June 16, 2021
Geriatric Research Day
Regional Geriatric Program of Eastern Ontario

Cognitive Impairment and Falls

Evidence, assumptions, and therapeutic options

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Objectives

1- To review the role of cognitive deficits in falls risk

2- To appraise assumptions in current fall prevention management

3- To propose emerging cognitive treatment to reduce risk of falls

What makes a person look old?

- Slow Gait
- Mental Slowing

Falls & Fall-related Injuries Special Interest Group: a Call to Action

Manuel Montero-Odasso, MD, PhD, AGSF, FRCP[1], and David B. Hogan, MD, FRCPC[2]
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DOI: http://dx.doi.org/10.5770/cgj.19.258

Canadian Geriatric Journal 2018

Gaps Identified: Falls in Cognitively Impaired

- Why are falls so common in the cognitively impaired?
- Why does fall prevention not work in this population?
- Are we assuming facts?
- Are we missing a treatment component?

Evidence and Assumptions in Fall prevention

- **Evidence**
  Cognitive impairment is a risk factor for falls
- **Assumption**
  Falls are not related to cognitive problems when a normal MMSE/MoCA is present

Age and Ageing (1978), 7, Supplement

ARE FALLS A MANIFESTATION OF BRAIN FAILURE?

B. ISAACS

The probability that members of this audience will reach the age of eighty is about one in three. The probability that, having done so, they will suffer a damaging fall is about the same. Self-interest alone therefore dictates an active thrust towards fall prevention. Yet is the ability to prevent falls in old age a realistic research objective for the physician or for the pharmacologist? Can anything practical be done other than the avoidance of external hazards and unsuitable drugs?

In the hope of answering these questions I propose to review briefly some aspects of falls in old people; to put forward a classification of falls based on mechanical principles; to discuss the research implications of this classification; and to speculate on a possible pharmacological approach to fall prevention.

Falls in the Cognitively Impaired - Facts

- Falls are two-fold in people with Dementia[1-3]
- Fallers with cognitive problems have
  - ↑ risk of injuries & fractures
  - ↓ functional outcomes
  - ↓ access to rehabilitation
  - ↑ institutionalization
  - ↑ mortality
- Fall prevention is not successful in those with MMSE < 20[4]

1.Tinetti et al. *N Engl J Med* 1988
2. Shaw. *J Neural Transm* 2007
3. Montero-Odasso et al. JAGS 2012, 2018
4. Oliver et al. *BMJ* 2007

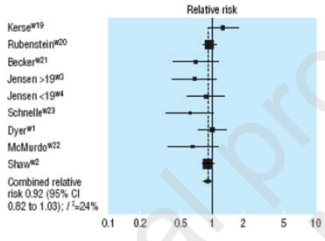
Falls in the Cognitively Impaired - Interventions

Meta-analysis for multifactorial interventions in care homes

8 Studies fulfill criteria for inclusion

The relative risk reduction for fallers was **0.92 (0.82-1.03)**

Confidence intervals included **1**



Oliver et al. *BMJ* 2007

SYSTEMATIC REVIEW

The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis

SUSAN W. MUIR[1], KAREN GOPAUL[1], MANUEL M. MONTERO ODASSO[1,2,3,4]

Fall Outcome	Odd Ratio(95%CI)	I^2 (%)
Any fall	1.32 (1.18,1.49)	74.3%
Serious injury	2.33 (1.61,3.36)	5.9%
Fractures	1.78 (1.34,2.37)	0%
Any fall – low executive function	1.44 (1.20,1.83)	70.9%

Age and Ageing, 2012

Key points

1-Cognitive impairment (MMSE<26) confers high risk of serious injury from a fall **OR=2.33**

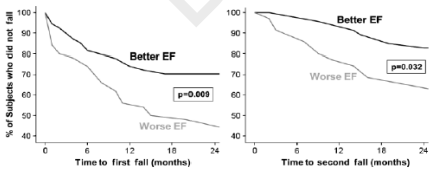
2- Executive dysfunction increases fall risk **OR=1.44**

3- Executive dysfunction can be present despite normality in "global cognition"

4- Executive function should be assessed in falls risk evaluation

Deficits in executive function (EF) predict future falls (2 years of follow up)

HERMAN ET AL.



Herman T, Mirelman A, Giladi N, Schweiger A, Hausdorff JM .Executive control deficits as a prodrome to falls in healthy older adults: a prospective study linking thinking, walking, and falling. J Gerontol A Biol Sci Med Sci. 2010 Oct;65(10):1086-92.

Herman et al. *J Gerontol Med Soc* 2010

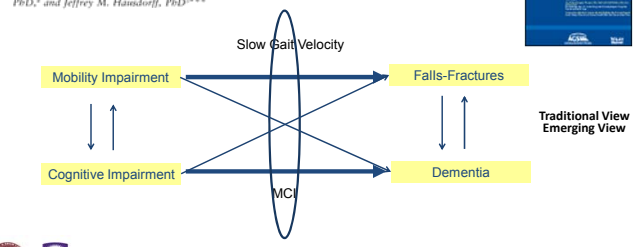
How cognitive deficits may increase risk of falls, at early stages?

PROGRESS IN GERIATRICS

JOURNAL AMERICAN GERIATRICS SOCIETY

Gait and Cognition: A Complementary Approach to Understanding Brain Function and the Risk of Falling

Manuel Montero-Odasso, MD, PhD, AGSF,*† Joe Verghese, MB, BS,‡ Olivier Beauchet, MD, PhD,§ and Jeffrey M. Hausdorff, PhD‖*†



J Am Geriat Soc 2012; 60(11):2127-36.

Gait and cognition: Is there a relationship?

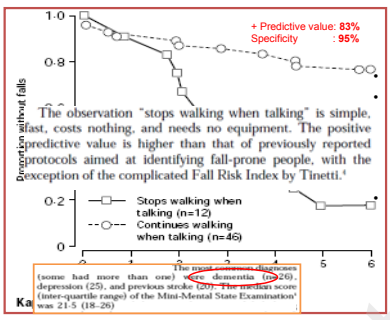
- Gait is an automatic process
- Adults can talk, walk, chew gum at the same time
- Descerebrate cats can walk, why not humans?

BUT…

"Stops walking when talking" as a predictor of falls in elderly people

Lillemor Lundin-Olsson, Lars Nyberg, Yngve Gustafson

THE LANCET Vol 349 • March 1, 1997



The observation "stops walking when talking" is simple, fast, costs nothing, and needs no equipment. The positive predictive value is higher than that of previously reported protocols aimed at identifying fall-prone people, with the exception of the complicated Fall Risk Index by Tinetti.[4]

The most common diagnoses (some had more than one) were dementia (n=26), depression (25), and previous stroke (20). The median score (inter-quartile range) of the Mini-Mental State Examination[5] was 21·5 (18–26)

Walking When Talking

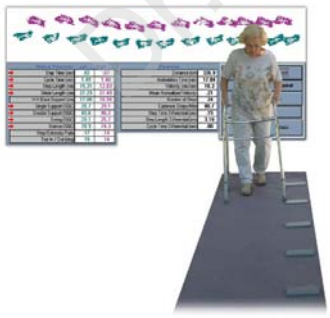
Unmonitored conversations
Reciting names
Counting backward/serial subtractions
Naming animals
Reaction time to auditory stimuli
Q & A
Alphabets

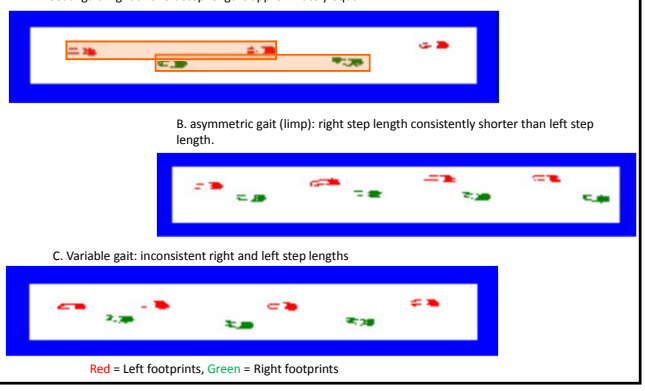
Gait and cognition: Is there a relationship?

YES!

- Patients often explain that they fell when they became distracted
- While performing more that one task in the kitchen, bathroom, etc.

Gait Assessment: quantitative





Which cognitive domains are associated with increased risk of falls?

19

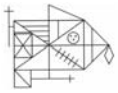
Cognition and falls risk

Executive function/attention

- Victoria Stroop

- Controlled Oral Word Association Test
- Digit span

Visuospatial ability



Rey Complex Figure

Processing speed

- Digit symbol coding
- Symbol search

Memory

- Hopkins Verbal Learning Test
  - Immediate
  - Delay
  - Recognition
- Rey Complex Figure - Delayed

Martin K and Callisaya ML J Gerontology Med Sci 2013

Cognitive Function, Gait, and Gait Variability in Older People: A Population-Based Study

Kara L. Martin,[1] Leigh Blizzard,[1] Amanda G. Wood,[2,3] Velandai Srikanth,[1,4] Russell Thomson,[1] Lauren M. Sanders,[1] and Michele L. Callisaya[1,4]

Multivariable linear regressions between cognition and gait measures

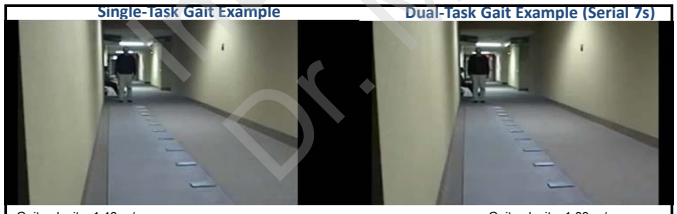
Gait	Processing speed	Executive function	Visuospatial function
Gait speed (cm/s)	✓	✓	
Cadence	✓		
Step length (cm)	✓	✓	
Support base (cm)	✓		
DSP (ms)	✓	✓	
Gait variability			
Step time (ms)		✓	
Step length (cm)			
Support base (cm)			
DSP (ms)	✓	✓	✓

How can we study the gait and cognition relationship?

The dual-task paradigm

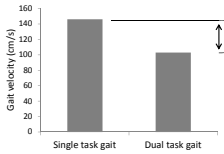
Western

Single-Task Gait Example | **Dual-Task Gait Example (Serial 7s)**



Gait velocity: 1.46 m/sec
Gait variability: 2.83% CoV

Gait velocity: 1.03 m/sec
Gait variability: 13.06% CoV



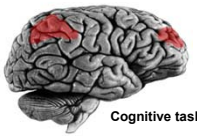
$$\text{Dual task cost} = \frac{Single\ gait - Dual\ task\ gait}{Usual\ gait} \times 100 = \mathbf{30\%}$$

Dual-task paradigm - How does it work?

Brain areas activated while…

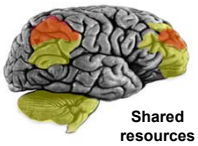
Walking

Single task



Cognitive task

Single task



Shared resources

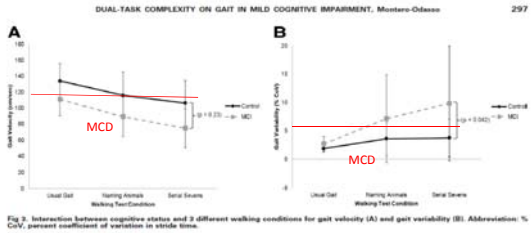
Dual-task

Western

Pashler H. Psychol Bull. 1994

Dual-Task Complexity Affects Gait in People With Mild Cognitive Impairment: The Interplay Between Gait Variability, Dual Tasking, and Risk of Falls

Manuel Montero-Odasso, MD, PhD, Susan W. Muir, PhD, Mark Speechley, PhD



MCD: minimal clinical difference

Arch Phys Med Rehabil. 2012 Feb;93(2):293-9

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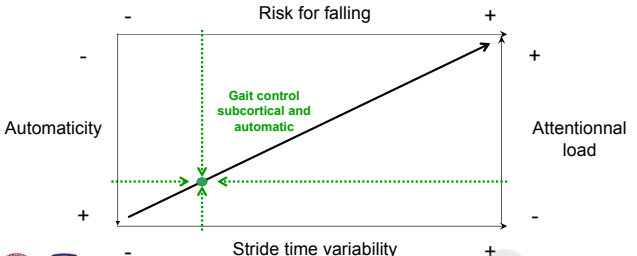

Arch Phys Med Rehabil Vol 93, February 2012

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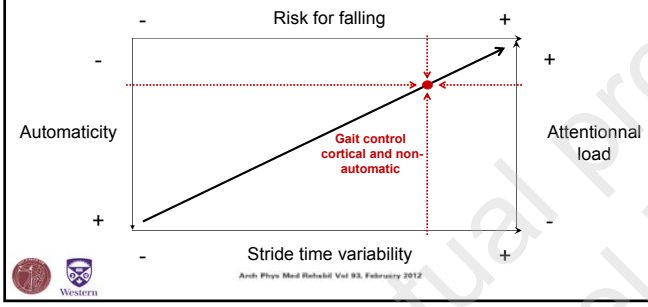
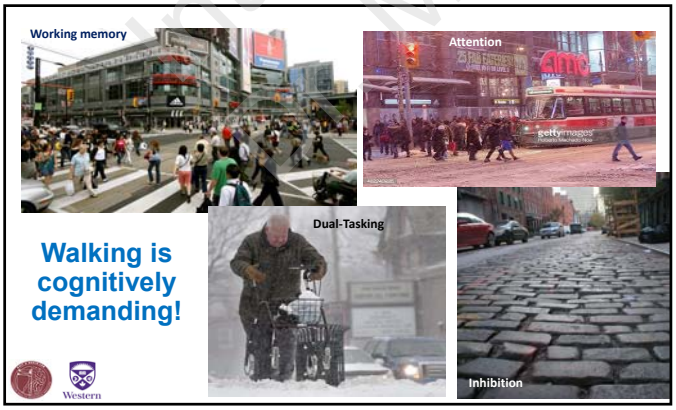


Arch Phys Med Rehabil Vol 93, February 2012

Dual-task paradigm - Why is it relevant?

"How long have you been multitasking?"

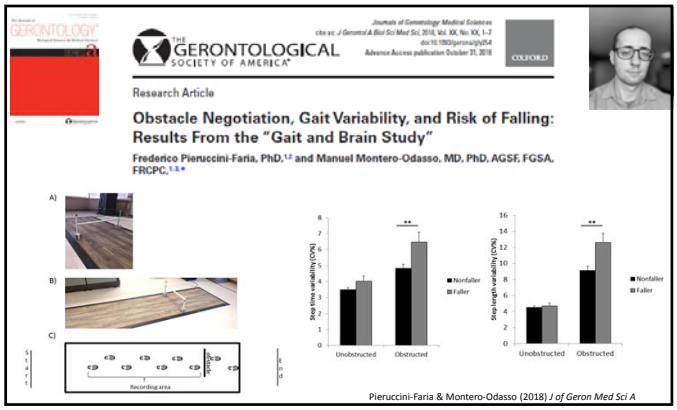
- Dual-task paradigm
  - Observing gait/balance while performing a secondary task
  - "Walking while talking"
- Relevant
  - Daily activities involve the simultaneous performance of two or more cognitive/motor tasks
  - Represents real life situations where falls are likely to occur

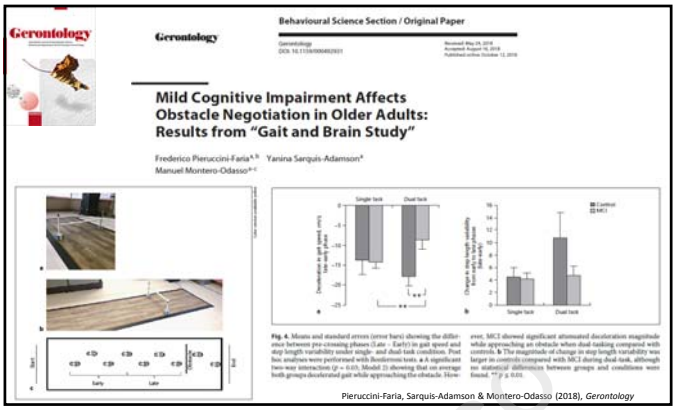


Walking is cognitively demanding!

How does gait-cognitive interaction may increase the risk of falls?

Obstacle negotiation, gait variability, and so on…





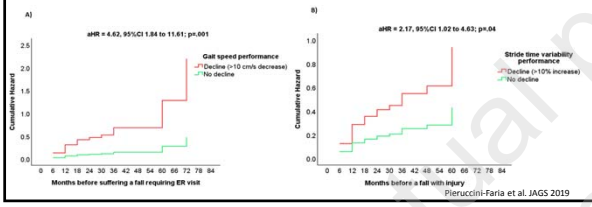
Mapping Associations between Gait Decline and Falls Risk in MCI

Non-rhythmic domains
- Gait speed and Stride time variability

Rhythmic domains
- Swing time and cadence

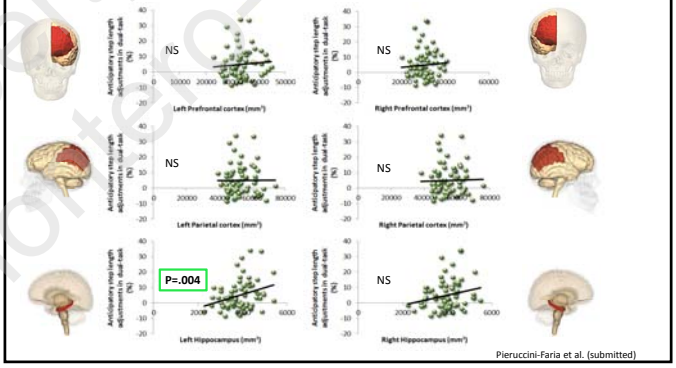
Less automatic control

More automatic control



Pieruccini-Faria et al. JAGS 2019

Human Navigation Network and Obstacle Negotiation in MCI



Pieruccini-Faria et al. (submitted)

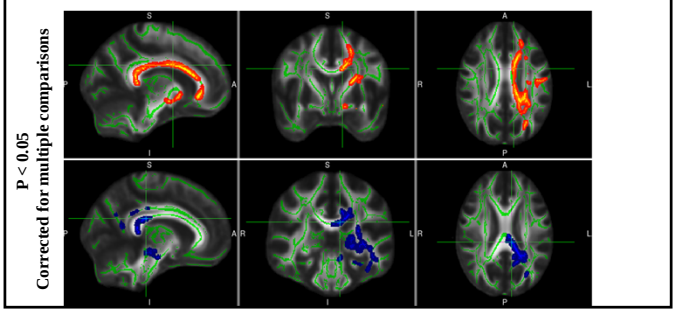
White matter integrity, gait, and falls

- Corpus callosum WMI significantly ($p<0.05$) correlated(+) with single- and dual-task gait velocity and with gait variability(-).

Snir J et al, Neuroimage Clin, 2019

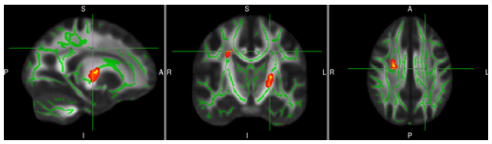
Results: Voxel-wise

Lower WM integrity on the left versus right brain hemispheres (FA – red, MD – blue)

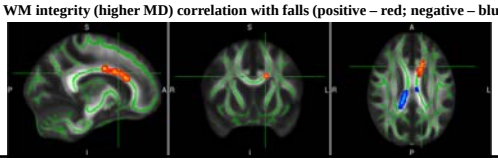


Results: Voxel-wise

Lower WM integrity (lower FA) correlation with falls



Lower WM integrity (higher MD) correlation with falls (positive – red; negative – blue)



White matter integrity, gait, and falls

- Poor WM integrity in the corpus callosum predicted a 3 year gait decline.

FA ↓ MD ↑ → Gait velocity ↓ Gait variability ↑

- Poor WM integrity predicted fall incidence.

FA ↓ MD ↑ → Falls ↑

Snir J et al, Neuroimage Clin, 2019

White matter integrity, gait, and falls

DTI WM integrity → **Gait Performance** → **Falls**

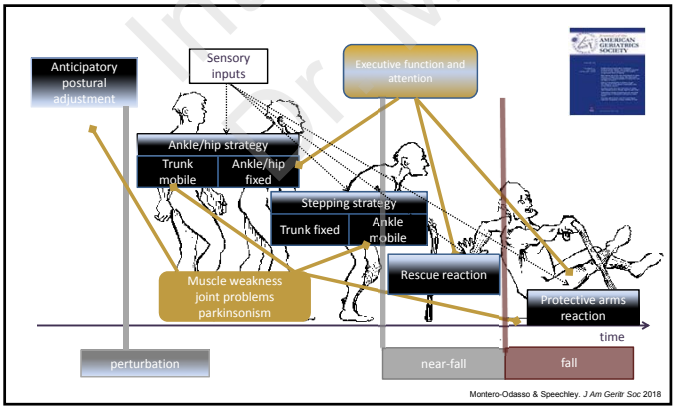
Precursor of White Matter Lesions

Snir J et al, Neuroimage Clin, 2019

Conclusion and framework

How cognition, executive processes, may affect gait and posture before falling?

How is the neurobiology of falls ?



Montero-Odasso & Speechley. *J Am Geritr Soc* 2018

If we purposely target cognition,

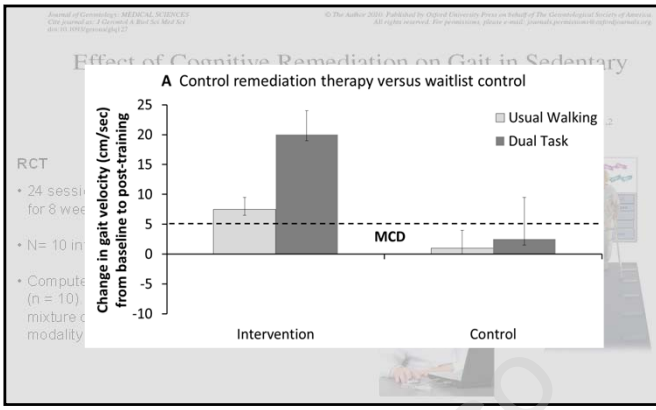
can we improve gait & reduce falls?

Effect of Cognitive Remediation on Gait in Sedentary Seniors

Joe Verghese,[1] Jeannette Mahoney,[1,2] Anne F. Ambrose,[3] Cuiling Wang,[4] and Roee Holtzer[1,2]

RCT

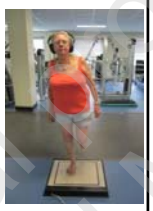
- 24 sessions, 45-60 min each, 3 times/week for 8 weeks
- N= 10 intervention/10 control
- Computerized 'Mindfit' program (n = 10) Each training session included a mixture of 21 visual, auditory and cross-modality tasks compared with wait-list controls (n= 10)

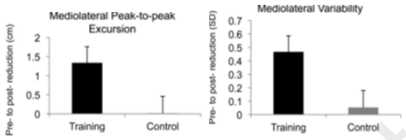


Benefits of Cognitive Dual-Task Training on Balance Performance in Healthy Older Adults

Karen Z. H. Li,[1] E. Roudaia,[2] M. Lussier,[3,4] L. Bherer,[3,4] A. Leroux,[5] and P. A. McKinley[6]

- N=20 healthy older adults (76y/o)
- Randomly assigned to attentional training or no-treatment
- 5 (1-hour) sessions x 3 weeks





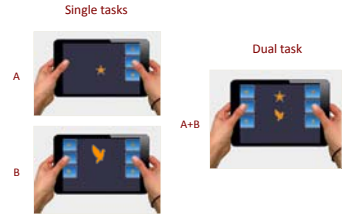
Transfer effect!

Attentional training method

(Bherer, Kramer, et al., 2005; Erickson et al., 2008)

Cognitive Training

- 30 minutes of single and dual-task blocks
- Task A: celestial bodies
- Task B: Animals
- Adaptive increase in difficulty over sessions



Donepezil Improves Gait Performance in Older Adults with Mild Alzheimer's Disease: A Phase II Clinical Trial

Manuel Montero-Odasso[a,b,c,*], Susan W. Muir-Hunter[a,b], Afua Oteng-Amoako[a], Karen Gopaul[a], Anam Islam[a], Michael Borrie[b], Jennie Wells[b] and Mark Speechley[c]
[a]"Gait and Brain Lab", Parkwood Hospital and Lawson Health Research Institute, London, ON, Canada
[b]Department of Medicine, Division of Geriatric Medicine, Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada
[c]Department of Epidemiology & Biostatistics, Schulich Interfaculty Program in Public Health, University of Western Ontario, London, ON, Canada

Design: Phase II clinical trial
Participants: 43 seniors with mild AD received donepezil.
Primary outcome: Gait velocity and variability under single and dual-tasking using an electronic walkway
Secondary outcomes: Attention and executive function
Intervention: 5 mg/day of donepezil for 1 month
10 mg/day for the subsequent 3 months (4 month follow-up)

Donepezil Study

Participants took donepezil/placebo for 6 months

Donepezil group had lower number of falls, lower participants who fell, and lower risk of falls

	6 months prior to intervention		6 months after intervention		
	Placebo (n= 29)	Donepezil (n= 31)	Placebo (n= 25)	Donepezil (n= 20)	p value
Total # of falls	6	5	21	13	0.209
# participants who fell (%)	5 (17%)	5 (17%)	12 (41%)	7 (23%)	0.159
Falls per participant	0.21	0.17	0.72	0.42	

Phase III RCT Study
2013-2018

BMC Neurology

BioMed Central

Study protocol

Open Access

Can cognitive enhancers reduce the risk of falls in older people with Mild Cognitive Impairment? A protocol for a randomised controlled double blind trial

Manuel Montero-Odasso*[1,2,3], Jennie L Wells[1,3], Michael J Borrie[1,3] and Mark Speechley[2,3]

Address: [1]Department of Medicine, Division of Geriatric Medicine, Parkwood Hospital, University of Western Ontario, London, ON, Canada, [2]Department of Epidemiology and Biostatistics, University of Western Ontario, London, ON, Canada and [3]Lawson Health Research Institute, London, ON, Canada

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* Corresponding author

Montero-Odasso, M et al *BMC neurology* 9.1 (2009): 42. **ClinicalTrials.gov Identifier: NCT00934531**

ORIGINAL ARTICLE

Donepezil for gait and falls in mild cognitive impairment: a randomized controlled trial

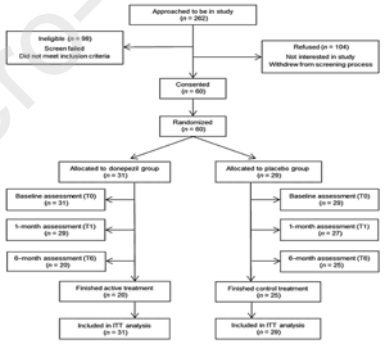
M. Montero-Odasso[a,b,c], M. Speechley[c,d], H. Chertkow[e], Y. Sarquis-Adamson[a], J. Wells[b], M. Borrie[b], L. Vanderhaeghe[f], G. Y. Zou[g,g], S. Fraser[h], L. Bherer[i] and S. W. Muir-Hunter[a,i]

[a]Gait and Brain Lab, Parkwood Institute and Lawson Health Research Institute, University of Western Ontario, London, ON; [b]Division of Geriatric Medicine, Department of Medicine, Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON; [c]Department of Epidemiology and Biostatistics, University of Western Ontario, London, ON; [d]Schulich Interfaculty Program in Public Health, University of Western Ontario, London, ON; [e]Jewish General Hospital Memory Clinic, McGill University, Montreal, QC; [f]Pharmacy Services, St Joseph's Health Care, London, ON; [g]Robarts Research Institute, London, ON; [h]Interdisciplinary School of Health Sciences, University of Ottawa, Ottawa, QC; [i]Department of Medicine, Université de Montréal and Montreal Heart Institute, Montreal, QC; and [j]School of Physical Therapy, University of Western Ontario, University of Western Ontario, ON, Canada

Montero-Odasso et al. *Eur J Neurol. 2019 Apr;26(4):651-659.* doi: 10.1111/ene.13872. Epub 2018 Dec 26.

Consort Diagram

ClinicalTrials.gov Identifier: NCT00934531



Mixed effects model with repeated measures for the primary outcomes comparing the effect between placebo and donepezil treatments at T6.

	Full sample (n = 45)	Placebo (n = 25)	Donepezil (n = 20)	P-value[a]	P-value[b]
Gait speed (cm/s)					
Single-task	110.35 (20.49)	111.60 (18.80)	108.85 (22.76)	0.362	0.137
Dual-task					
Counting	102.91 (23.44)	101.26 (24.93)	104.80 (22.07)	0.263	0.511
Serial 7	87.66 (19.39)	88.09 (20.77)	87.20 (18.41)	0.323	0.533
Naming animals	90.73 (20.86)	90.71 (22.62)	90.75 (19.49)	0.459	0.642
DTC (%)					
Counting	6.30 (16.94)	10.25 (12.35)	1.75 (20.43)	**0.048**	0.056
Serial 7	18.10 (21.14)	21.38 (14.92)	14.64 (26.19)	**0.033**	**0.037**
Naming animals	15.50 (21.15)	18.84 (17.97)	11.78 (24.19)	0.282	0.269
Gait variability (CoV)					
Single-task	4.10 (2.61)	3.77 (1.28)	4.51 (3.66)	0.223	0.239
Dual-task					
Counting	5.35 (5.06)	5.26 (4.15)	5.45 (6.09)	0.221	0.389
Serial 7	6.31 (6.63)	5.80 (6.84)	6.93 (6.51)	0.133	0.201
Naming animals	4.72 (3.79)	4.82 (4.47)	4.59 (2.76)	0.526	0.370

CoV, coefficient of variation; DTC, dual-task gait cost; [a]Mixed model adjusted for baseline values of each variable; [b]Mixed model adjusted for baseline values of each variable plus age, sex and previous falls. Data are given as mean (SD). Values in bold are statistically significant.

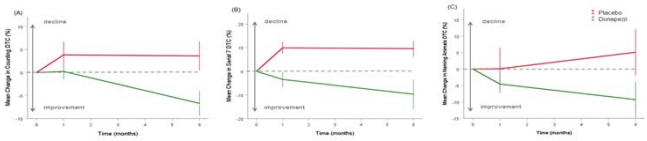
Donepezil Study and Falls

Donepezil group had lower number of total falls and lower participants who fell, although not significant

	6 months prior to intervention		6 months after intervention		
	Placebo (n = 29)	Donepezil (n = 31)	Placebo (n = 25)	Donepezil (n = 20)	P-value
Total no. of falls	6	5	21	13	0.209
No. of participants who fell (%)	5 (17%)	5 (17%)	12 (41%)	7 (23%)	0.159
Falls per participant	0.21	0.17	0.72	0.42	

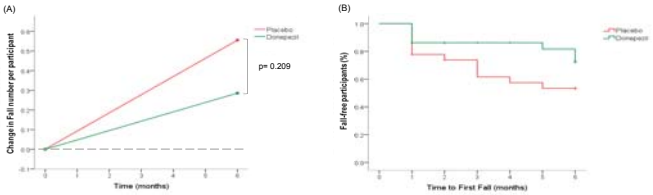
Donepezil Study and Falls

Dual-task cost (DTC) mean change for A) counting, B) serial sevens subtractions, and C) naming animals conditions. Error bars represent ±1 S.E.



Donepezil Study and Falls

Falls during intervention/follow up
A) changes in number of falls after intervention
B) Kaplan-Meier survival curve for falls.



Final Summary

- Current state of the knowledge precludes formulating strong evidence-based recommendations to manage falls in cognitively impaired older adults by **targeting cognition**, but *practical suggestions* can be made:

1. ***Exercise combined with cognitive and dual-task training*** can improve gait performance and balance in older adults with *MCI and executive dysfunction* and reduce their falls risk.
2. Exercise interventions, including dual-task training, are ***feasible*** in older adults with *mild AD.*
3. ***Pharmacological interventions*** may reduce falls in *PD populations*, and thus, a trial treatment with cholinergic inhibitors can be used.

Final Summary

4. **Cognitive deficits** exacerbate falls risk even in ***"cognitively normal"***

5. ***Falls risk screening*** should include assessment of cognitive processes (i.e., selective attention, inhibition, conflict resolution, and dual-tasking).

6. ***Falls prevention*** should consider intervention components that target cognition, specifically executive function.

- **Complementary Approach: Improve Cognition to Reduce Falls**
  Enhancing attention/executive function may reduce falls risk
  (*caution*: publication bias, small studies, larger RCTs needed)

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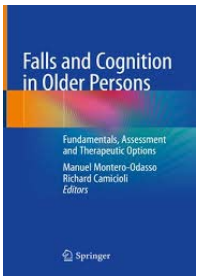
If you want to learn more!



Thank you!!!!

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Non-Pharmacological Interventions: Cognitively Normal Population

Study (year)	Design	Type of intervention and control	Duration	Participants	Summary of findings
You *et al.* (2009) [44]	RCT	Dual-task training with simultaneous motor (walking 30 m) and cognitive (memory recall) task (n= 8), and control group (n= 5) walked while music listening	18 sessions, 30-min per session over 6 weeks	13 participants (age: 68.3 ± 6.5 years) with history of falls	Working memory under the dual-task condition improved ($p< 0.05$). No significant changes in gait velocity and variability were found
Silsupadol *et al.* (2009) [41]	RCT	Three intervention arms: sSingle-task training (n= 7), dual-task training with fixed-priority instructions (n= 8), and dual-task training with variable-priority instructions (n= 6)	12 sessions; 45-min individualized sessions, 3 times/week for 4 weeks	21 participants (aged ≥65 years) with balance impairment	All groups improved balance and gait velocity. Only the DT training with variable-priority instructions group demonstrated a DT training effect at the second week maintained at 12-week follow-up
Verghese *et al.* (2010) [39]	RCT	Computerized 'Mindfit' program vs wait-list control. Each training session included a mixture of 21 visual, auditory and cross-modality tasks compared with wait-list	24 sessions; 45-60 min/ session, 3 times a week for 8 weeks	20 Sedentary older adults (age: 77.4 ± 7.0 y) at training, and wait-list (age: 79.9 ± 7.5 years)	Gait velocity and DT gait velocity improved $p< 0.05$ and $p= 0.002$, respectively) only in intervention group. Processing speed improved significantly in the intervention group ($p= 0.03$)
Van het Reve *et al.* (2014) [34]	RCT	Strength-balance (SB, n=98) or strength-balance-cognitive (SBC, n=84) training	2 times/week; 40-min SB. SBC received cognitive training, 3 times/week for 12 weeks	182 participants (aged ≥65 years) living in autonomous residences for the elderly	SBC group improved fast gait velocity ($p=0.04$), dual-task gait cost ($p=0.03$), executive function (TMT B, $p=0.001$), and fall rate ($p=0.001$).
Smith-Ray *et al.* (2015) [40]	RCT	Computer-based cognitive training intervention (n= 27) or measurement-only control (n= 24)	10 weeks; 3 times per week, for 60 minutes per session	51 participants (age:82 ± 6 years) from independent living facilities	Intervention group performed better than controls on the TUG
Falbo *et al.* (2016) [42]		Physical single task (ST) training (n= 16) and physical-cognitive dual task (DT) training (n= 20)	12 weeks; 1 hour twice weekly in group-based exercise classes	36 healthy active individuals (age: 72.3 ± 5.8 years)	Gait performance increased in both groups, but executive function increased only in DT group.

Non-Pharmacological Interventions: Clinical Populations

Study (year)	Design	Type of intervention and control	Duration	Participants	Summary of findings
PD and MCI Populations					
Yogev-Seligmann *et al.* (2012) [60]	Open-label, pilot	A 4-week program of one-on-one training included walking while performing several distinct cognitive tasks	12 sessions; 3 per week for 4 weeks	7 participants with PD (age: 63.8 ± 8.4 years)	Gait velocity and gait variability during DT significantly improved. Untrained DT also improved and was retained 1 month after the end of the training
Mirelman *et al.* (2011) [46]	Repeated measures design	TT with virtual obstacles. The VR simulation required obstacle negotiation while continuing to walk on the treadmill. Comparison was made to a historical control group that followed similar protocol of TT but without VR	18 sessions (3 per week for 6 weeks)	20 participants with PD (age: 67.1 ± 6.5 years) able to walk unassisted for at least 5 minutes	Dual-tasking, gait velocity ($p= 0.003$) and stride length ($p< 0.001$) were significantly improved after TT VR compared with TT alone. Dual-task gait variability decreased, and Trail Making Test improved after TT VR training
Mirelman *et al.* (2016) [47]	RCT	TT with non-immersive VR (participants walked on a treadmill while watching a large screen that projected a path with obstacles, multiple pathways, and distracters). Control group consisted of TT alone with no VR	18 sessions (3 per week for 6 weeks)	300 participants with normal cognition, MCI and PD (aged 60 to 90 years) with a history of at least 2 falls	After 6 months of training, incident rate of falls was lower in TT with VR group compared with their rate of falls before the training ($p<0.001$) and compared with the TT alone group ($p=0.033$)
van Ooijen *et al.* (2016) [48]	RCT	Inpatient adaptability treadmill (AT) training, conventional treadmill (CT) training or usual physical therapy (UPT)	30 sessions (40 min each); 5 per week for 6 weeks	70 participants with a fall related hip-fracture (aged ≥ 65 years)	Subgroup of participants with executive dysfunction improved walking adaptability and fear of falling.
Mild Dementia Population					
Schwenk et al. (2010) [45]	RCT	Intervention group (n= 20) underwent dual-task-based exercise training (motor: throwing or catching a ball, and cognitive: arithmetic tasks, repeating names of animals). Control group (n= 29) performed low-intensity exercise	24 sessions over 12 weeks, 1 hour twice a week	49 participants (mean age: 81.9 ± 7.5 years) with mild-to-moderate dementia (MMSE: 21.4 ± 2.9)	DT training improved gait velocity under dual-task ($p< 0.001$), cadence ($p= 0.007$), stride length ($p= 0.001$), single support ($p= 0.003$) under complex three-step backward calculation conditions compared with the control group

Pharmacological Cognitive Interventions: Cognitively Normal Population

Study (year)	Study design	Type of intervention	Duration	Participants	Summary of findings
Ben-Itzhak *et al.* (2008) [49]	RCT, double-blind, placebo-controlled	Before and 2 h after taking 20 mg MPH or a placebo	2 h	26 participants without dementia with subjective memory complaints (age: 73.8 ± 1.2 years, mean MMSE: 27.8 ± 1.4)	MPH improved Timed Up and Go ($p= 0.004$), stride time variability ($p= 0.03$) and EF ($p= 0.03$); effects not observed after treatment with the placebo
Shorer *et al.* (2013) [50]	RCT, double-blind, placebo-controlled	Before and 1.5 h after taking 10 mg MPH or a placebo	2 h	30 participants without dementia (age: 74.9 ± 5.6 years, MMSE: > 24)	MPH improved narrow base walking by reducing number of step errors ($p= 0.040$) in single and dual-tasks; effects not observed in placebo group

Pharmacological Cognitive Interventions: Clinical Populations

Study (year)	Study design	Type of intervention	Duration	Participants	Summary of findings
MCI and AD Populations					
Assal *et al.* (2008) [53]	Before–after design	Galantamine mean dose of 17.8 ± 3.5 mg/day	6 months	9 participants with mild-to-moderate AD (age: 77.9±2.1 years; MMSE: 26.4±5.2) compared with 18 no-treatment control subjects (age: 78.1±1.0 years; MMSE: 29.4±0.8)	Stride time was shorter under dual-tasking after treatment ($p= 0.01$). There was no change in the controls
Montero-Odasso *et al.* (2009) [51]	Open-label study with controls	5 mg/day of donepezil for 1 month, and another 3 months with 10 mg/day. MCI group with no treatment	4 months	6 participants with mild AD (age: 79.9 ± 4.8 years; MMSE: 22.3 ± 1.2; MoCA: 15 ± 1.4) compared with 8 participants with MCI (age: 75.6 ± 6.2 years; MMSE: 27.9 ± 1.7; MoCA: 22.9 ± 1.7)	Participants with mild AD increased their single ($p= 0.045$) and dual-task gait velocity ($p= 0.047$) after 1 month. Stride time variability decreased (improved). Control group declined in gait velocity and variability
Beauchet *et al.* (2011) [56]	Before–after design	Memantine mean dose of 20 mg/day, titrated in 5 mg increments over 4 weeks	4.4 to 8 months	17 participants with AD (age 83.8±5.8 years; 52.9% women; MMSE: 14.5±4.2) and 32 age-sex-matched controls with AD without any anti-dementia drug (age: 0.0±6.6 years; MMSE: 23.2±5.3)	Stride time variability decreased (improved) during follow-up in the memantine group (6.3±6.1 versus 3.6±1.3, P=0.038)
Montero-Odasso *et al.* (2015) [54]	Before-after design	5 mg/day of donepezil for 1 month, and 5 months with 10 mg/day	5 months	43 patients with mild AD (age: 76.9 ± 8 years; MMSE: 24.63 ± 2; MoCA: 18.5 ± 4)	Gait velocity improved from 108.4±18.6 to 113.3±19.5 cm/s ($p=0.01$); dual-task gait velocity from 80.6±23.0 to 85.3±22.3 cm/s ($p=0.03$). Trail Making Tests A ($p=0.030$), B ($p=0.001$) and B-A ($p=0.042$) improved after intervention
Montero-Odasso *et al.* (2018) [55]	RCT, double-blind, placebo-controlled	First month with 5 mg/day of donepezil , and next 5 months with 10 mg/day	6 months	60 patients with MCI (age: 75.3 ± 7 years; MMSE: 27.5 ± 2; MoCA: 23.6 ± 2.5)	Gait velocity improved only under dual –task conditions, and there was a reduction in falls, albeit not significant.

Pharmacological Cognitive Interventions: Clinical Populations

Study (year)	Study design	Type of intervention	Duration	Participants	Summary of findings
PD Populations					
Auriel *et al.* (2006) [57]	Open-label, before-after design	Before and 2 h after taking a single dose of 20 mg of MPH	2 h	21 participants with PD who receive l-Dopa, (age: 70.2 ± 9.2 years, MMSE: 28.8 ± 1.7)	Improvement in Attention ($p= 0.025$), EF Index showed only a trend ($p= 0.09$). Improvements in Timed Up and Go ($p = 0.001$), gait velocity ($p = 0.005$) and stride time variability ($p = 0.013$)
Chung *et al.* (2010) [58]	Randomized, crossover, double-blind	Donepezil vs placebo. 5 mg/day of donepezil or placebo for 3 weeks, and increase to 10 mg/day for the remaining 3 weeks	6 weeks, 3 weeks washout, 6 weeks of placebo	23 participants with PD who reported falling or nearly falling (age: 68.3 ± 10.8 years; MMSE: 27.6 ± 4.5)	Less falls with donepezil than placebo ($p= 0.049$). Participants with the most falls at baseline tended to show the largest improvements. No differences found in Balance Confidence, Berg Balance, UPDRS III or MMSE tests
Henderson *et al.* (2016) [59]	RCT, double-blind, placebo-controlled	Rivastigmine titrated from 3 mg/day (or placebo); incremented every 4 weeks to a maximum of 12 mg/day at week 13 onwards	8 months	130 patients with mild PD (mean age: 71.9 ± 4.8 years; 1.2; MoCA: 25 ± 1.4); half in the intervention groups and half in the placebo group	Intervention improved gait velocity (greatest effect) and dual-task gait velocity. Stride time variability decreased (improved) not significantly. Falls rate (secondary outcome) was significantly lower in intervention group