



59° Congresso SIGG

Bologna, 26-29 Novembre 2014



SIMPOSIO

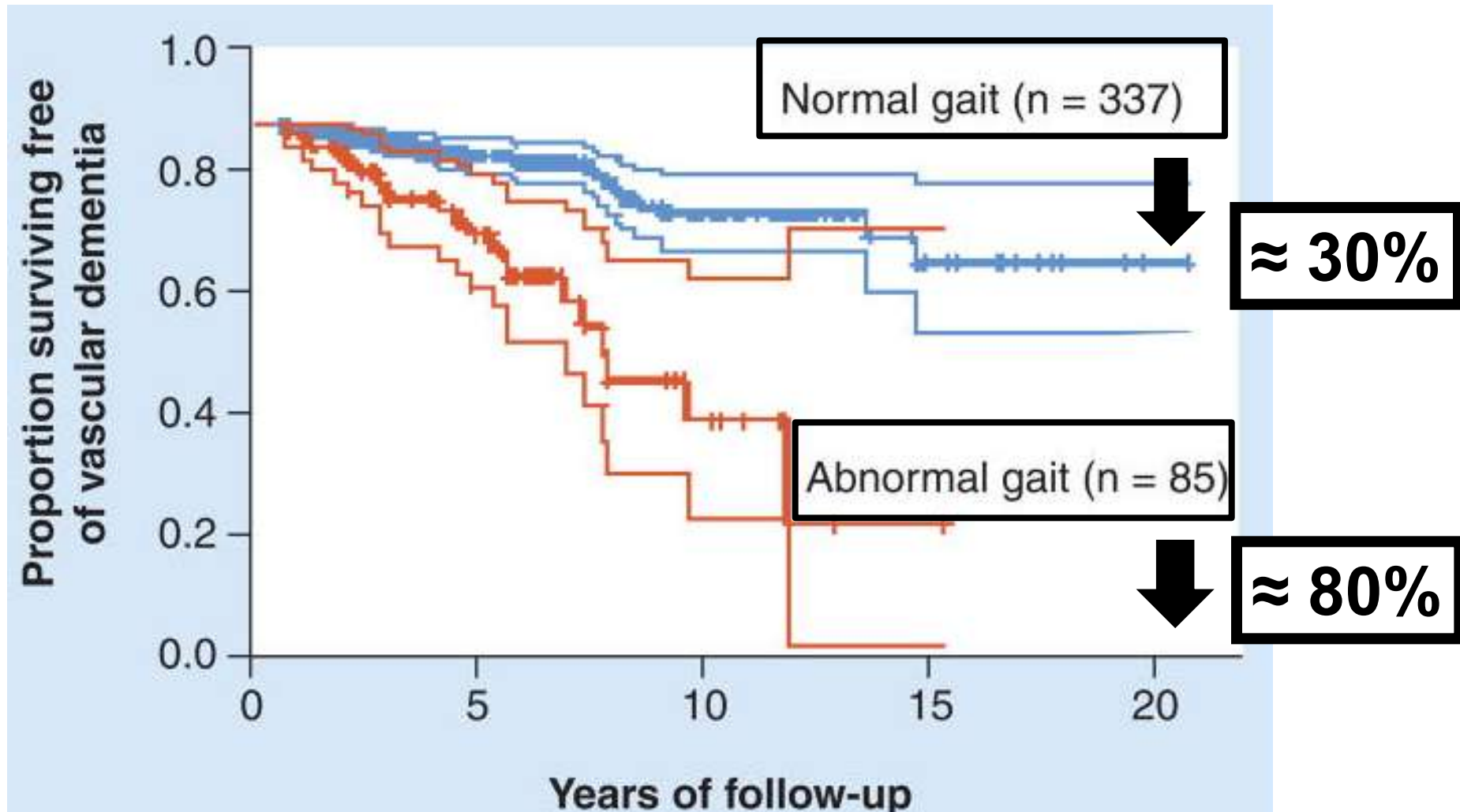
“Le perdite di coscienza nell’anziano con demenza:
un territorio da esplorare”

“Farmaci per la demenza e rischio di cadute e sincope”

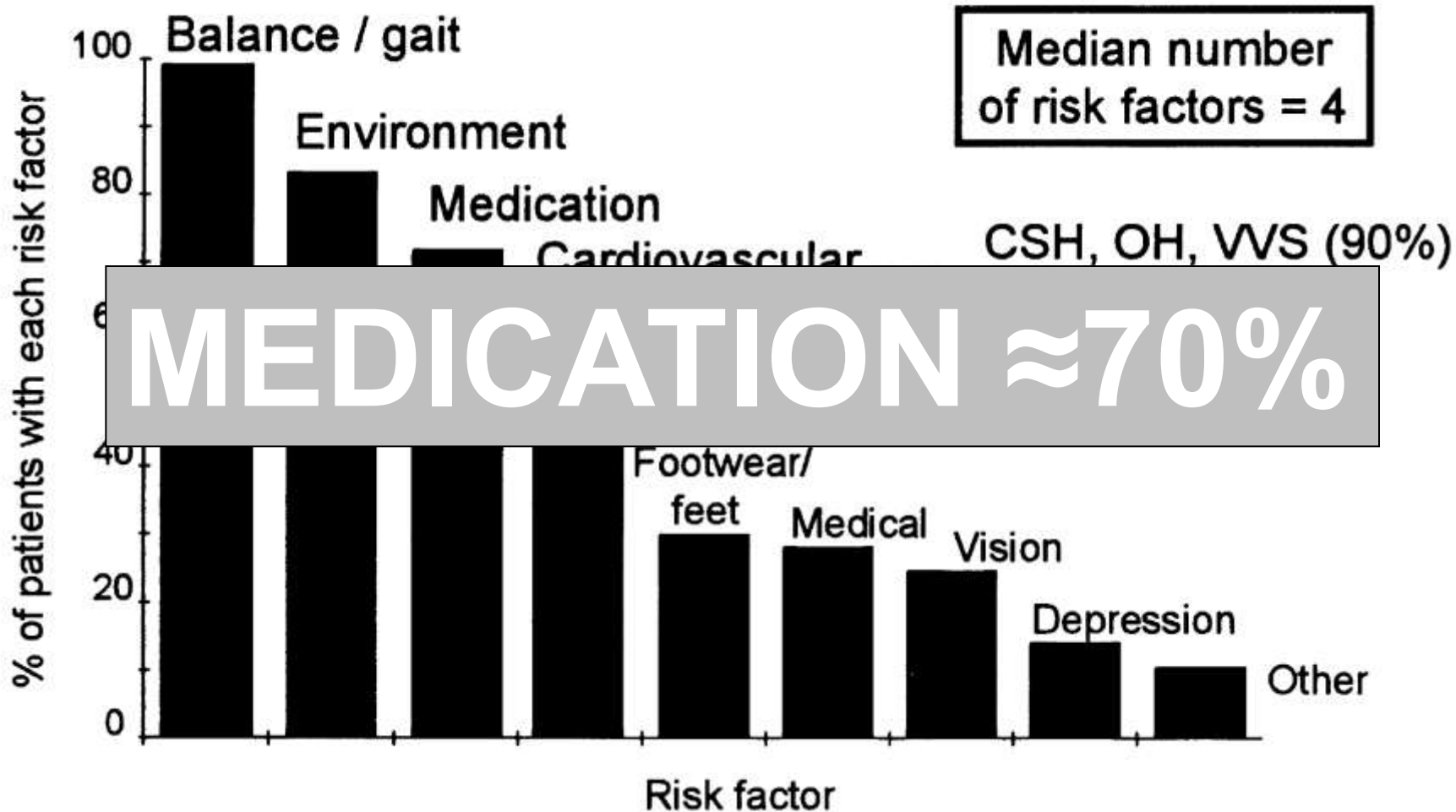
Abete P, MD, PhD

Dipartimento di Scienze Mediche Traslazionali
Università di Napoli Federico II

Kaplan–Meier curves for the cumulative risk of dementia with and without gait alterations



Attributable cause of falls in patients with cognitive impairment and falls



CSH=Carotid sinus hypersensitivity
OH=Ortostatic Hypotension
VSS=Vaso-vagal syndrome

Meta-analysis of the Impact of 9 Medication Classes on Falls in Elderly Persons

MEDICATIONS	OR (95 CI)
Antidepressants	1.72 (1.40-2.11)
Neuroleptics/antipsychotics	1.71 (1.44-2.04)
Benzodiazepines	1.60 (1.46-1.75)
Sedatives/hypnotics	1.31 (1.14-1.50)
Antihypertensives	1.26 (1.08-1.46)
NSAIDs	1.65 (0.98-2.77)
B-Blockers	1.14 (0.97-1.33)
Diuretics	1.03 (0.84-1.26)
Narcotics	0.89 (0.50-1.58)
Cholinesterase inhibitors	0.88 (0.74-1.04)



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“Le perdite di coscienza nell’anziano con demenza: un territorio da esplorare”

Farmaci per la demenza e rischio di cadute e sincope



- Negative chrono/dromotropic effect**
- Long QT syndrome**
- Brugada syndrome**
- Orthostatic hypotension**

**Negative
chrono/dromotropic
effect**

**Orthostatic
hypotension**

**DRUGS-INDUCED
FALL AND/OR
SYNCOPE
IN THE ELDERLY**

**Long QT
syndrome**

**Brugada
syndrome**



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“Le perdite di coscienza nell’anziano con demenza: un territorio da esplorare”

Farmaci per la demenza e rischio di cadute e sincope



-
- **Cholinesterase inhibitor/Memantine**
 - **Anti-epileptic**
 - **Anti-psychotic**
 - **Benzodiazepines**
 - **Anti-depressant**
 - **Anti-Parkinson**



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Anti-dementia drugs

ACETYLCHOLINESTERASE INHIBITORS	N-methyl-D-aspartate (NMDA) RECEPTOR ANTAGONIST
Donepezil	Memantine
Rivastigmine	
Galantamine	

Dementia Medications and Risk of Falls, Syncope, and Related Adverse Events: Meta-Analysis of Randomized Controlled Trials

Dae Hyun Kim, MD, MPH,^{*†‡} Rebecca T. Brown, MD,^{*‡} Eric L. Ding, ScD,[§]
Douglas P. Kiel, MD, MPH,^{*‡} and Sarah D. Berry, MD, MPH^{*‡}

OBJECTIVES: To evaluate the effect of cholinesterase inhibitors (ChEIs) and memantine on the risk of falls, syncope, and related events, defined as fracture and accidental injury.

DESIGN: Meta-analysis of randomized controlled trials that were identified from MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (no language restriction, through July 2009), and manual search.

SETTING: Community and nursing homes.

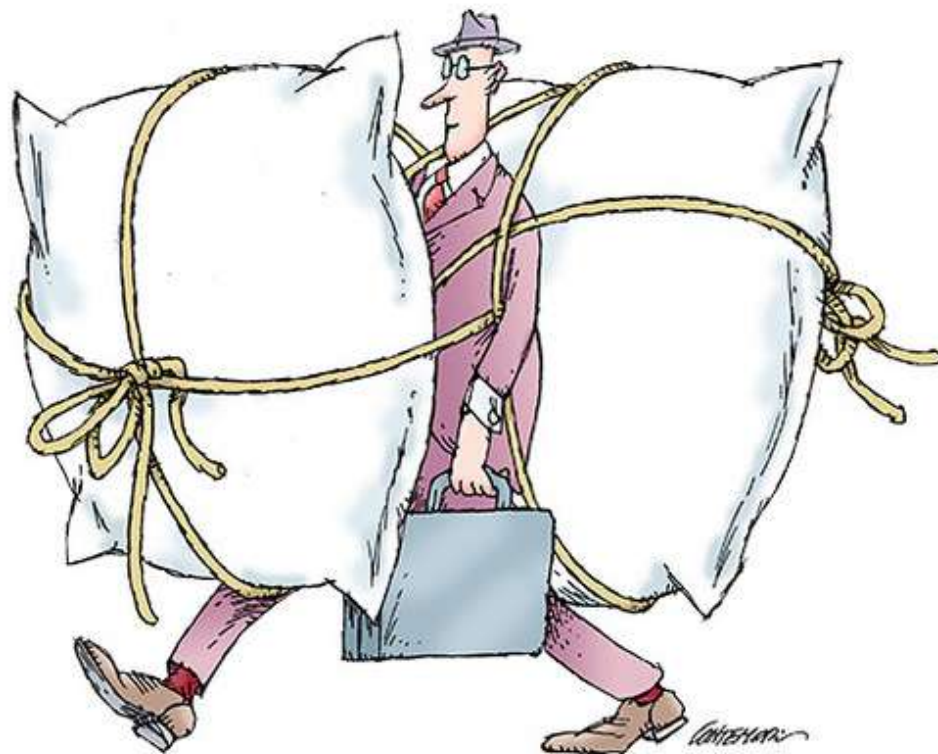
PARTICIPANTS: Participants in fifty-four placebo-controlled randomized trials and extension studies of ChEIs and memantine that reported falls, syncope, and related events in cognitively impaired older adults.

MEASUREMENTS: Falls, syncope, fracture, and accidental injury.

RESULTS: ChEI use was associated with greater risk of syncope (odds ratio (OR) = 1.53, 95% confidence interval (CI) = 1.02–2.30) than placebo but not with other events (falls: OR = 0.88, 95% CI = 0.74–1.04; fracture: OR = 1.39, 95% CI = 0.75–2.56; accidental injury: OR = 1.13, 95% CI = 0.87–1.45). Memantine use was associated with fewer fractures (OR = 0.21, 95% CI = 0.05–0.85) but not with other events (falls: OR = 0.92, 95% CI = 0.72–1.18; syncope: OR = 1.04, 95% CI = 0.35–3.04; accidental injury: OR = 0.80, 95% CI = 0.56–1.12). There was no differential effect according to type and severity of cognitive impairment, residential status, or length of follow-up, although because of underreporting and small number of events, a potential benefit or risk cannot be excluded.

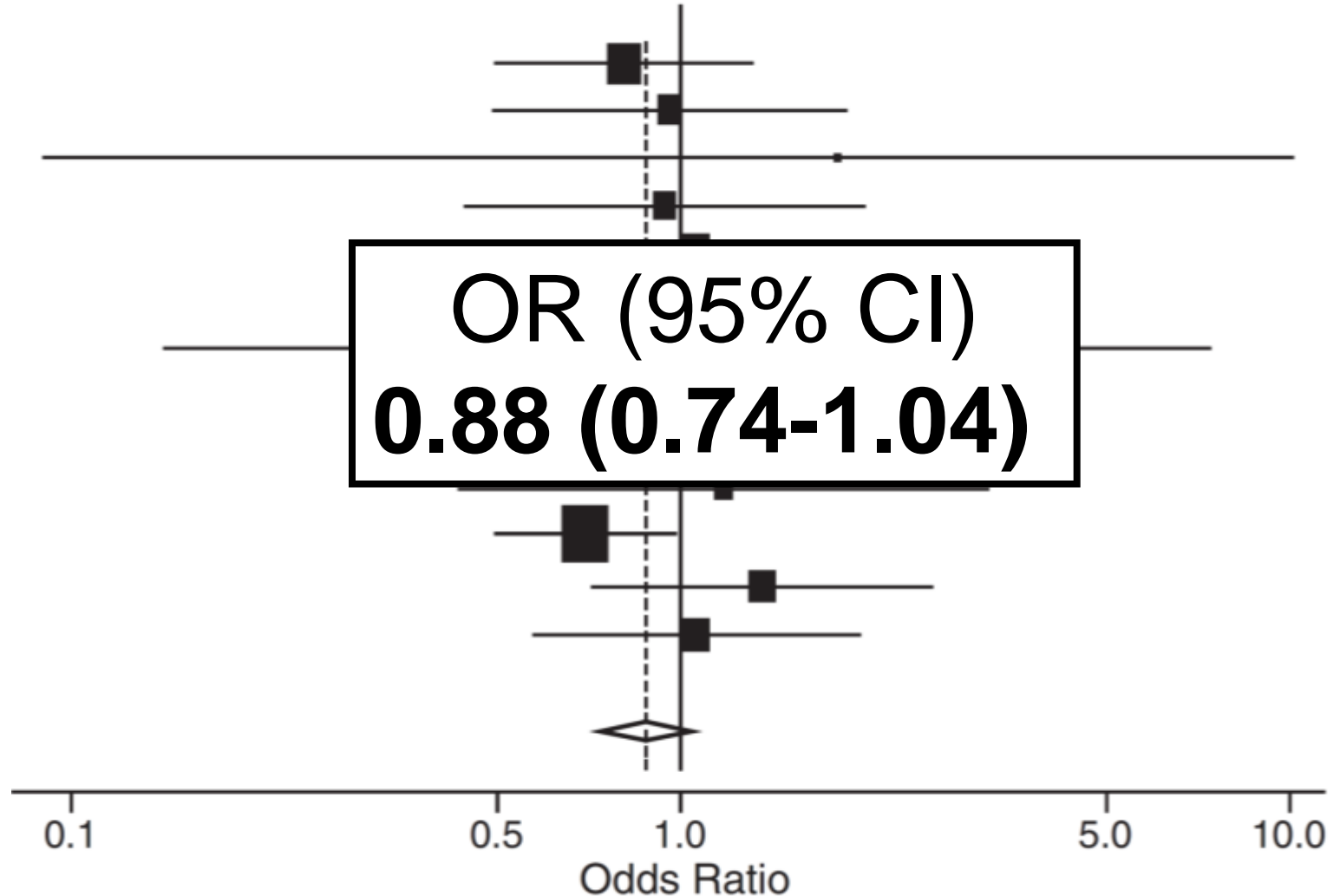
CONCLUSION: ChEIs may increase the risk of syncope, with no effects on falls, fracture, or accidental injury in cognitively impaired older adults. Memantine may have a favorable effect on fracture, with no effects on other events. More research is needed to confirm the reduction in fractures observed for memantine. *J Am Geriatr Soc* 59:1019–1031, 2011.

Key words: cholinesterase inhibitors; memantine; falls; syncope; dementia

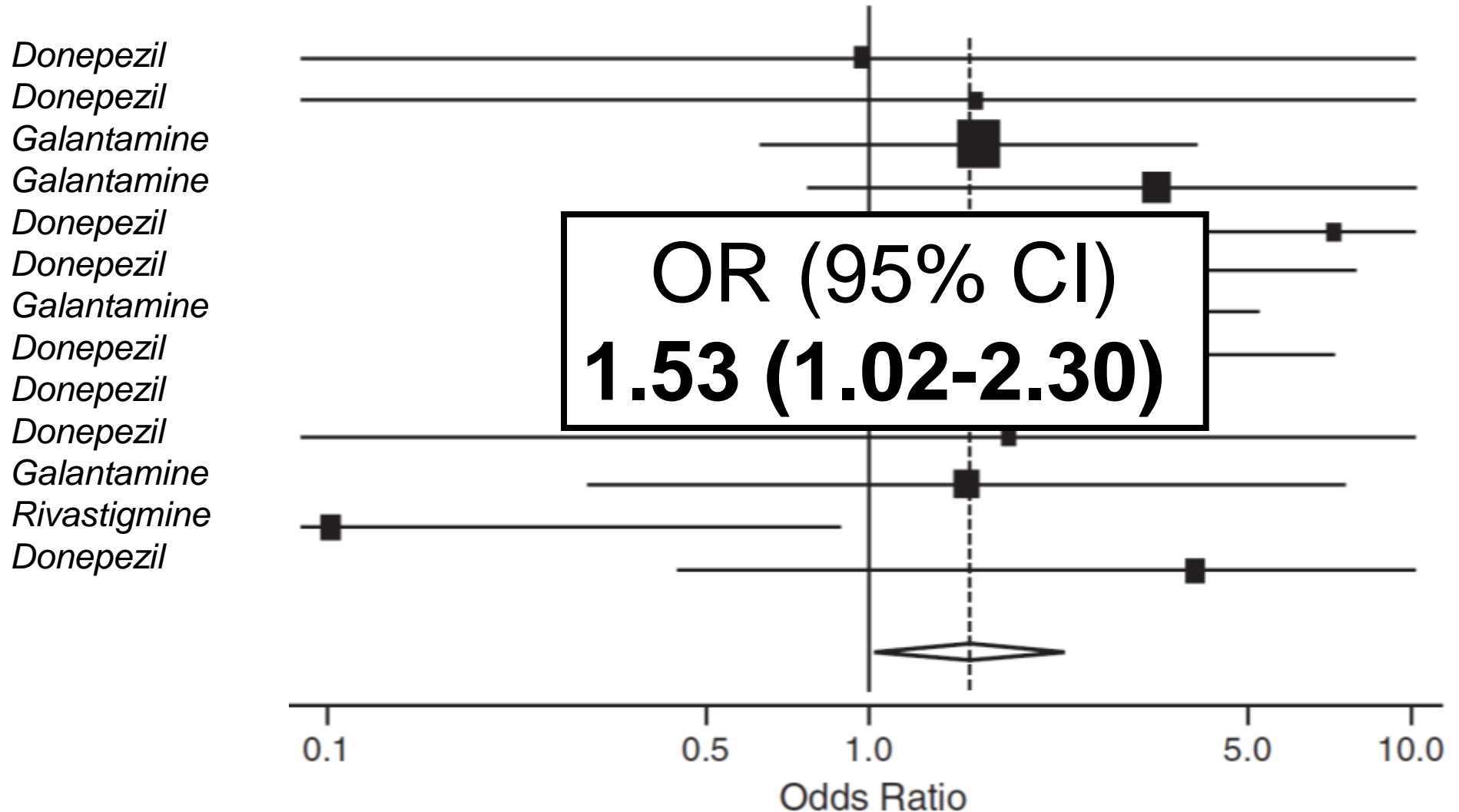


Meta-analysis of “cholinesterase inhibitors” and FALLS

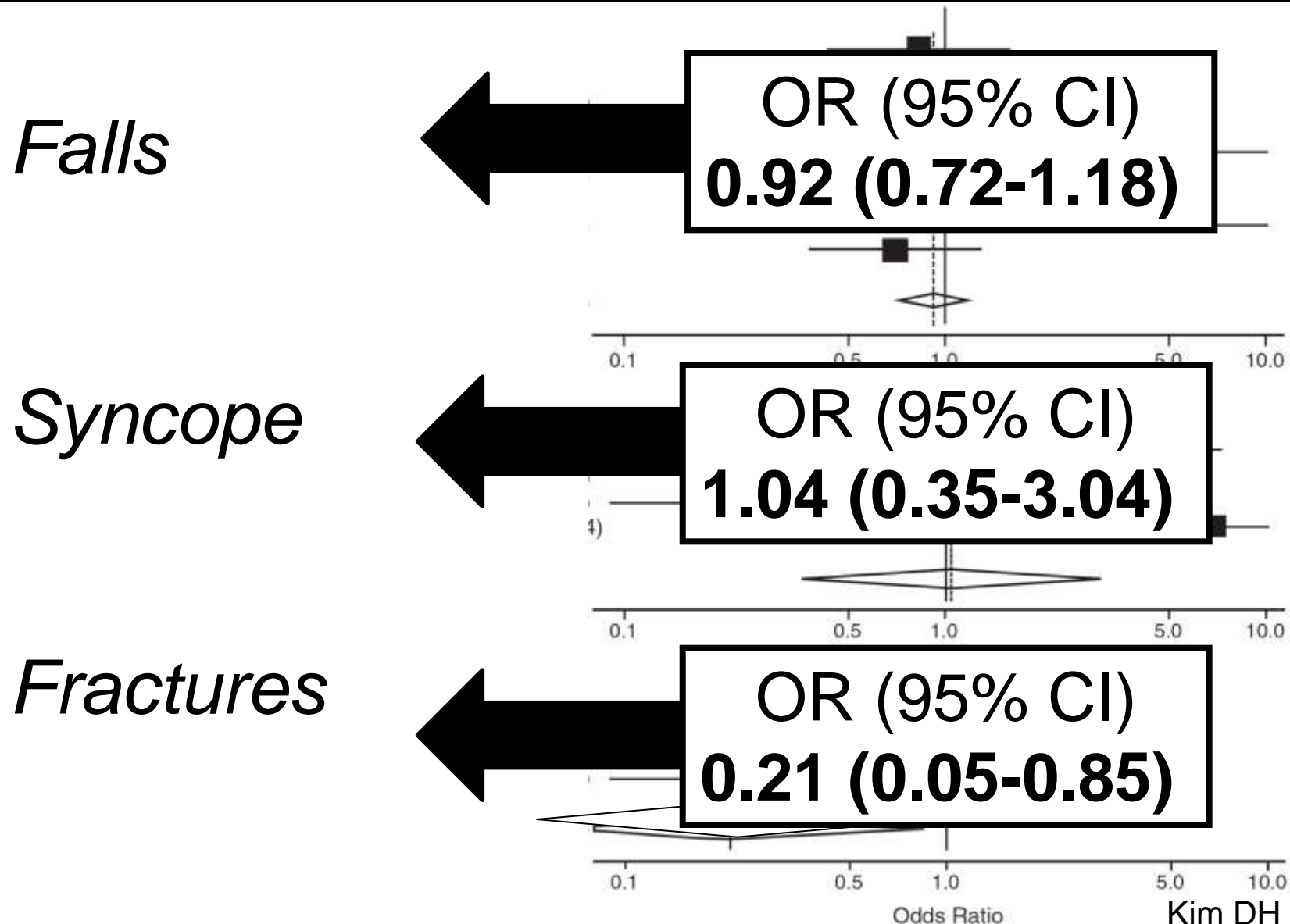
Galantamine
Galantamine
Donepezil
Rivastigmine
Galantamine
Donepezil
Donepezil
Galantamine
Rivastigmine
Donepezil
Galantamine
Rivastigmine
Galantamine



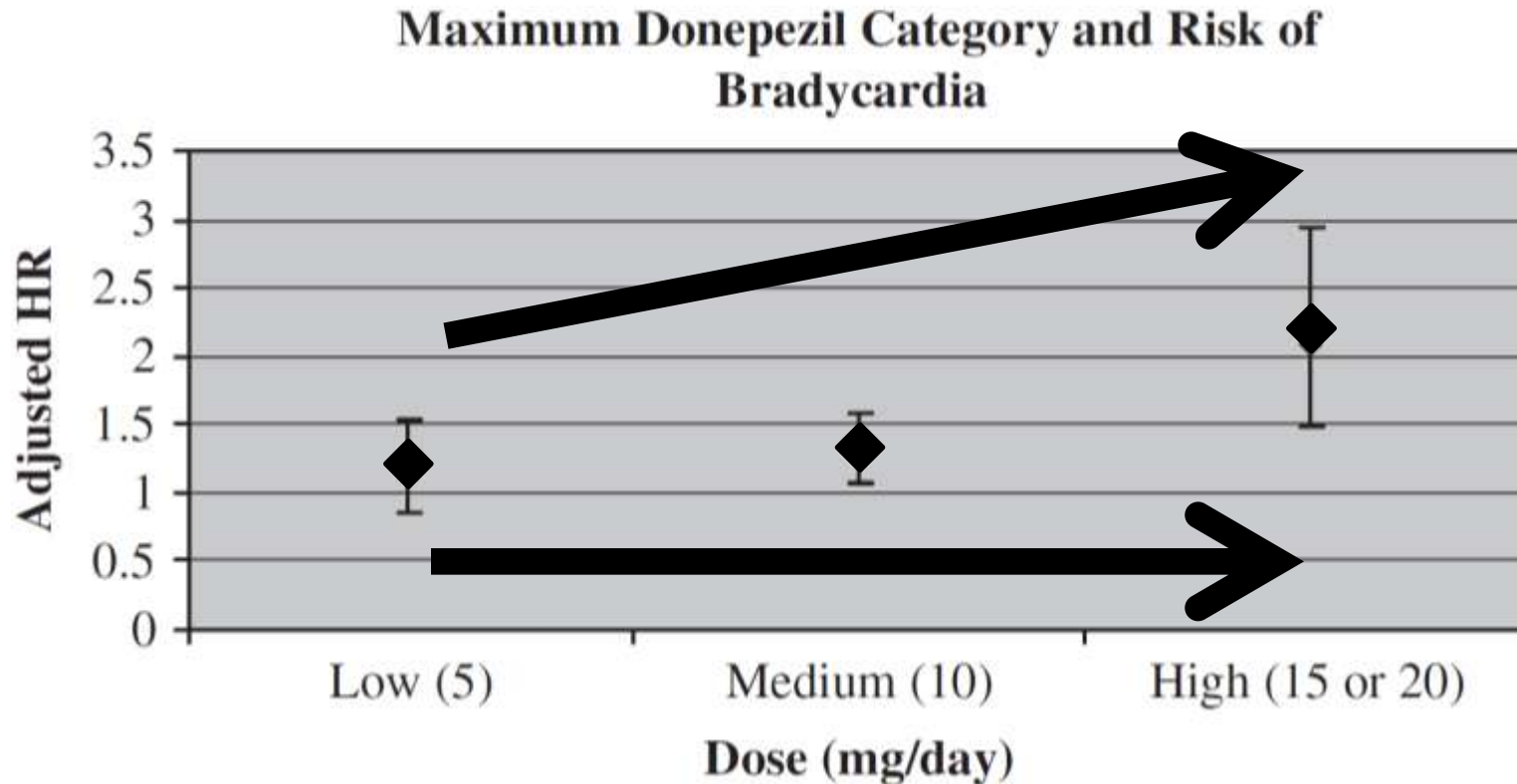
Meta-analysis of “cholinesterase inhibitors” and SYNCOPE



Meta-analysis of “Memantine” and FALLS, SYNCOPE and FRACTURES



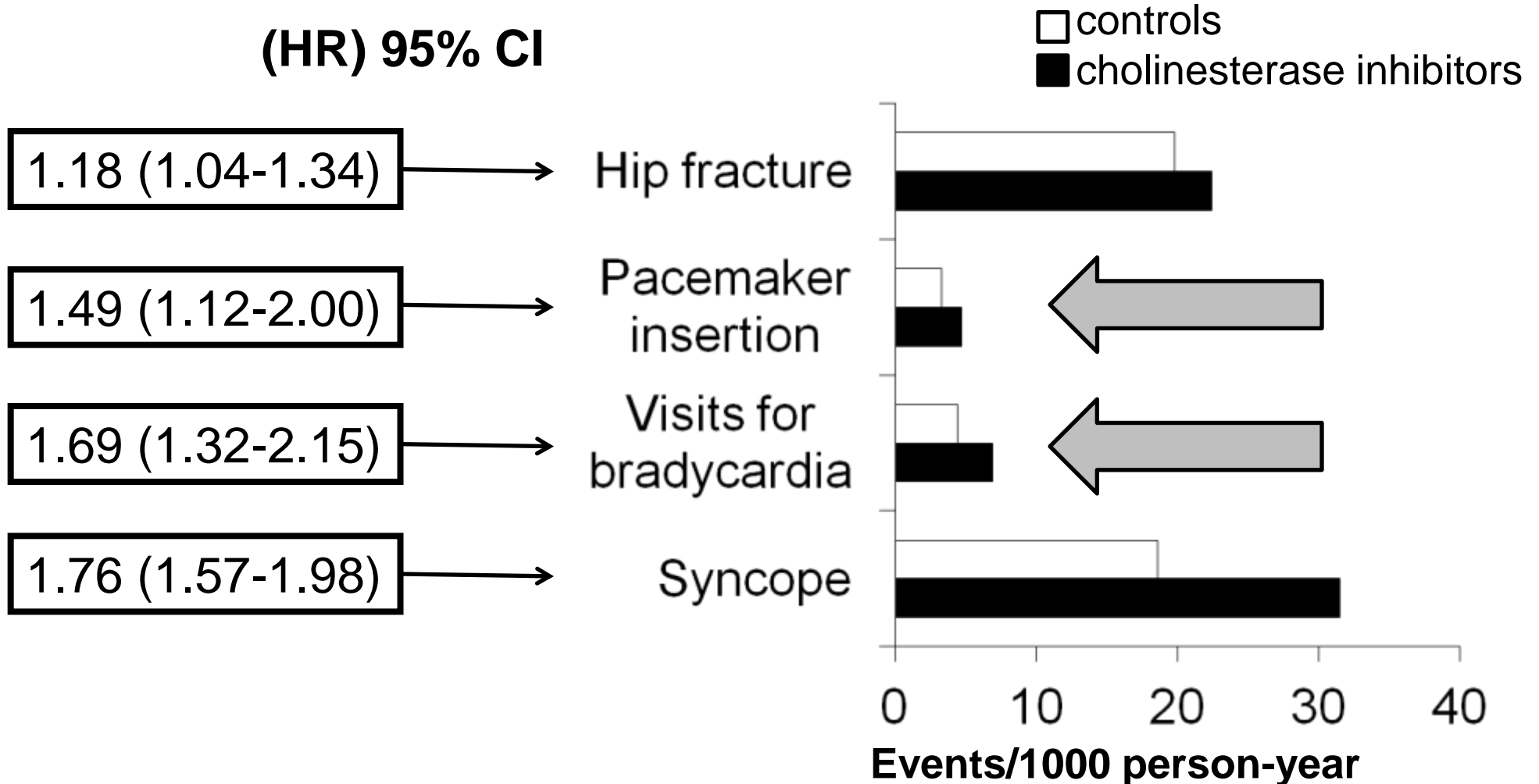
Hazard ratio for risk of bradycardia among dosage categories of maximum donepezil



Adjusted for age, race, long-term care, hypertension, acute myocardial infarction, chronic heart disease, heart failure, stroke, falls since diagnosis, tricyclic antidepressants, psychotropics, and anti-arrhythmics.

Syncope and its Consequences in patients with dementia receiving cholinesterase Inhibitors

A Population-Based Cohort Study





SIMPOSIO

“Le perdite di coscienza nell’anziano con demenza: un territorio da esplorare”

Farmaci per la demenza e rischio di cadute e sincope



-
- Cholinesterase inhibitor/Memantine
 - **Anti-epileptic**
 - Anti-psychotic
 - Benzodiazepines
 - Anti-depressant
 - Anti-Parkinson

Fall Frequency by use of anti-epileptic drugs

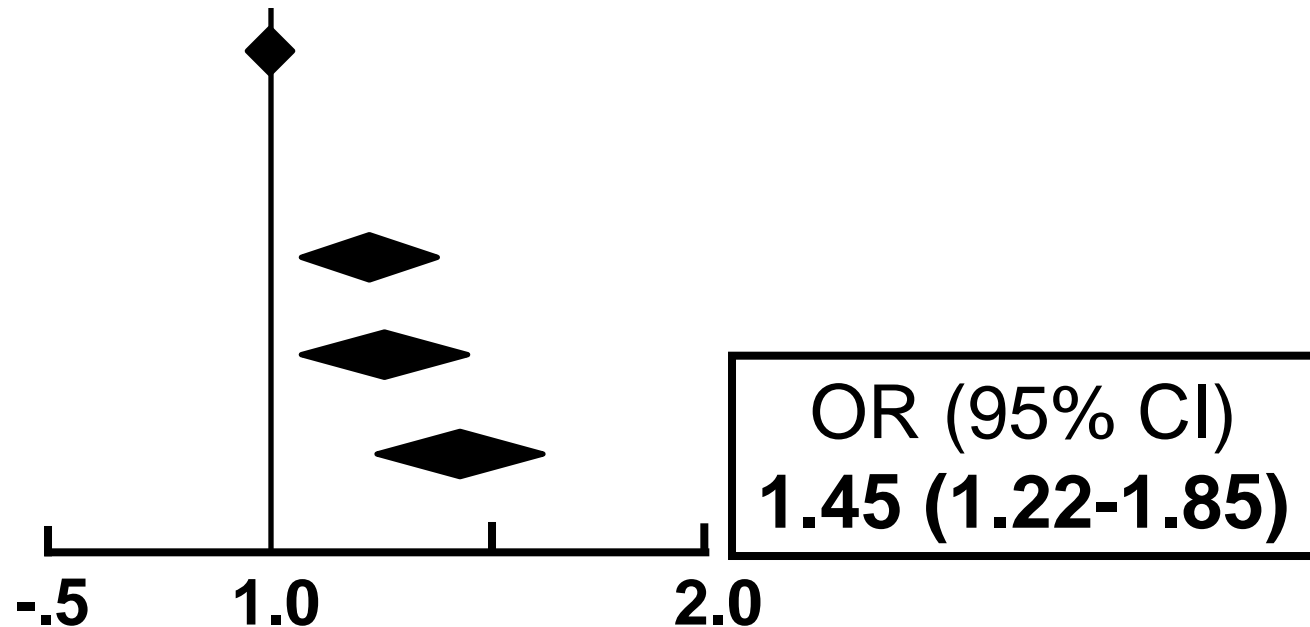
Non users

Users

< 2 years

2-5 years

> 5 years



Model adjusted for:

age, race/ethnicity, BMI, smoking, alcohol, calcium and vitamin D intake, history of fractures, history of falls (two or more in the year prior to enrollment), bisphosphonates, past/current use of HT, SERMs, calcitonin, age of menopause, physical activity levels, physical function construct, diabetes, stroke, parental history of hip fractures, study site region, self-reported health, multiple sclerosis, Parkinson's.

Frequency of and risk factors for oxcarbazepine (OXC)-induced severe and symptomatic “HYPONATREMIA”

Factors	OR	95% CI	P value
<i>Multivariate analysis</i>			
Age	1.034	1.014–1.055	0.001
Other medical drugs used	1.272	0.662–2.444	0.469
Diuretics	2.222	1.058–4.666	0.035

Conclusion

Our study recommended that serum sodium be monitored regularly in patients taking OXC, **especially in old age and/or concomitant use of diuretics**



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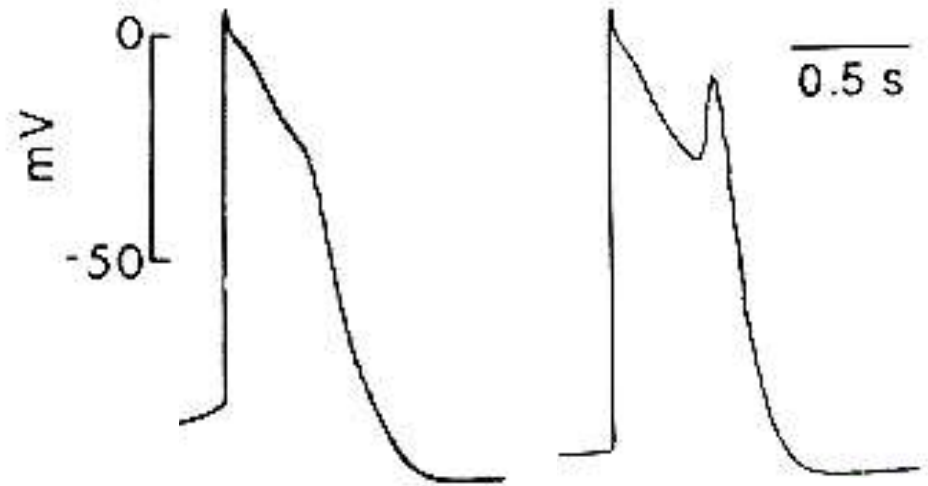
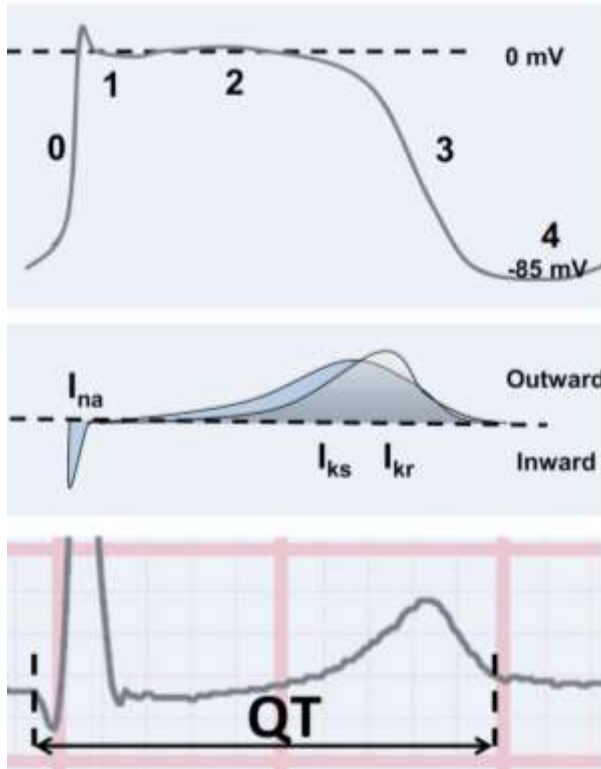
Conventional and atypical antipsychotics drugs

AYPICAL	CONVENTIONAL
Clozapine	Chlorpromazine
Olanzapine	Chlorprothixene
Quetiapine fumarate	Fluphenazine enanthate
Risperidone	Haloperidol
	Loxapine
	Molindone hydrochloride
	Perphenazine
	Promazine hydrochloride
	Thioridazine hydrochloride
	Thiothixene
	Trifluoperazine hydrochloride

Risk of anti-psycotic drugs on different outcomes

	ATYPICAL	CONVENTIONAL	BOTH
Outcomes	OR (95% CI)	OR (95% CI)	OR (95% CI)
FALLS	2.16 (1.26–3.69)	2.11 (0.97– 4.61)	2.88 (1.17–7.11)
HIP FRACTURE	1.47 (0.82–2.65)	2.33 (1.08–5.03)	2.64 (1.04–6.72)
SYNCOPE	0.87 (0.55–1.37)	0.75 (0.37–1.54)	2.47 (1.21– 5.06)

QT prolongation and early after-depolarization



QTc-Prolongation Risk Stratification for Commonly Used Antipsychotic Medications

Drug	QTc Prolongation	Torsades de Pointes
High risk		
Thioridazine	+++	+++
Haloperidol (IV)	+++	+++
Moderate risk		
Haloperidol (PO/IM)	++	++
Risperidone	++	++
Low risk		
Olanzapine	+	+
Quetiapine	+	+

Risk Factors for Prolonged QT

- Female
- **Increased age**
- Congenital LQTS
- **Hypokalemia**
- **Hypocalcemia**
- **Hypomagnesemia**
- Anorexia nervosa*
- **Diuretic use***
- **Bradycardia**
- **Heart failure****
- **Renal dysfunction***
- Hepatic dysfunction
- Hypoglycemia*
- **Hypertension****
- **Diabetes***
- **Hypothyroidism***
- Pituitary insufficiency*
- CNS injury (stroke, trauma, tumor, infection)*
- AIDS
- **Malnutrition***
- Obesity (including acute weight gain)*
- Myocardial infarction

* Causes QTc prolongation via effects on electrolytes

** Causes QTc prolongation via diastolic dysfunction.

Nonpsychiatric Medications Associated with QTc Prolongation

Antiarrhythmics

Class I

Quinidine

Disopyramide

Procainamide

Class III

Sotalol

Amiodarone

Antibiotics

Macrolides

Quinolones

Antifungals

Fluconazole

Antimalarials

Chloroquine

Other Medications

Tamoxifen

Vandetanib

Furosemide

Terfenadine (withdrawn due to TdP)

Cisapride (withdrawn due to TdP)

Methadone

Risk of being hospitalized for ventricular arrhythmias or cardiac arrest among residents using antipsychotics

Variable	Crude OR	Adjusted OR	95% CI
Atypical vs no use	0.70	0.87	0.58-1.32
Conventional vs no use	1.53	1.86	1.27-2.74
Conventional vs atypical	2.19	2.13	1.27-3.60

Second-generation “ANTI-PSYCOTICS” considered to carry the risk of prolonging QTc interval and causing torsade de pointes.

Drug (no. of case reports)	Age range (years); sex (F/M)	Dose range (mg); overdoses (%)	QTc interval <500 or ≥500 ms (all cases)	All TdP Cases n (%)
Amisulpiride (10)	22-67 5F/5M	100-32.000 7 (70)	<500 = 3; ≥500 = 7	3 (30)
Clozapine (5)	30-61 1F/4M	150-550 0	<500 = 2; ≥500 = 3	0
Olanzapine (6)	15-70 4F/2M	5-600 1	<500 = 5; ≥500 = 1;	0
Quetiapine (16)	14-77 10F/6M	25-30.000 43.7	<500 = 0; ≥500 = 4;	4 (25)
Risperidone (13)	2.5/84 9F/4M	0.5-240 15.4	<500 = 3; ≥500 = 2	5 (39)



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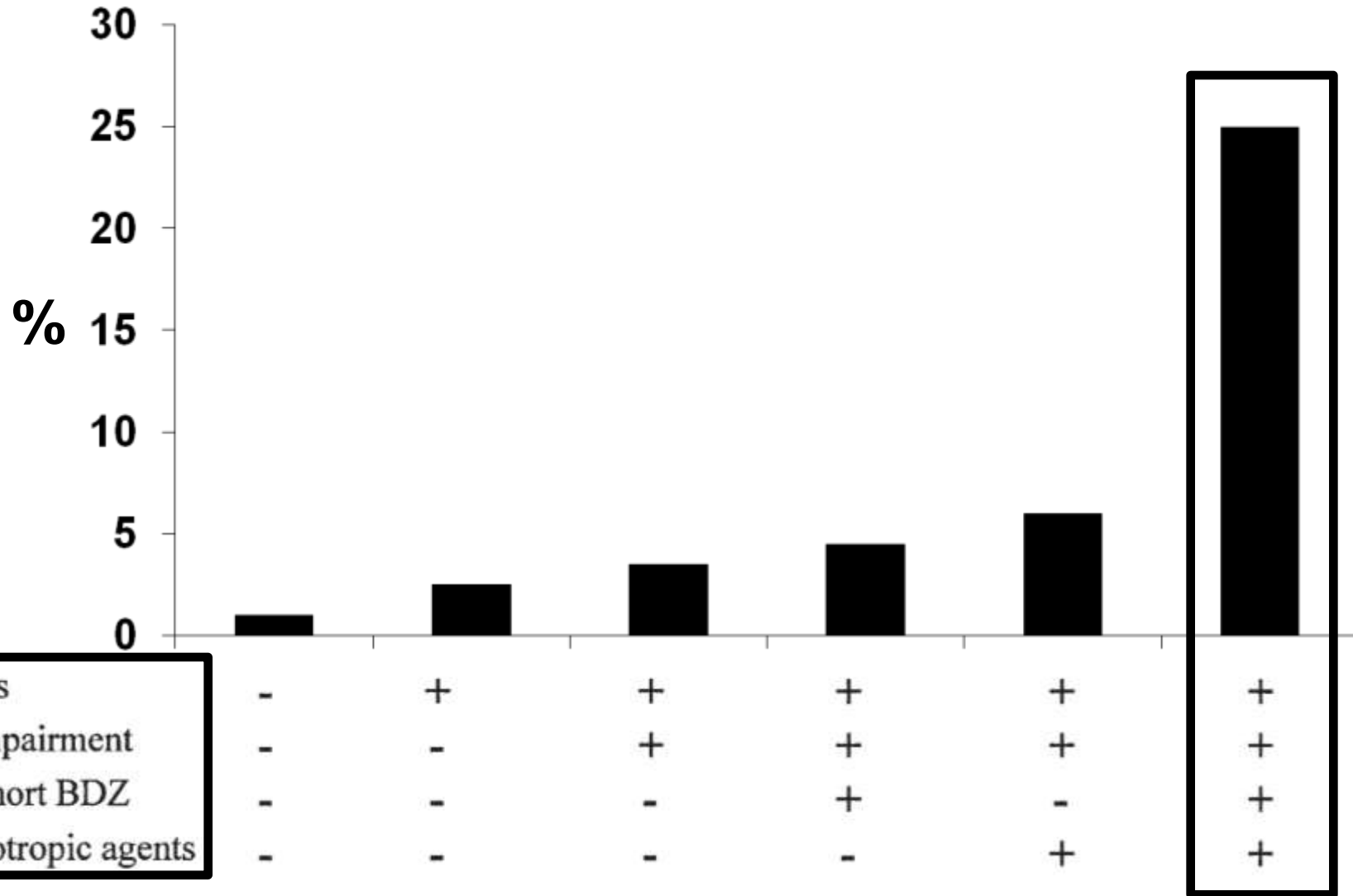


-
- Cholinesterase inhibitor/Memantine
 - Anti-epileptic
 - Anti-psychotic
 - **Benzodiazepines**
 - Anti-depressant
 - Anti-Parkinson

Benzodiazepines and benzodiazepine-like drugs with an elimination half-life of 10 h or less are categorised as short acting, the other benzodiazepines are long acting

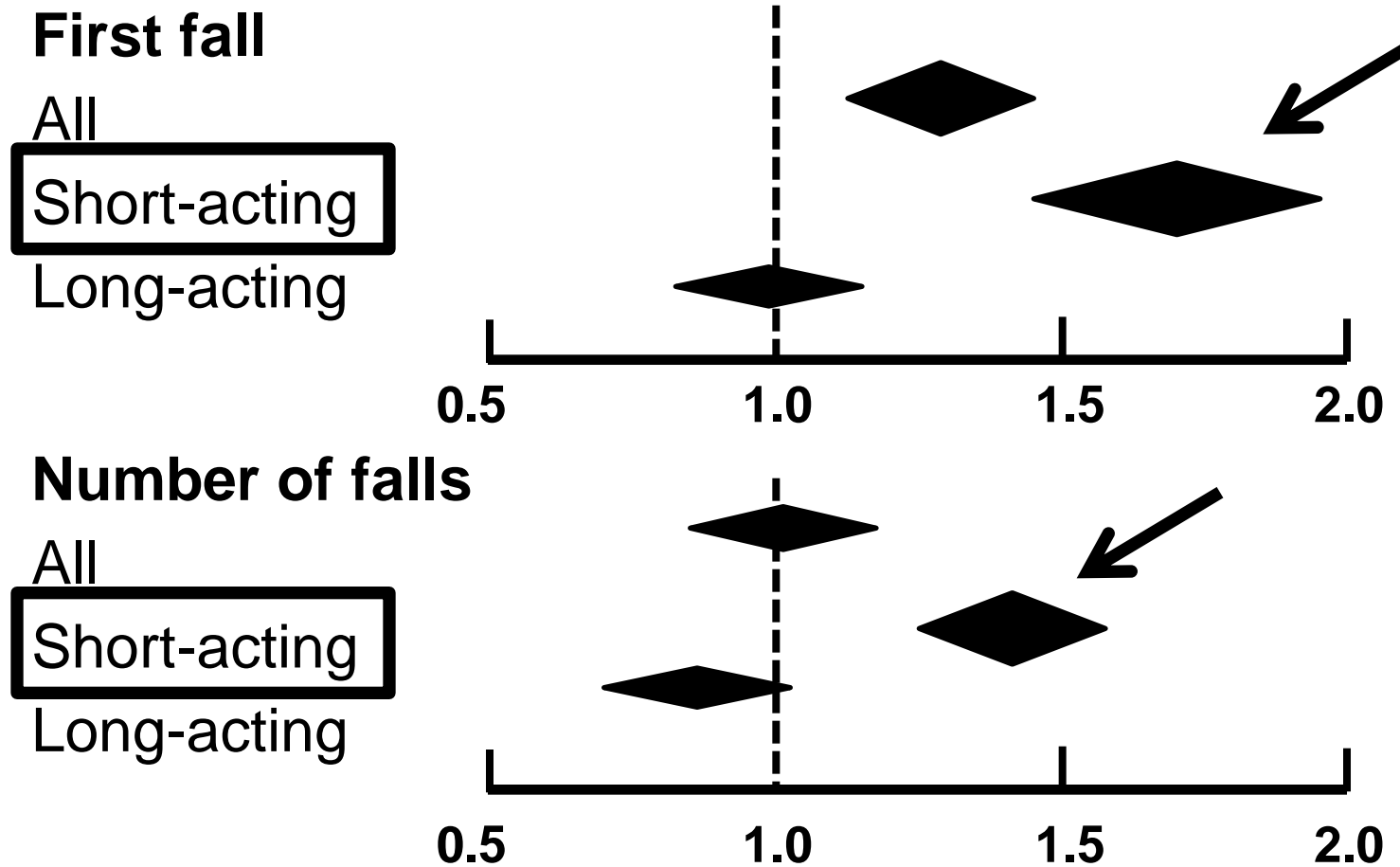
SHORT ACTING	LONG ACTING
Lorprazolam	Alprazolam
Oxazepam	Bromazepam
Temazepam	Chlordiazepoxide
Triazolam	Clonazepam
Zolpidem (z-drug)	Clorazepate
Zopiclone (z-drug)	Diazepam
	Flunitrazepam,
	Flurazepam
	Lorazepam
	Nitrazepam

Incidence of falls according to the different combinations of independent risk factors.



Associations between benzodiazepines with short and long elimination half-life and FALLS

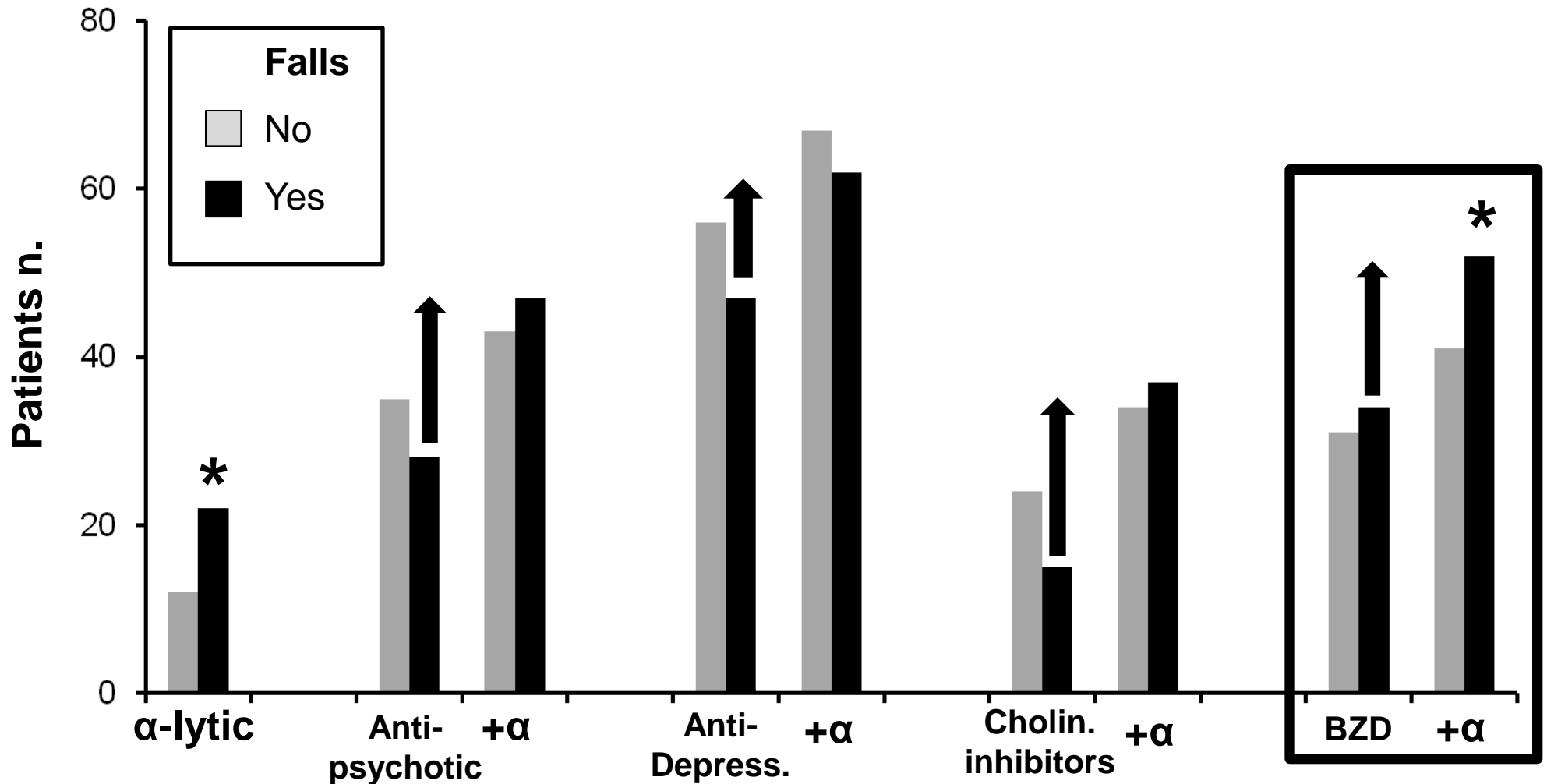
“Longitudinal Aging Study Amsterdam - Fall prevention study”



Syncopal/Dementia (SYD) study

Prevalence of "FALLS"

in patients with POLIPHARMACY

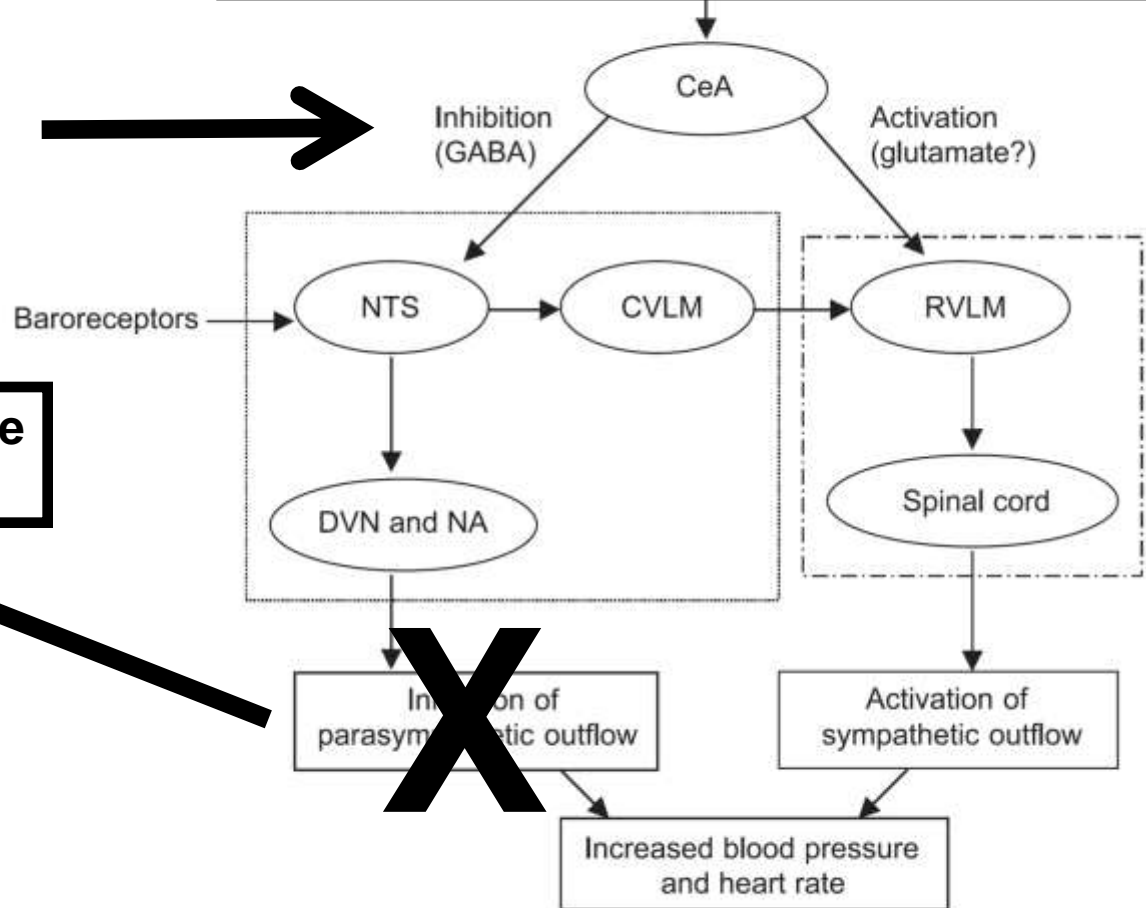


*p<0.05 vs yes

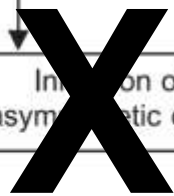
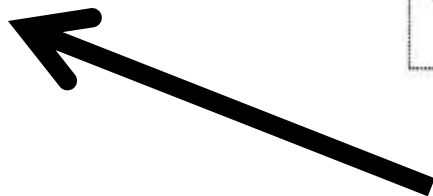
Mechanism of action of Benzodiazepines on GABA-receptors

Short-term alerting stimuli
or long-term mental stress (e.g. anxiety)

Benzodiazepines



Decreased blood pressure
and heart rate





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Farmaci per la demenza e rischio di cadute e sincope



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 - **Anti-depressant**
 - Anti-Parkinson

Different types of anti-depressant

Te/TrCAs	SSRIs	SNRIs	MAOIs
Amitriptyline	Sertraline	Duloxetine	Selegiline
Clomipramine	Citalopram	Venlafaxine	Metralindole
Mirtazapine	Fluoxetine	Desvenlafaxine	Moclobemide
Nortriptyline	Escitalopram	Trazodone	Pirlindole
	Paroxetine		Toloxatone
	Fluvoxamine		

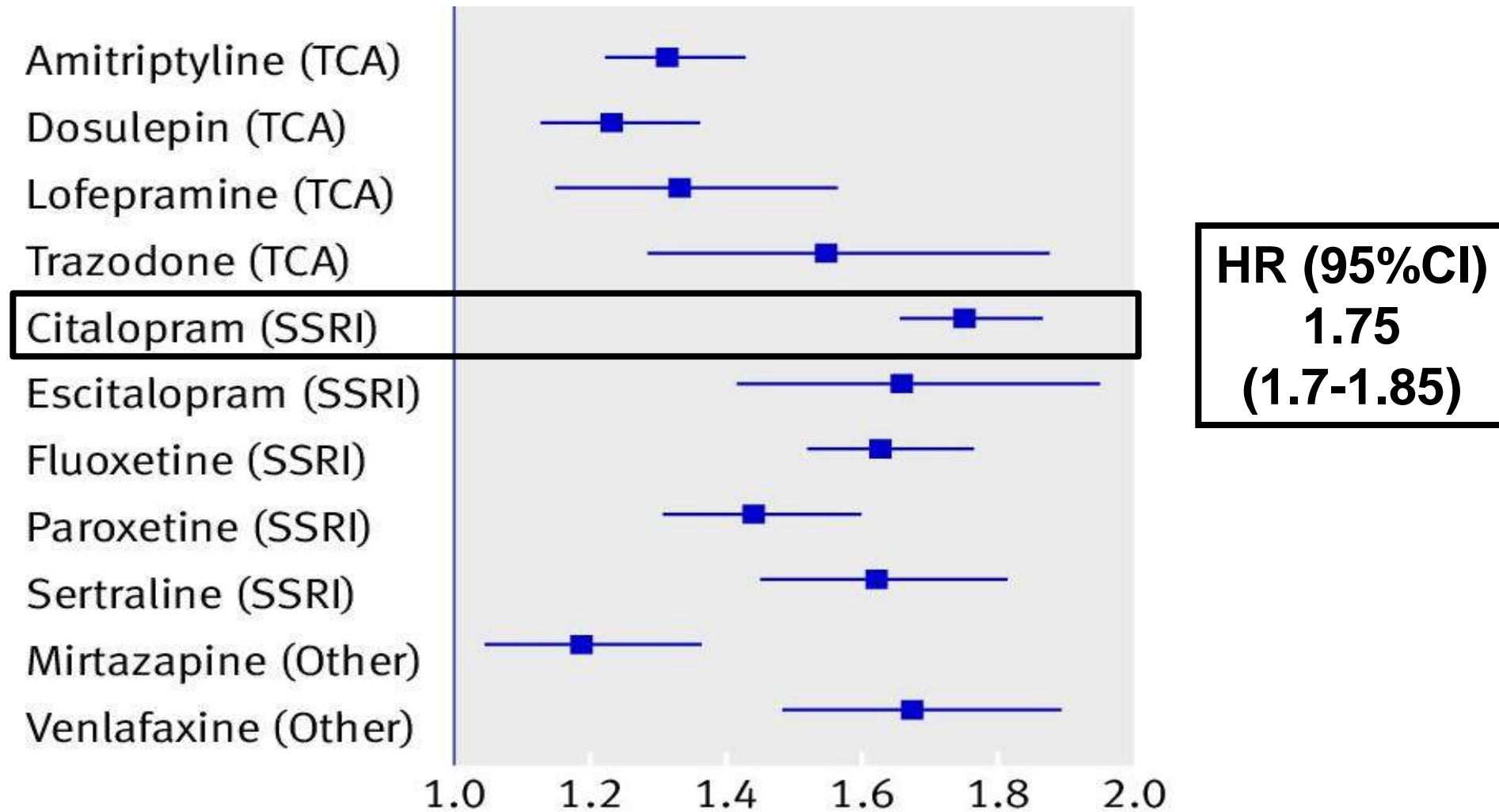
Tetra/tricyclic antidepressants (Te/TrCAs)

Serotonin reuptake inhibitors (SSRIs)

Serotonin norepinephrine reuptake inhibitors (SNRIs)

Monamine oxidase inhibitors (MAOIs)

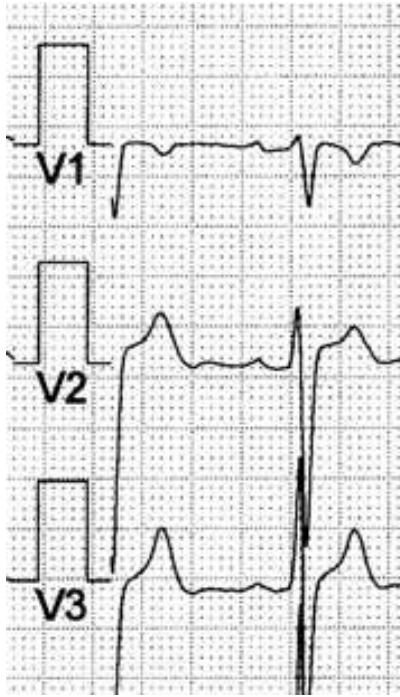
Hazard Ratios (with 95% CI) for FALLS of most commonly prescribed antidepressant drugs



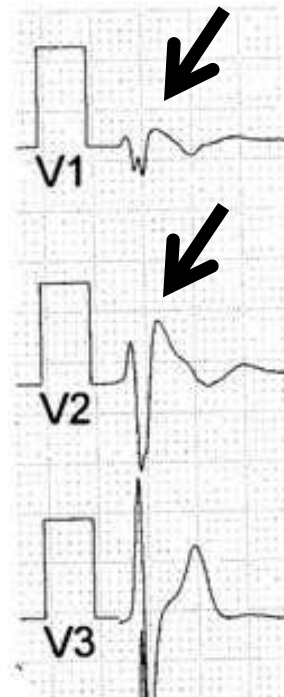
Second-generation “ANTI-DEPRESSANT” considered to carry the risk of prolonging QTc interval and causing torsade de pointes.

Drug (no. of case reports)	Age range (years); sex (F/M)	Dose range (mg); overdoses [n (%)]	QTc interval <500 or ≥500 ms (all cases)	All TdP Cases [n (%)]
Citalopram (16)	14–89; 13F/ 3M	20–11,600; 8 (50)	<500 = 4; ≥500 = 12	9 (56.2)
Escitalopram (6)	14–60; 5F/1M	5–500; 4 (66.7)	<500 = 4; ≥500 = 2	0
Fluoxetine (9)	83; 6F/3M	10–2,400; 2 (22.2)	<500 = 3; ≥500 = 5;	3 (30)
Sertraline (2)	40-72; 2F/0M	NS and 2,250; 1 (50)	<500 = 0; ≥500 = 1;	1 (50)
Venlafaxine (5)	36–64; 3F/2M	150–13,500; 3 (60)	<500 = 0; ≥500 = 5	1 (20)

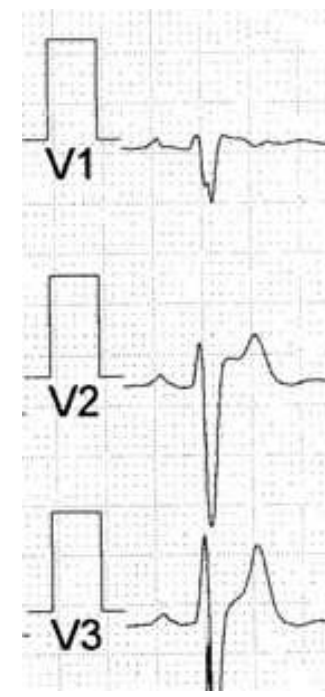
Brugada syndrome ECG provoked by the selective serotonin reuptake inhibitor fluvoxamine



**Normal
ECG**

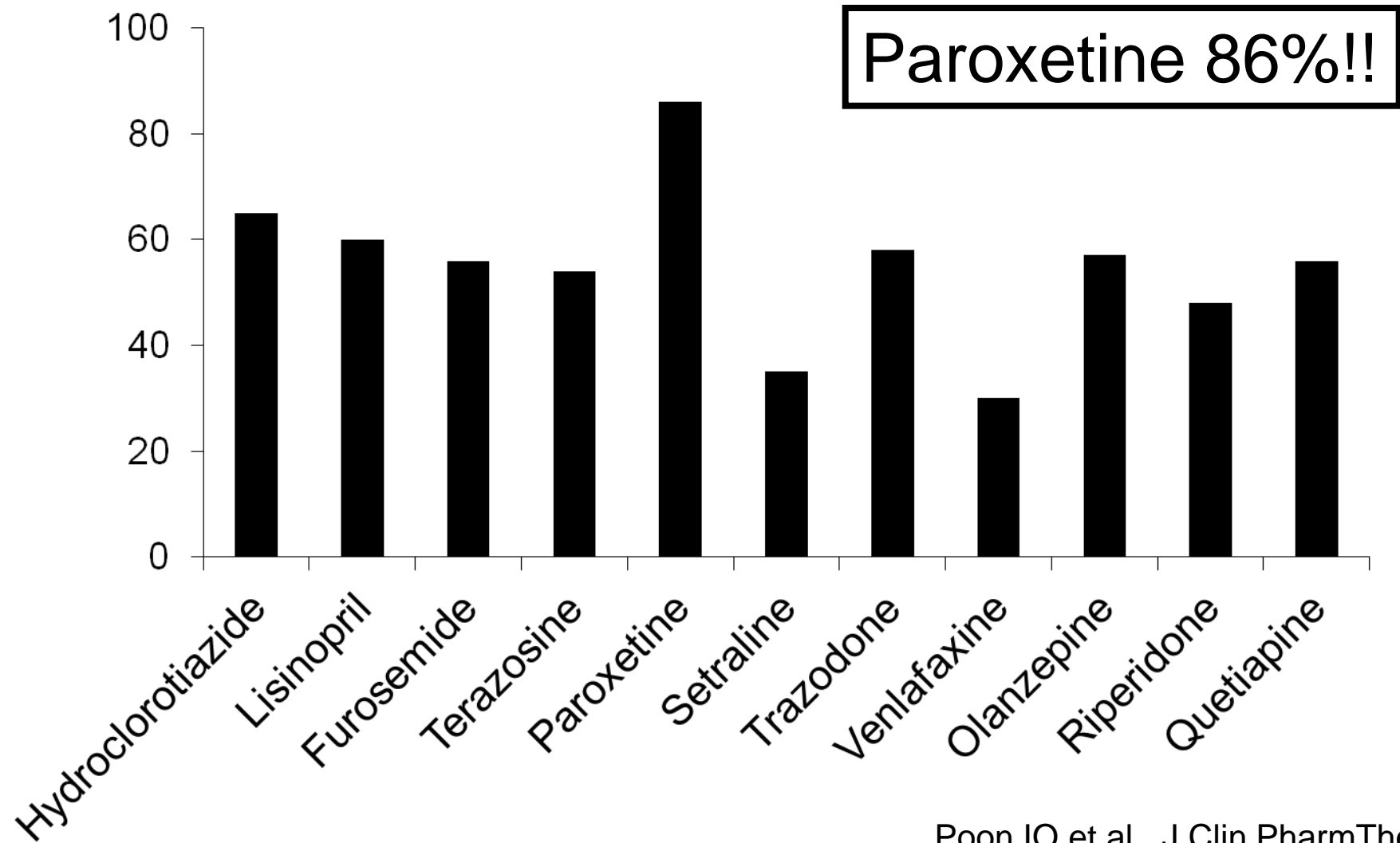


**Brugada 1 pattern
under therapy**



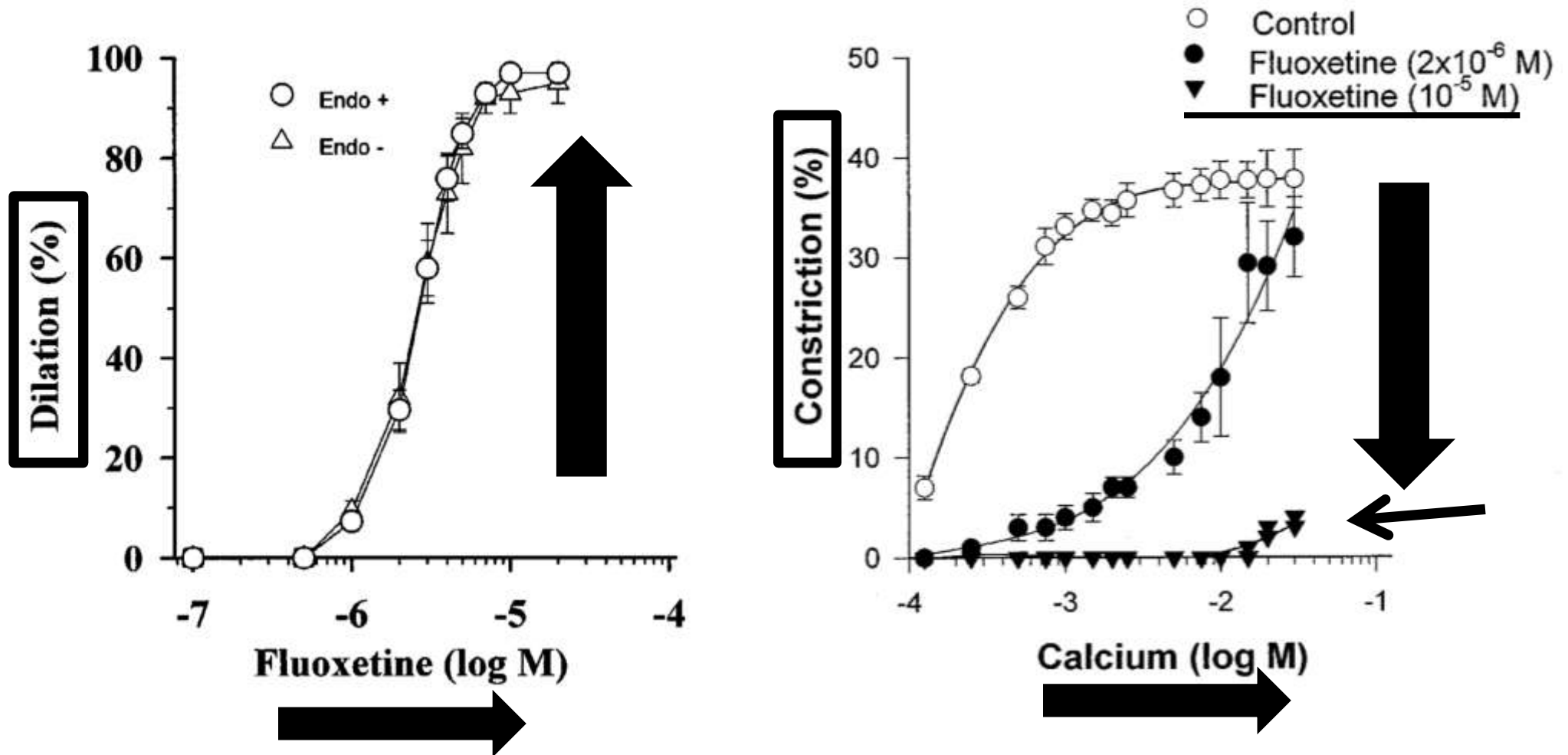
**ECG with little saddleback
after stopping therapy**

High prevalence of orthostatic hypotension and its correlation with potentially causative medications among elderly veterans



Serotonin reuptake inhibitor dilates isolated skeletal muscle arterioles.

Possible role of altered Ca²⁺ sensitivity





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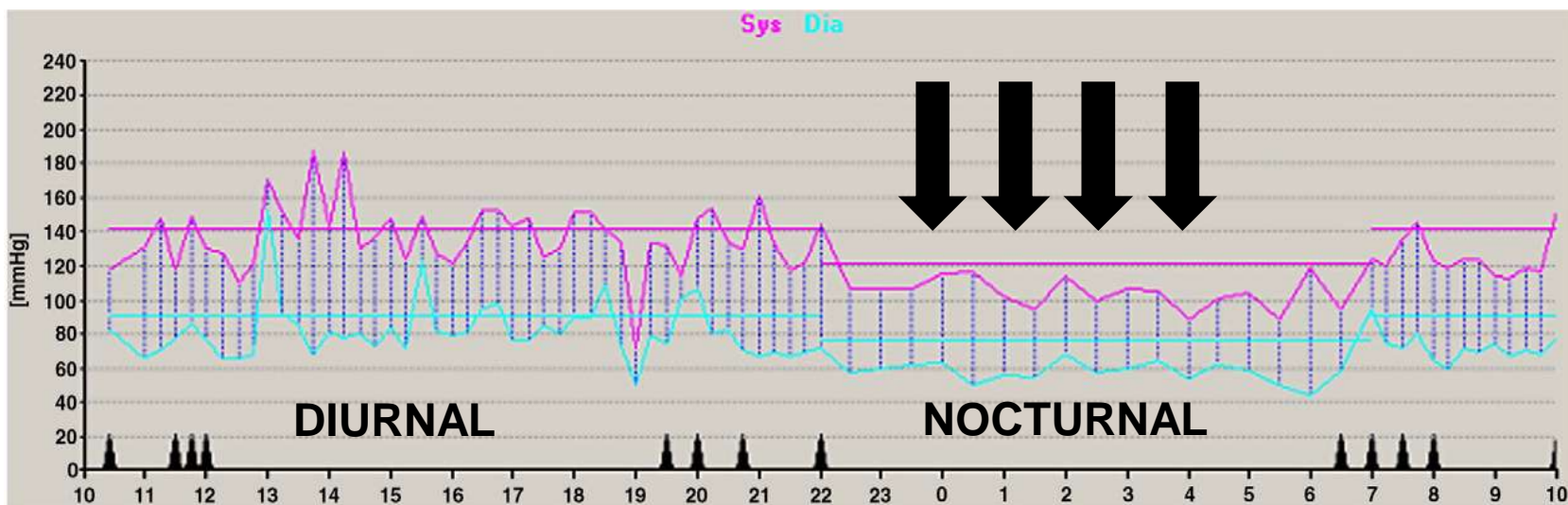
Farmaci per la demenza e rischio di cadute e sincope



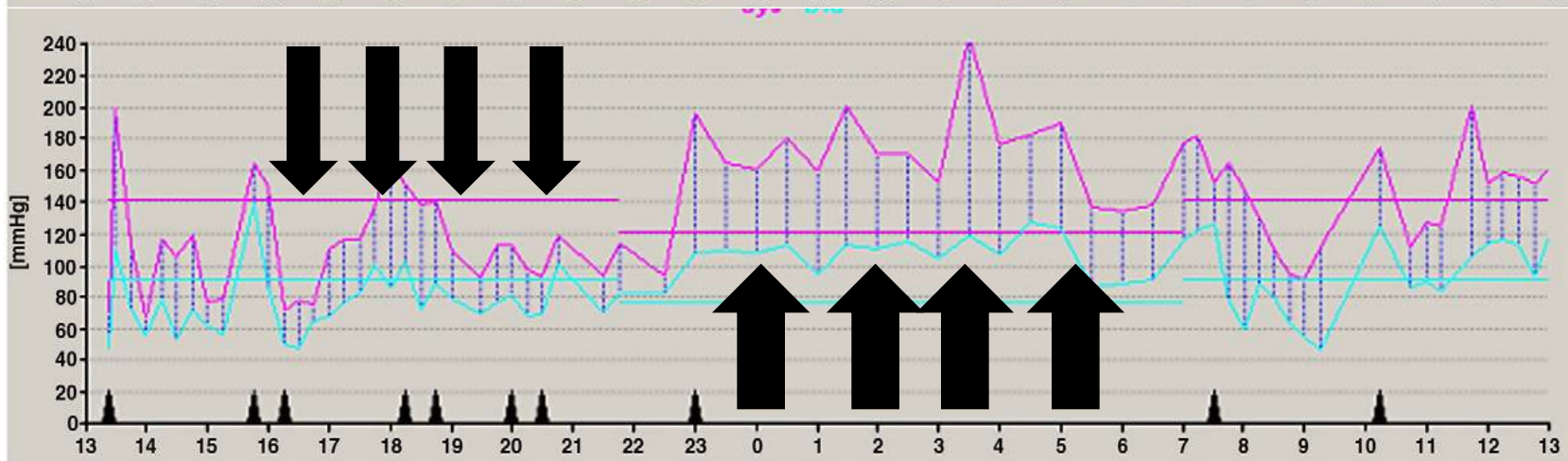
-
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 - **Anti-Parkinson**

24-h ambulatory blood pressure monitoring with diurnal hypotension and nocturnal hypertension in a Parkinson disease (Hyp-Hyp)

Healthy person



Parkinson patient



Orthostatic hypotension and attention in Parkinson's disease without (PD) and with dementia (PDD)

	PD	PDD	p
Age (years)	74.1±4.8	77.3±7.5	n.s.
Disease duration (years)	6.4±4.6	7.8±5.0	n.s.
Hoehn & Yahr	2.1 (1.8–2.4)	2.9 (2.6–3.5)	0.001
Mini Mental Status	28±1.4	15±6.8	<0.001

**PARKINSON'S DISEASE WITH DEMENTIA
≈ -30 mmHg !**

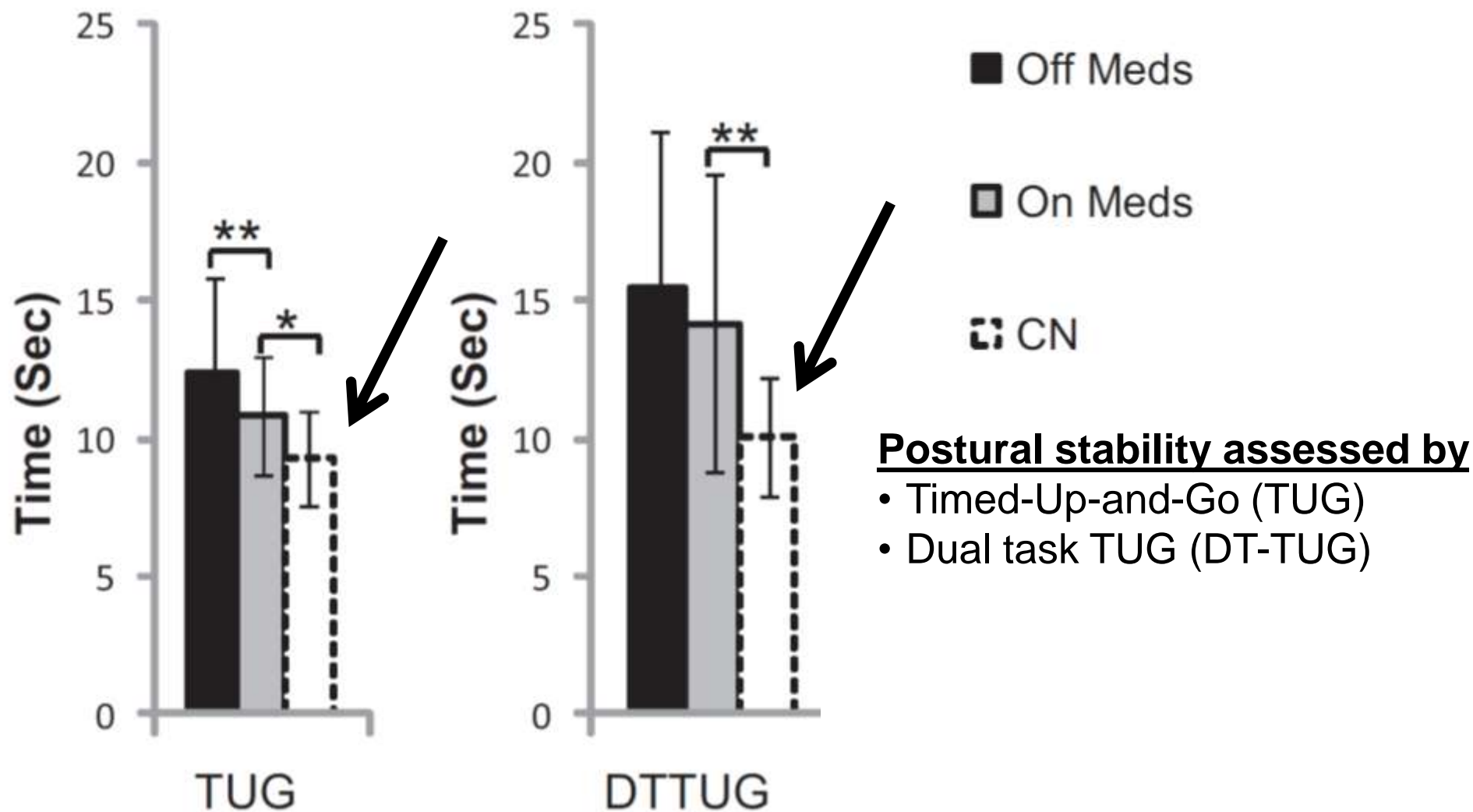
Trail A	59±26.5	180±17.5	<0.001
Trail B	161 (_81.9)	n.a.	n.a.
Δ SBP	11.8±27.2	-28.3±36.2	<0.05
Δ DBP	6.7±11.6	5.3±15.3	n.s.
Δ HR	2.9±12.3	5.1±6.6	n.s.

Orthostatic Hypotension Syndrome as cause of syncope in patients older than 65 years admitted to emergency departments

Multivariate Analysis

	OR	95% CI	<i>p</i>
Parkinson's disease	10.91	2.645–45.	.001
Use of diuretics	3.73	1.23–11.2	.020
Use of nitrates	5.20	1.99–13.6	.001

Medication improves balance and complex gait performance in Parkinson disease

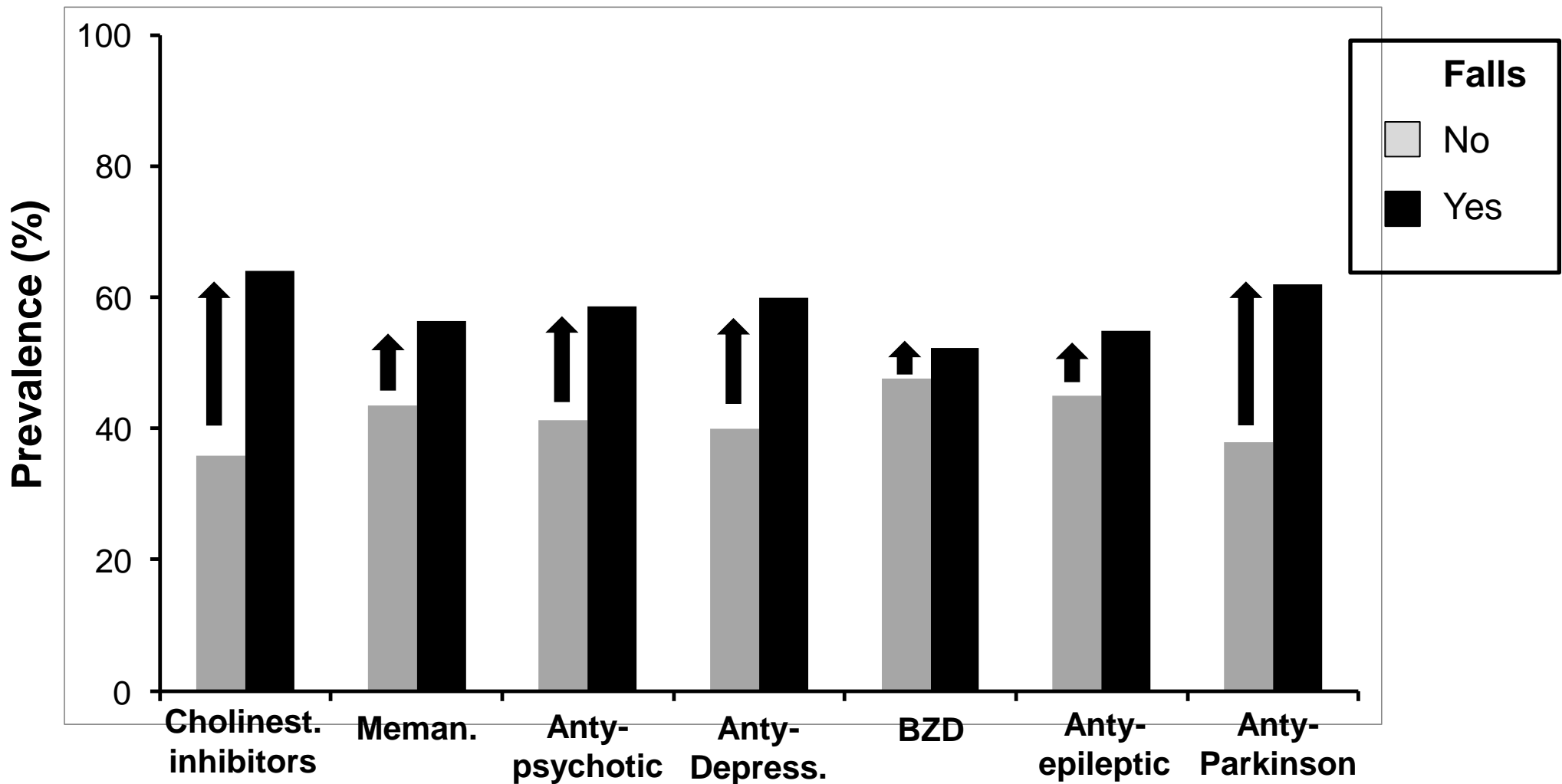


*p 0.05; **p 0.01; ***p 0.001.

Syncope/Dementia (SYD) study

Prevalence of "SYNCOPE"

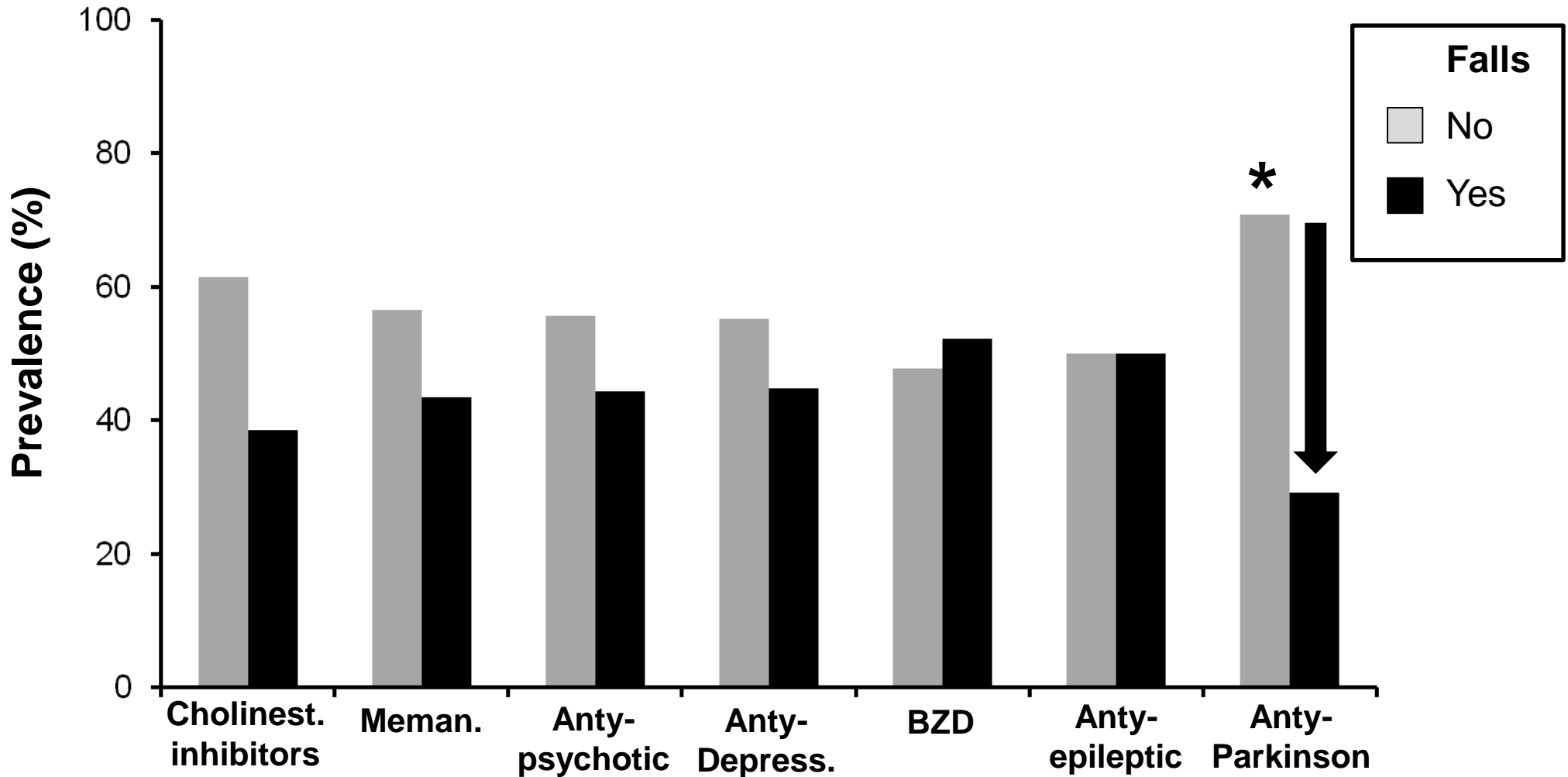
in patients with neuropsychiatric pathologies



Syncope/Dementia (SYD) study

Prevalence of "FALLS"

in patients with neuropsychiatric pathologies



*p<0.05 vs yes

Take home messages

- Prescribed anti-dementia drugs, and **their potential negative drug-interactions**, are an important contributors to falls and syncope in elderly patients with dementia.
- Fall/syncope-induced mechanism of cholinesterase inhibitors and anti-psychotic drugs seems to be attributable **cardiogenic mechanism** (negative chronotropic effect/long QT syndrome) while benzodiazepines/anti-depressant drugs to **orthostatic hypotension**.
- Moreover, anti-Parkinson drugs seems to be effective **in reducing falls in Parkinson's patient with dementia**.
- **Further studies should be conducted** in this area, such as investigating whether medication could decrease the rate of syncope and or falls.