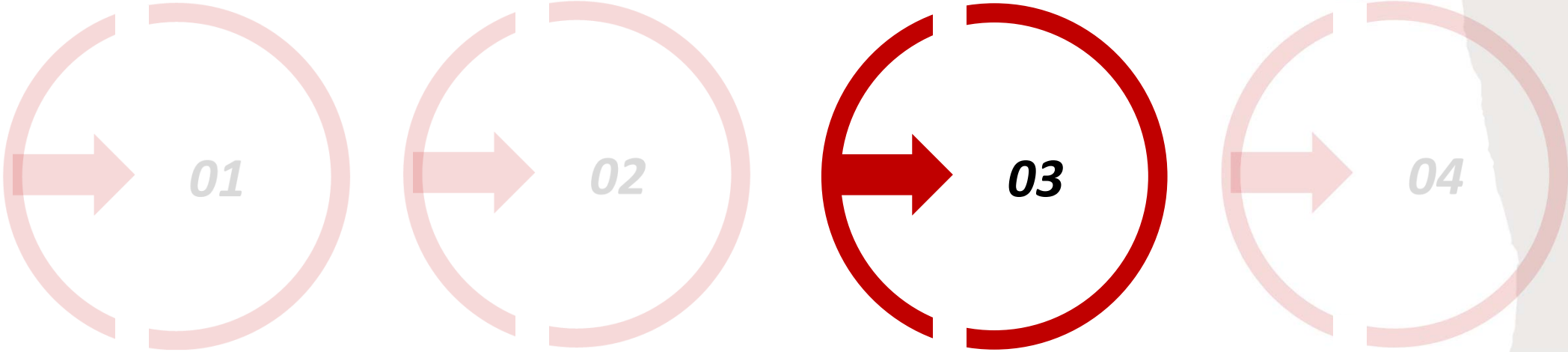
maintaining erection

- **Sildenafil** → short half-life (4 hs); 30-60 min in advance
  OH and syncope → recommend not to stand for several hours after the intake

Treatment of sexual dysfunction

- Penile **prostheses**
- **Female**: very **limited treatment** → vaginal lubrication, hormonal therapy, psychotherapy

OUTLINE



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Treatment

Urinary / Sexual

Main clinical features

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OUTLINE

01

Introduction

Predictive role

Impact on QoL/caregiver

02

Gastrointestinal

Main clinical features

Treatment

03

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Main clinical features

Treatment

04

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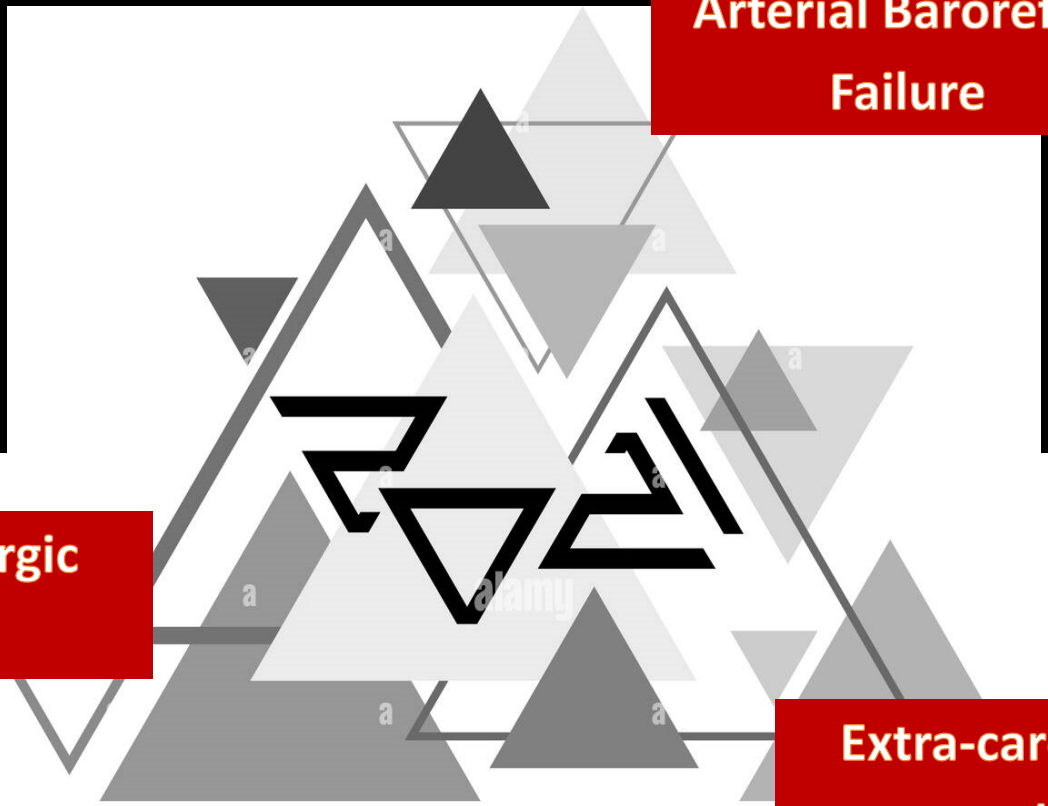
What's wrong in CV dysautonomia?

Cardiovascular dysautonomia in Parkinson Disease: From pathophysiology to pathogenesis

Neurobiol Dis. 2012 June ; 46(3): 572–580.

Samay Jain, MD, MS[1] and **David S. Goldstein, MD, PhD**[2]

Arterial Baroreflex Failure



Cardiac noradrenergic denervation

Fatigue
Orthostatic intolerance
Exercise intolerance

Extra-cardiac noradrenergic denervation

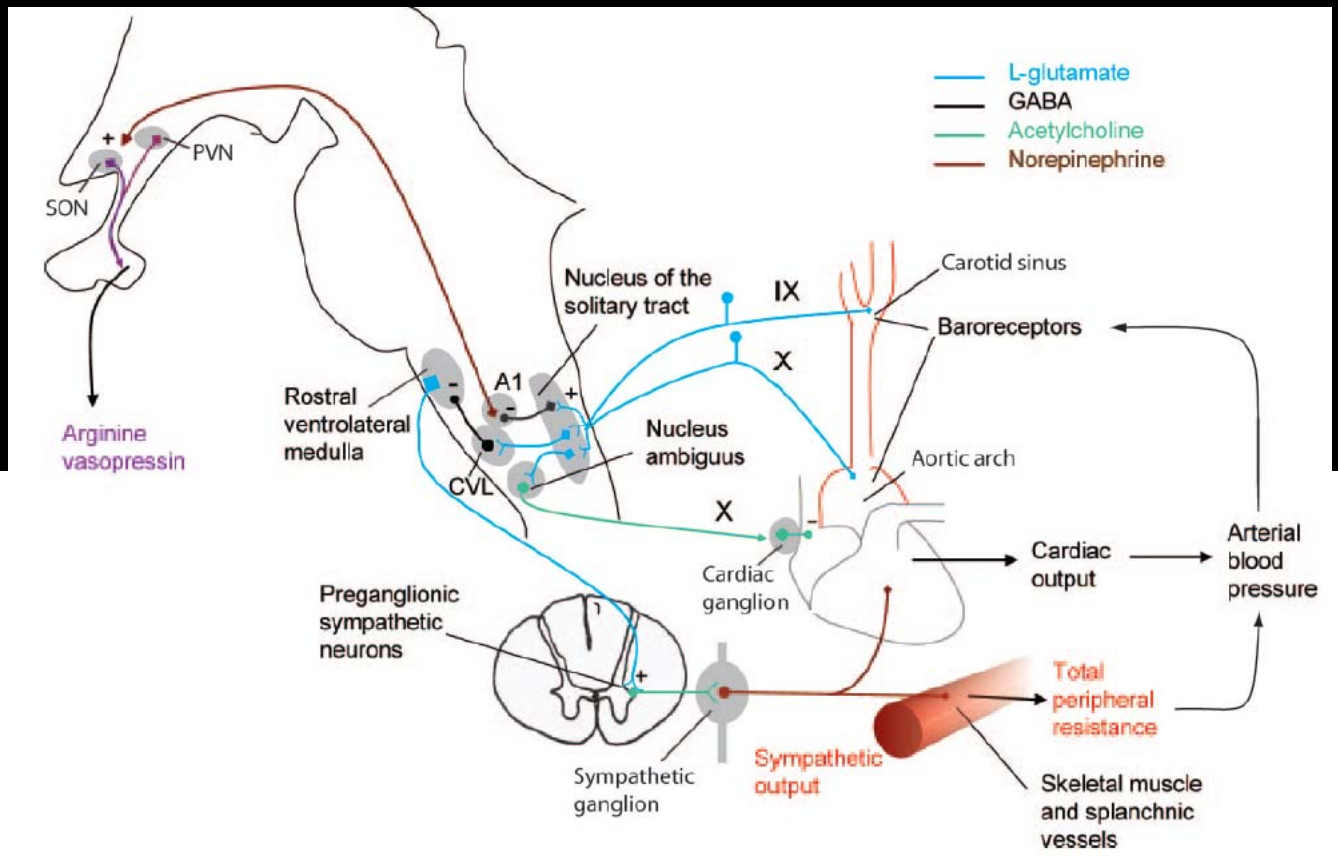
What's wrong in CV dysautonomia?

The arterial baroreflex

Functional organization and involvement in neurologic disease

Eduardo E. Benarroch

Neurology 71 November 18, 2008



all synucleinopathies

Central

DLB

Post-ganglionic degeneration:

PD-OH

DLB

PAF

What's wrong in CV dysautonomia?

Cardiac noradrenergic denervation

Extra-cardiac noradrenergic Denervation: ↓ NE release

Test	PD	MSA	DLB	PAF
Plasma NE, E				
Supine	– ↓	–	↓	↓ ↓
Standing	– ↓	↓	↓	↓ ↓

Adapted from Rafanelli M et al, Handb Clin Neurol. 2019;167:123-137

Different pathophysiology of OH: Treatment implications

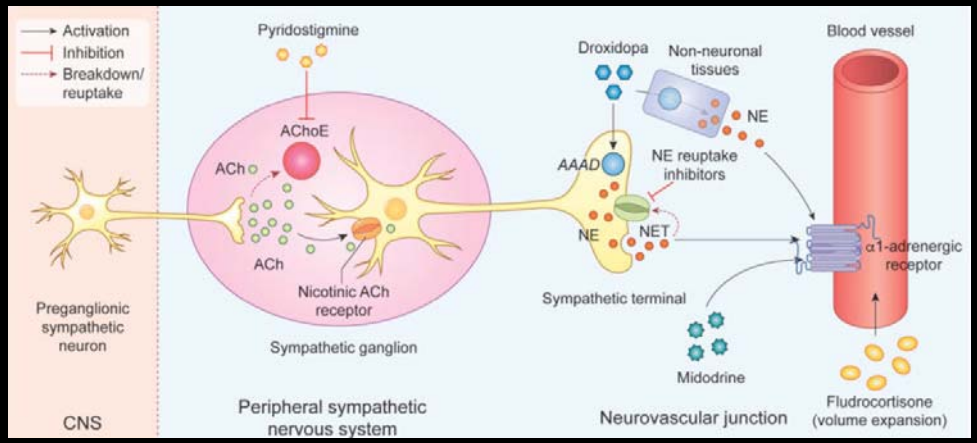
Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies

Mov Disord. 2018 March ; 33(3): 372–390.

Jose-Alberto Palma, MD, PhD and **Horacio Kaufmann, MD**

strategies are commonly used: a) Expanding intravascular volume with fludrocortisone, and b) Increasing peripheral vascular resistance with midodrine, droxidopa or norepinephrine transporter (NET) inhibitors. Selection of one or the others or both depends on the specific features and needs of each patient as well as the degree of peripheral sympathetic denervation.

That peripheral sympathetic neurons are affected in LB disorders but spared in MSA is an important difference when planning therapeutic strategies for nOH. In healthy subjects, NET inhibitors have little effect on BP. This is because the peripheral effects of NET inhibitors on the sympathetic neurovascular junction enhancing noradrenergic vasoconstriction are counteracted by the increase in CNS norepinephrine stimulating central α_2-receptors thus reducing central sympathetic outflow. In patients with MSA, however, only the peripheral vasoconstriction is apparent. Preliminary studies show that atomoxetine, a short acting NET inhibitor, increases BP in patients with nOH according to their supine plasma norepinephrine levels. The higher the norepinephrine levels the greater the pressor effect and symptomatic improvement after atomoxetine.[63] Conversely, lower supine plasma norepinephrine levels appear to predict a greater symptomatic and pressor response to droxidopa, an oral norepinephrine synthetic precursor.[64] These responses can be explained by denervation supersensitivity of adrenergic receptors.[65] Thus, patients with low plasma



Low plasma NE
→ midodrine
→ droxidopa

Normal plasma NE
→ atomoxetine
→ ampreloxetine

New insights

Clinical Autonomic Research (2021) 31:699–711
https://doi.org/10.1007/s10286-021-00827-0

RESEARCH ARTICLE

Safety and efficacy of ampreloxetine in symptomatic neurogenic orthostatic hypotension: a phase 2 trial

Horacio Kaufmann[1] · Ross Vickery[2] · Whedy Wang[3] · Jitendra Kanodia[4] · Cyndya A. Shibao[5] · Lucy Norcliffe-Kaufmann[4] · Brett Haumann[6] · Italo Biaggioni[5]

18 MSA
9 PD
7 PAF

Clinical Autonomic Research
https://doi.org/10.1007/s10286-024-01051-2

RESEARCH ARTICLE

Published online: 19 September 2024

Atomoxetine on neurogenic orthostatic hypotension: a randomized, double-blind, placebo-controlled crossover trial

Naome Mwesigwa[1] · Patricio Millar Vernetti[2] · Annet Kirabo[1] · Bonnie Black[1] · Tan Ding[1] · Jose Martinez[2] · Jose-Alberto Palma[2] · Italo Biaggioni[1] · Horacio Kaufmann[2] · Cyndya A. Shibao[1]

15 MSA
22 “peripheral” AF (?)

29.9 mmHg (7.6–52.3); $P=0.0112$]. Part C: Symptoms of dizziness/lightheadedness improved 3.1 ± 3.0 points from baseline and standing systolic blood pressure increased 11 ± 12 mmHg. After 4 weeks of withdrawal, symptoms returned to pretreatment levels. The effect of ampreloxetine on supine blood pressure was minimal throughout treatment duration.

Results A total of 68 patients were screened, 40 were randomized, and 37 completed the study. We found no differences in the OHQ composite score between atomoxetine and placebo at 2 weeks (−0.3 ± 1.7 versus −0.4 ± 1.5; $P=0.806$) and 4 weeks (−0.6 ± 2.4 versus −0.5 ± 1.6; $P=0.251$). There were no differences either in the OHSA scores at 2 weeks (3 ± 1.9 versus 4 ± 2.1; $P=0.062$) and at 4 weeks (3 ± 2.2 versus 3 ± 2.0; $P=1.000$) or in the OH daily activity scores (OHDAS) at 2 weeks (4 ± 3.0 versus 5 ± 3.1, $P=0.102$) and 4 weeks (4 ± 3.0 versus 4 ± 2.7, $P=0.095$). Atomoxetine was well-tolerated. **Conclusions** While previous evidence suggested that acute doses of atomoxetine might be efficacious in treating nOH; results of this clinical trial indicated that it was not superior to placebo to ameliorate symptoms of nOH.

New insights

Levodopa-induced orthostatic hypotension in parkinsonism: A red flag of autonomic failure

Eur J Neurol. 2024;31:e16061.
https://doi.org/10.1111/ene.16061

Ilaria Cani[1,2] | Pietro Guaraldi[2] | Giulia Giannini[1,2] | Luisa Sambati[2] | Giorgio Barletta[2] | Pietro Cortelli[1,2] | Giovanna Calandra-Buonaura[1,2]

Results: Basal supine blood pressure (BP) and heart rate (HR) decreased after LD. During post-LD HUTT, BP drop and HR increase were significantly greater than at pre-LD HUTT. Thirty-eight percent of patients had OH at post-LD HUTT compared to 22% of patients presenting OH at pre-LD HUTT ($p < 0.001$). Risk factors for LD-induced/worsened OH were pre-LD OH (odds ratio [OR] = 36, 95% confidence interval [CI] = 10–131), absence of overshoot at Valsalva maneuver (OR = 9, 95% CI = 4–20), and pathological Valsalva ratio (OR = 6, 95% CI = 2–15).

Conclusions: LD administration caused/worsened hypotension in both supine and orthostatic conditions. Patients with cardiovascular autonomic failure had a higher risk of developing LD-induced OH. In clinical practice, LD-induced OH could represent a red flag for cardiovascular autonomic failure.

137 PD
9 MSA
3 DLB
5 PSP
3 CBD
7 unknown

New insights

Movement Disorders
MOVEMENT DISORDERS CLINICAL PRACTICE 2024; 11(6): 698–703. BRIEF REPORT
CLINICAL PRACTICE

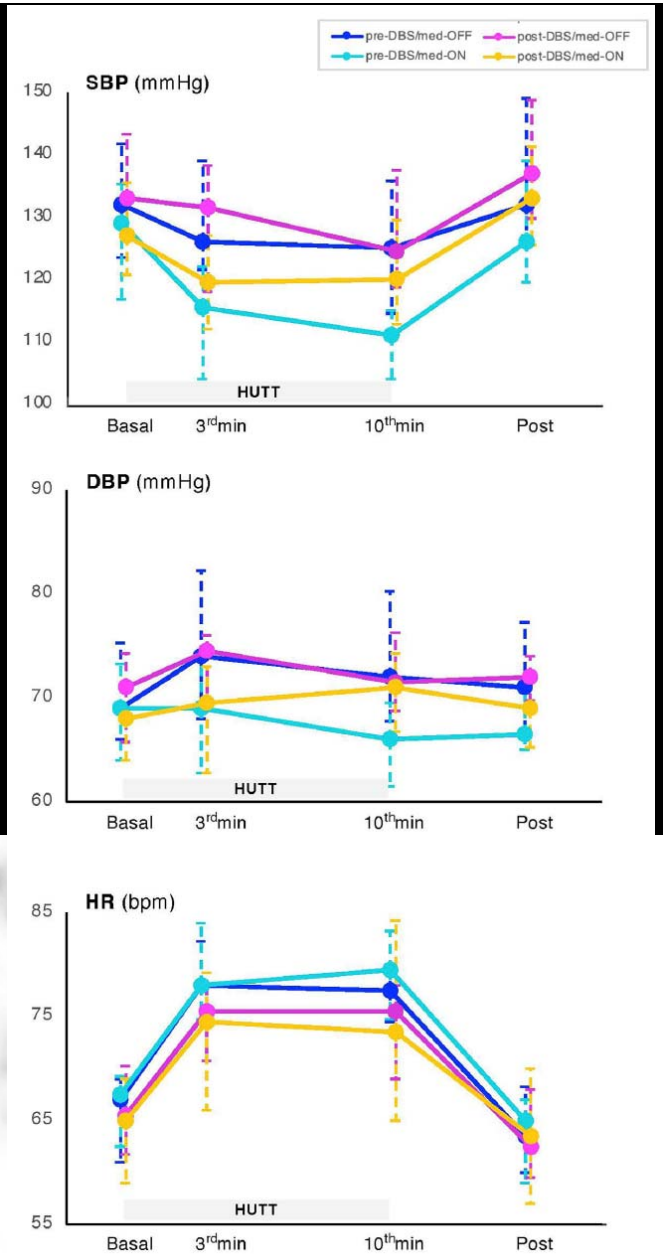
Exploring Cardiovascular Autonomic Function before and after Chronic Deep Brain Stimulation in Parkinson's Disease

Ilaria Cani, MD,[1,2] Giulia Giannini, MD, PhD,[1,2] Pietro Guaraldi, MD, PhD,[2] Giorgio Barletta, MSc,[1,2] Luisa Sambati, MD, PhD,[2] Luca Baldelli, MD,[1,2] Pietro Cortelli, MD, PhD,[1,2] and Giovanna Calandra-Buonaura, MD, PhD[1,2,*]

Results: CRT results and occurrence of neurogenic orthostatic hypotension (OH) did not differ between pre- and post-DBS studies in med-OFF condition. After levodopa intake, the BP decrease during HUTT was significantly greater compared to med-OFF, both at pre-DBS and post-DBS evaluation. Levodopa-induced OH was documented in 25% and 5% of patients in pre-DBS/med-ON and post-DBS/med-ON study.

Conclusion: Chronic stimulation did not influence cardiovascular responses, while levodopa exerts a relevant hypotensive effect. The proportion of patients presenting levodopa-induced OH decreases after STN-DBS surgery.

From this perspective, STN-DBS surgery may have a positive influence on cardiovascular autonomic functions. This improvement is likely attributed to the indirect reduction of dopaminergic therapy post-DBS. The detection of OH, by itself, should not necessarily be a contraindication for STN-DBS surgery, indeed STN-DBS can be an additional option in patients with LD-induced OH.

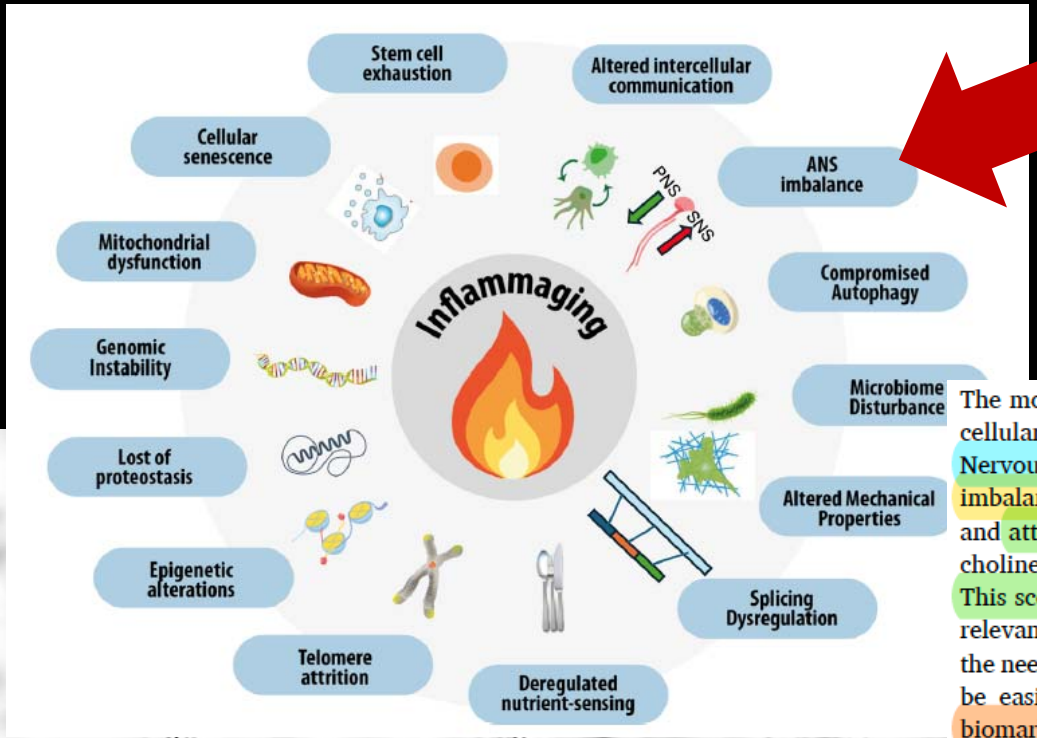


New insights

Heart rate variability and autonomic nervous system imbalance: Potential biomarkers and detectable hallmarks of aging and inflammaging

Fabiola Olivieri [a,b], Leonardo Biscetti [c], Lorenzo Pimpini [d], Giuseppe Pelliccioni [c], Jacopo Sabbatinelli [a,e,*], Sergio Giunta [f]

Available online 27 September 2024 Ageing Research Reviews 101 (2024) 102521



HRV simple marker ANS dysfunction

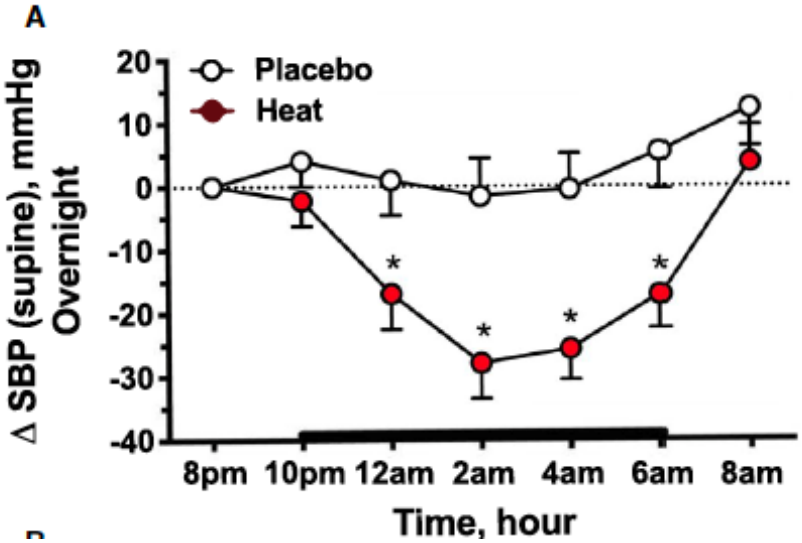
The most cutting-edge issue in the research on aging is the quest for biomarkers that transcend molecular and cellular domains to encompass organismal-level implications. We recently hypothesized the role of Autonomic Nervous System (ANS) imbalance in this context. Studies on ANS functions during aging highlighted an imbalance towards heightened sympathetic nervous system (SNS) activity, instigating a proinflammatory milieu, and attenuated parasympathetic nervous system (PNS) function, which exerts anti-inflammatory effects via the cholinergic anti-inflammatory pathway (CAP) and suppression of the hypothalamic-pituitary-adrenal (HPA) axis. This scenario strongly suggests that ANS imbalance can fuel inflammaging, now recognized as one of the most relevant risk factors for age-related disease development. Recent recommendations have increasingly highlighted the need for actionable strategies to improve the quality of life for older adults by identifying biomarkers that can be easily measured, even in asymptomatic individuals. We advocate for considering ANS imbalance as a biomarker of aging and inflammaging. Measures of ANS imbalance, such as heart rate variability (HRV), are relatively affordable, non-invasive, and cost-effective, making this hallmark easily diagnosable. HRV gains renewed significance within the aging research landscape, offering a tangible link between pathophysiological perturbations and age-related health outcomes.

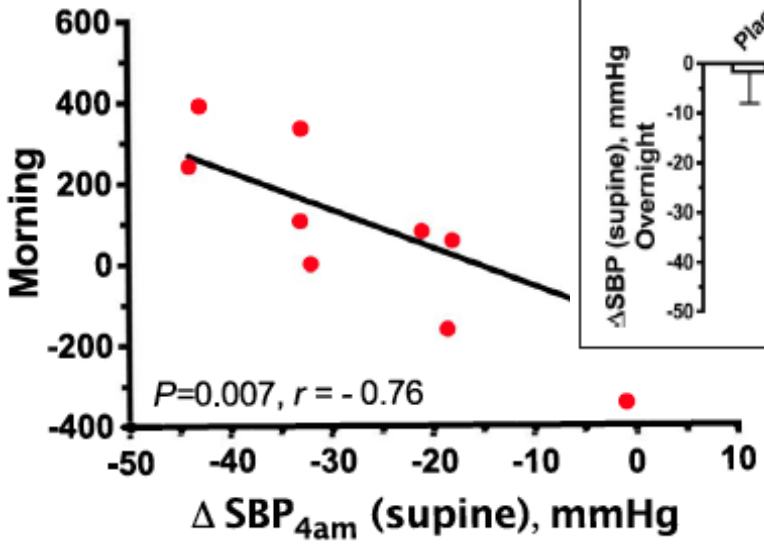
Future directions and innovation

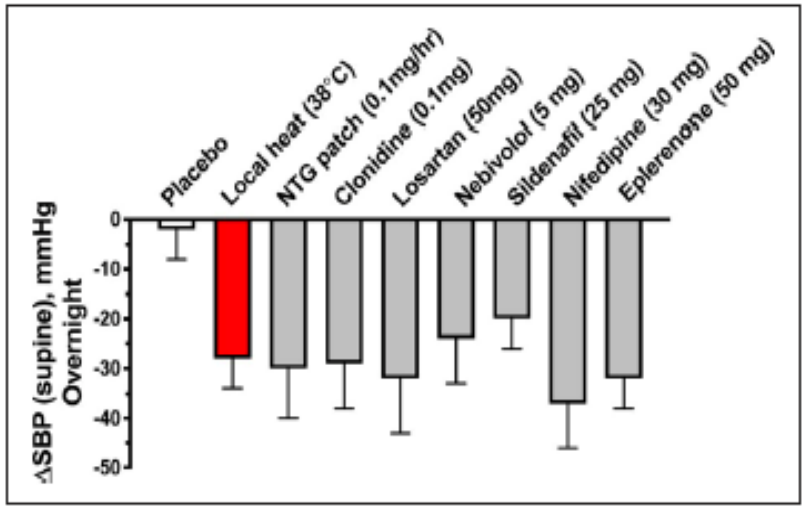
ORIGINAL RESEARCH *J Am Heart Assoc.* 2021;10:e018979.

Local Passive Heat for the Treatment of Hypertension in Autonomic Failure

Luis E. Okamoto, MD; Jorge E. Celedonio, MD; Emily C. Smith, BSN, MPH; Alfredo Gamboa, MD, MSCI; Cyndya A. Shibao, MD, MSCI; André Diedrich, MD, PhD; Sachin Y. Paranjape, BS; Bonnie K. Black, BSN, ANP; James A. S. Muldowney, III, MD; Amanda C. Peltier, MD, MS; Ralf Habermann, MD; Craig G. Crandall, PhD; Italo Biaggioni, MD





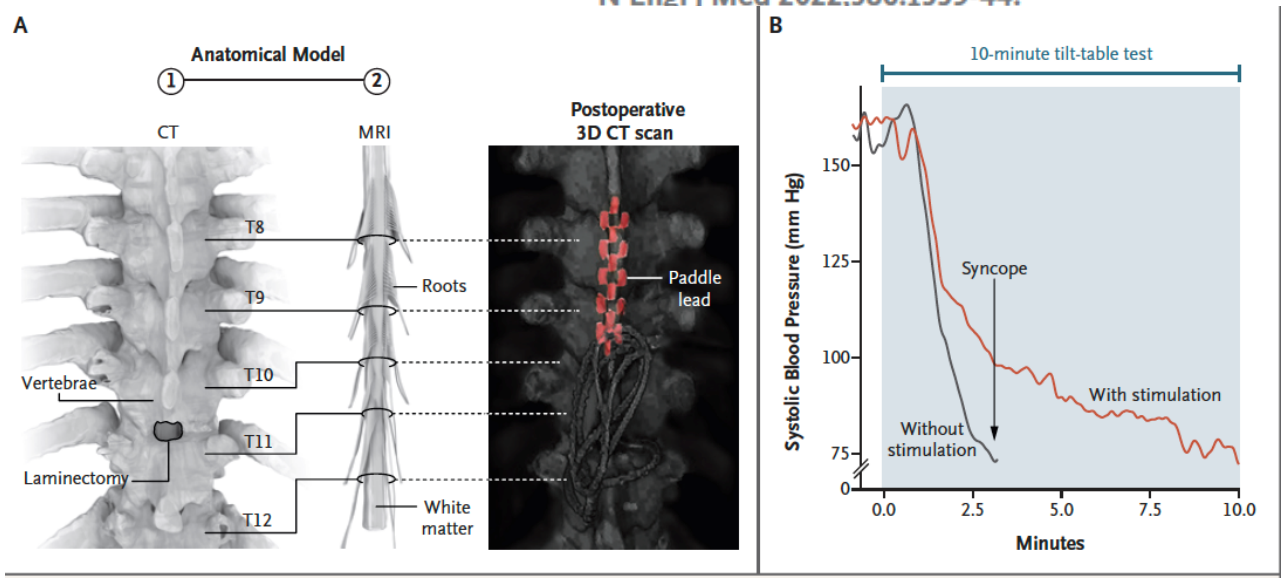


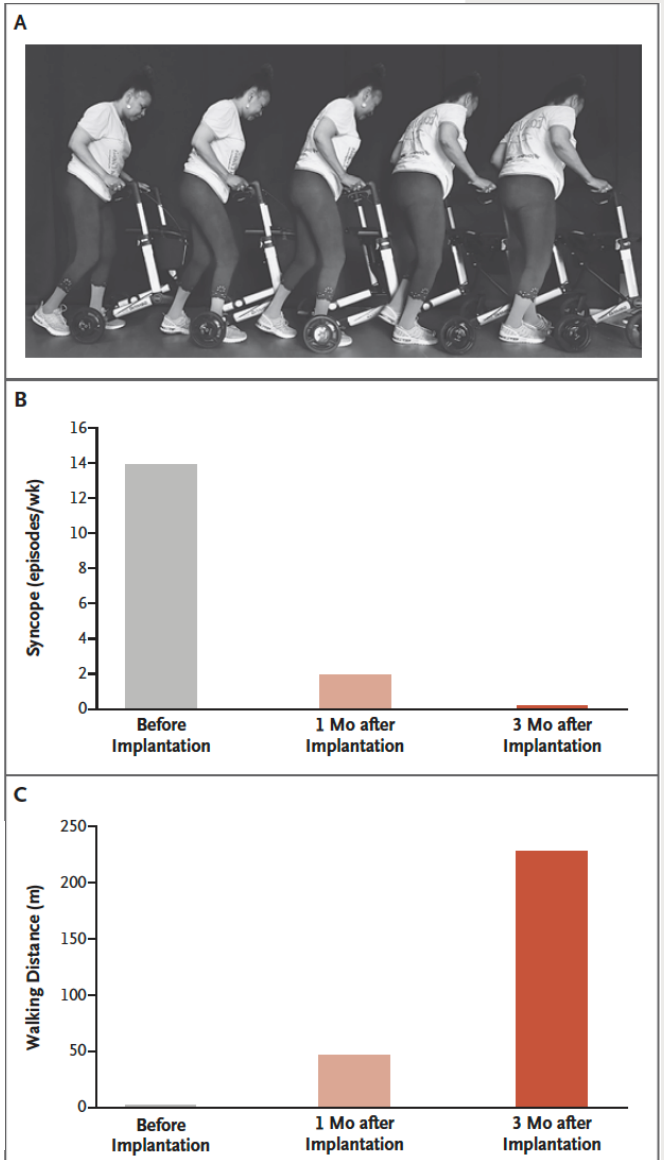
Future directions and innovation

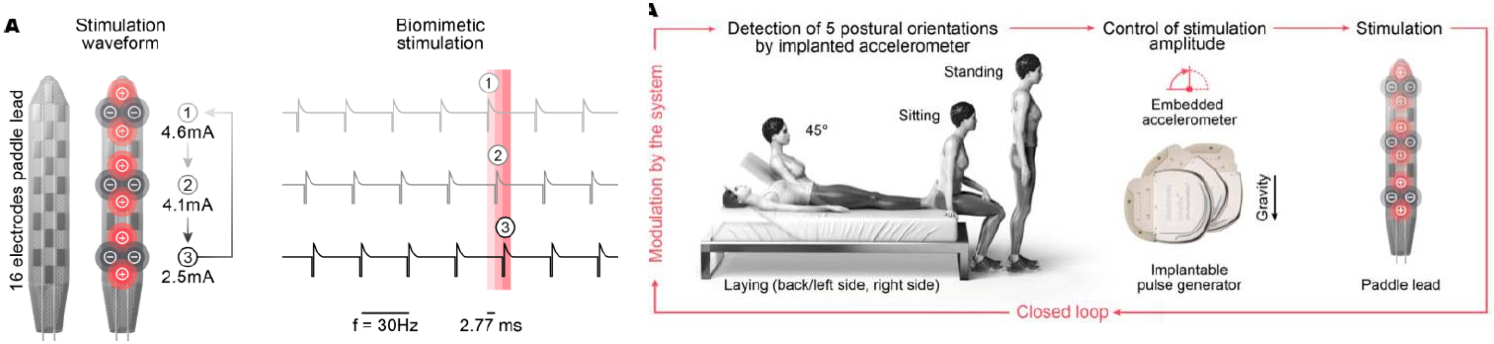
Implanted System for Orthostatic Hypotension in Multiple-System Atrophy

Jordan W. Squair, Ph.D., Maxime Berney, M.D., Mayte Castro Jimenez, M.D.,
Nicolas Hankov, M.Sc., Robin Demesmaeker, Ph.D., Suje Amir, M.Sc.

N Engl J Med 2022:386:1339-44.







GRAZIE PER L'ATTENZIONE