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SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

Potenzialità e rischi del trattamento antidepressivo nell'anziano con polipatologia

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Gruppo di Ricerca Geriatrica, Brescia

AIP ASSOCIAZIONE ITALIANA PSICOGERIATRIA

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

Outline della presentazione

- La relazione tra depressione & malattie
- I benefici e i rischi dei trattamenti antidepressivi
- Quale trattamento antidepressivo nel paziente anziano: in chi fare che cosa?
- Conclusioni

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Prevalence of depression in hip fracture patients

Author(s)	n	Mean age (yr)	Exclusions	Case-finding instrument	Prevalence (%)	Comment
Levitan et al.,'81	24	N/A	--	DSM-III	36	Anxiety 29%
Sharmash et al., '92	50	80	< 60 years	HAS	26	--
Billig et al., '86	50	80	--	GHQ, ZSRDS, DSM-III	28	Dual diagnosis in >50%
Holmes, '96	50	81	--	GMS	16	--
Lyons et al., '89	69	78	MMSE <21	GDS-30	47	High prevalence with 10/11 cut off
Strain et al., '91	139	N/A	--	GDS-30 DSM-III	9	Included adjust disord
Shepherd, '92	270	81	--	GDS-15	33	Prevalence approximated
Magaziner et al., '90	424	N/A	Severe dementia, NH	CES-D	32	Only 49% given CES-D

Modified from Holmes et al, Age Ageing 2000

Review on depression and coronary heart disease

Dépression et pathologie coronarienne : une revue

Jean-Christophe Chauvet-Gélinier [a,*], Benoit Trojak [a], Bénédicte Vergès-Patois [b], Yves Cottin [c], Bernard Bonin [a]

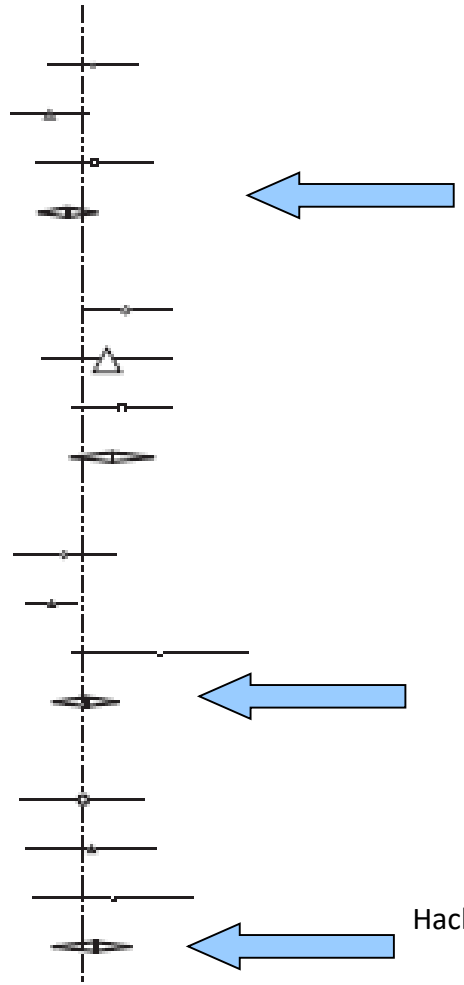
Table 1 Prevalence of depression in coronary heart disease.

Published studies	Number of subjects	Mean age (years)	Symptoms of depression (%)	Depression characterized by DSM IV-TR criteria (%)
Myers et al., 2012 [5]	632	52	27.8	NA
Davidson et al., 2010 [47]	453	25–93	24.0	17.0
Ziegelstein et al., 2000 [48]	204	60	17.2	15.2
Frasure-Smith et al., 1995 [4]	222	60	30.6	16.0

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; NA: not available.

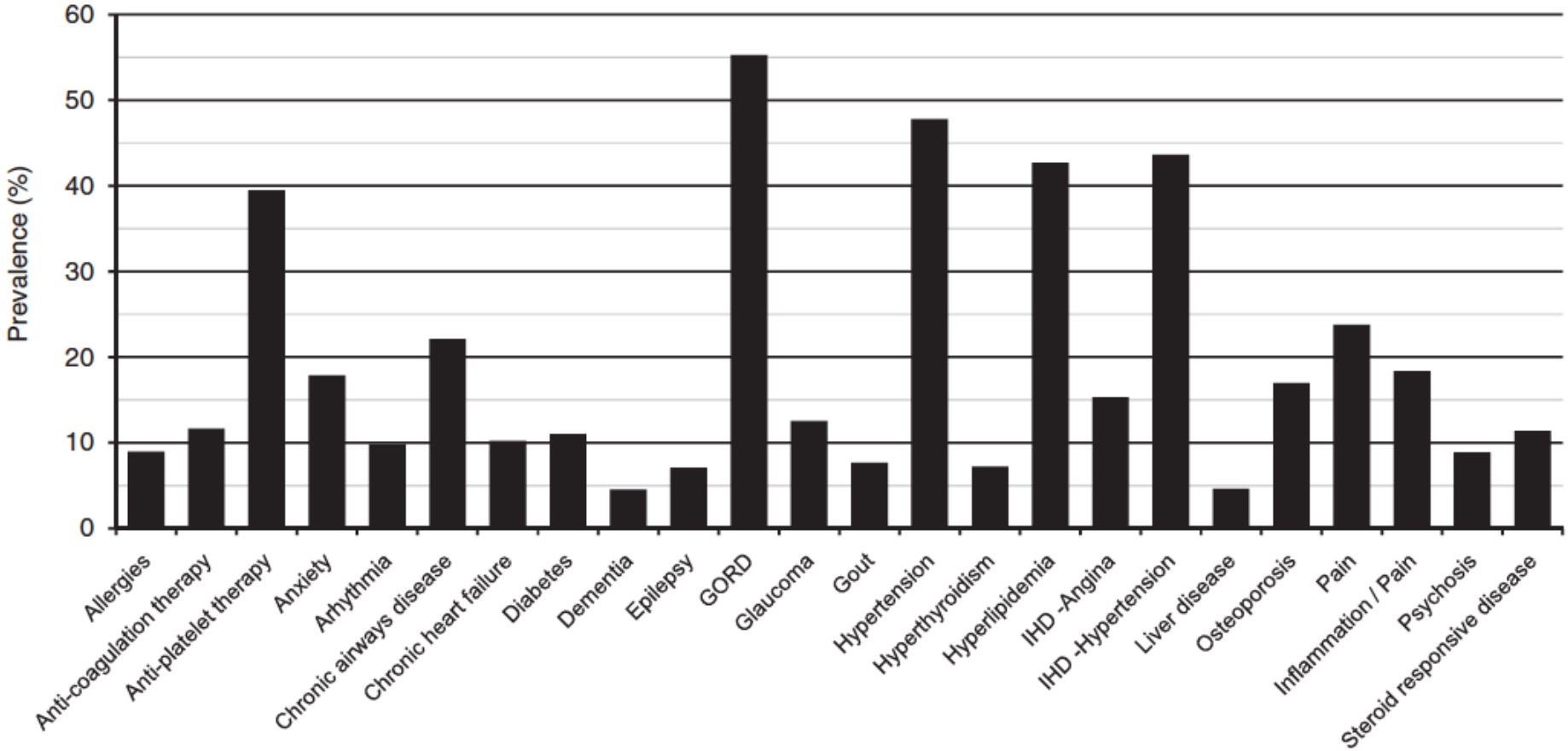
Observational studies of the proportional frequency of depression after stroke

Time since stroke Recruitment type	Proportional frequency (95% CI)	N
0-1 month		
Population	33% (26% to 40%)	455
Hospital	25% (19% to 32%)	2,194
Rehabilitation	33% (23% to 43%)	1,639
Sub-total	*28% (23% to 33%)*	*4,466*
2-5 months		
Population	38% (31% to 46%)	1,699
Hospital	35% (24% to 46%)	15,581
Rehabilitation	38% (29% to 46%)	1,022
Sub-total	*36% (29% to 43%)*	*18,254*
6-9 months		
Population	28% (19% to 37%)	1,254
Hospital	26% (22% to 30%)	722
Rehabilitation	44% (29% to 59%)	248
Sub-total	*31% (26% to 37%)*	*2,224*
1 year		
Population	31% (21% to 41%)	2,948
Hospital	32% (21% to 43%)	801
Rehabilitation	36% (23% to 50%)	274
Sub-total	*33% (26% to 39%)*	*4,001*



Hackett ML, World Stroke Organization 2014

Comorbidity of chronic disease and potential treatment conflicts in older people dispensed antidepressants



Caughey GE, Age Ageing 2010

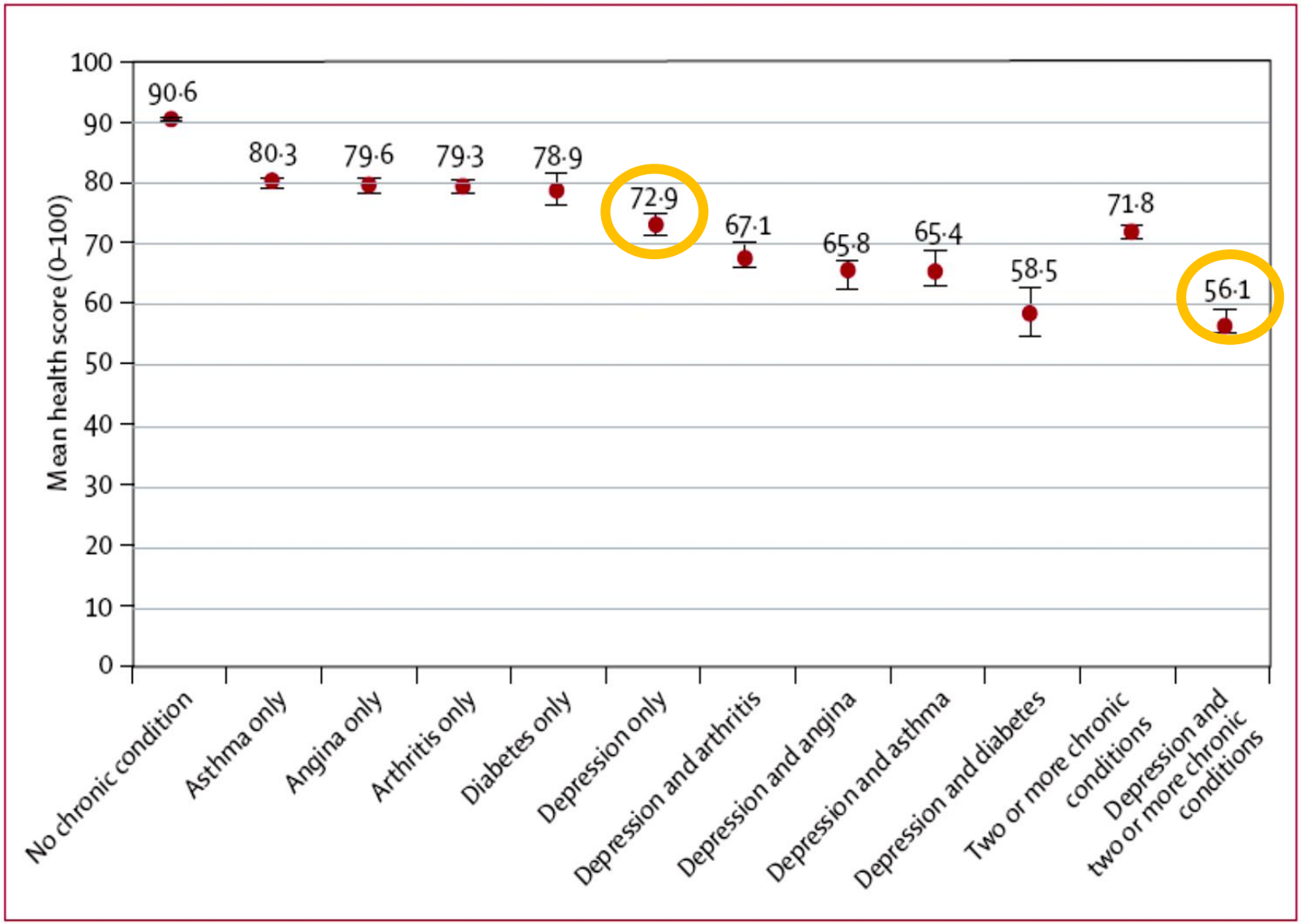


Figure: **Global mean health by disease status**
Data from WHS 2003.

Moussavi S et al, Lancet 2007; 370:851-58

Depression & multimorbidity

Table 1. Number of Physical Health Conditions in People With and Without Depression

Variable	Depression (n = 143,943), n (%)	Controls (n = 1,280,435), n (%)	OR Standardized by Age and Sex (95% CI)	OR Standardized by Age, Sex, and Deprivation Quintile (95% CI)
No physical condition	45,668 (31.7)	754,440 (58.9)	0.44 (0.43–0.45)	0.45 (0.44–0.46)
1 Physical condition	33,758 (23.5)	259,555 (20.3)	1.17 (1.16–1.19)	1.19 (1.17–1.20)
2 Physical conditions	24,210 (16.8)	125,514 (9.8)	1.58 (1.56–1.60)	1.55 (1.53–1.58)
3 Physical conditions	16,640 (11.7)	67,777 (5.3)	1.88 (1.84–1.91)	1.84 (1.81–1.87)
4 Physical conditions	10,586 (7.4)	37,022 (2.9)	2.11 (2.06–2.17)	2.06 (2.01–2.11)
≥5 Physical conditions	13,081 (9.1)	36,127 (2.8)	2.71 (2.65–2.77)	2.65 (2.59–2.71)

Abbreviation: OR = odds ratio.

Smith DJ, J Clin Psych 2014

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Clinical trials of potential antidepressants: to what extent are the elderly represented: a review

- Medline search of relevant articles of clinical trials of potential antidepressants.
- **RESULTS:** The maximum age of inclusion for most clinical trials was 65 years. The highest age reported for depressed subjects was 90 years. No clear consensus on who were considered to be elderly. Pharmacological studies on healthy subjects were most often done on young adults. The period of study was relatively shorter for clinical trials done on elderly subjects. No difference in the exclusion or inclusion criteria between studies done in young and elderly subjects.
- **CONCLUSIONS: Elderly subjects aged 75 years and over were clearly underrepresented in the clinical trials of potential antidepressants.**

Giron MS, Int J Geriatr Psych 2005

Efficacy, Safety, and Tolerability of Sertraline in Patients with Late-Life Depression and Comorbid Medical Illness

Javaid I. Sheikh, MD,† Erin L. Cassidy, PhD,*† P. Murali Doraiswamy, MD,‡ Ronald M. Salomon, MD,§ Mady Hornig, MD,‖ Peter J. Holland, MD,¶ Francine S. Mandel, PhD,# Cathryn M. Clary, MD,** and Tal Burt, MD#**

752 patients aged 60 and older with diagnosis of **MDD** according to DSM-IV-Edition, diagnosis.

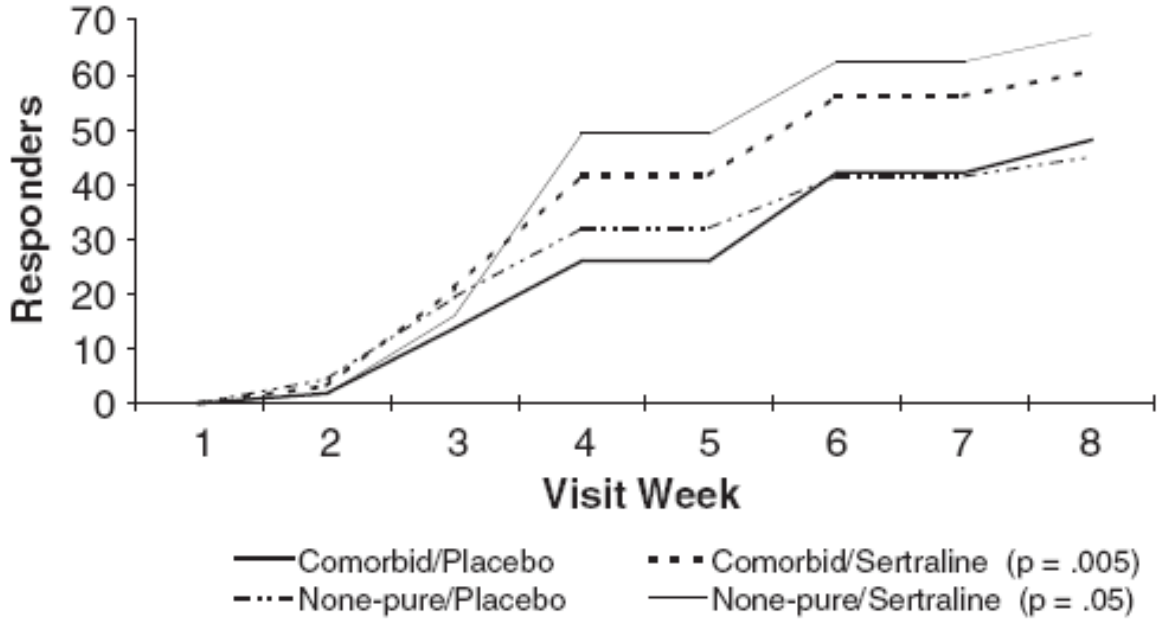
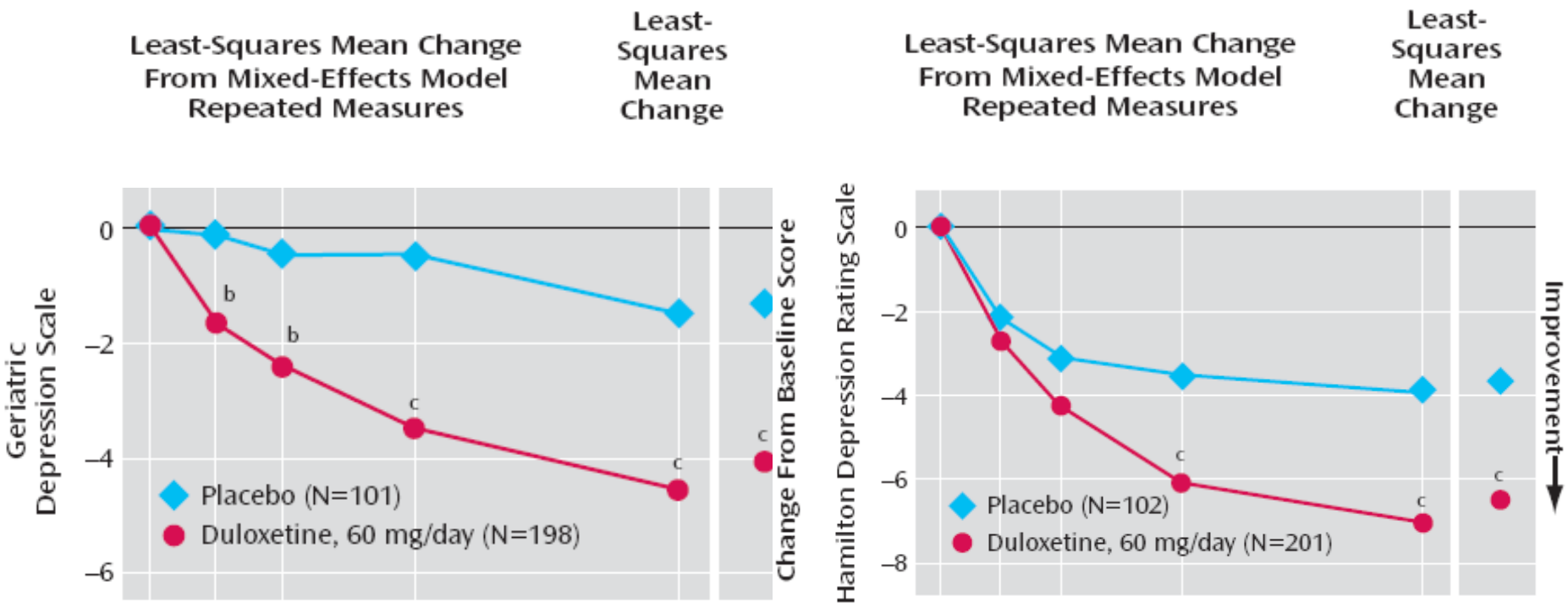


Figure 1. Percentage of patients with a 50% or greater improvement in HAMD.

J Am Geriatr Soc 2004

Efficacy of Duloxetine on Cognition, Depression, and Pain in Elderly Patients With Major Depressive Disorder: An 8-Week, Double-Blind, Placebo-Controlled Trial

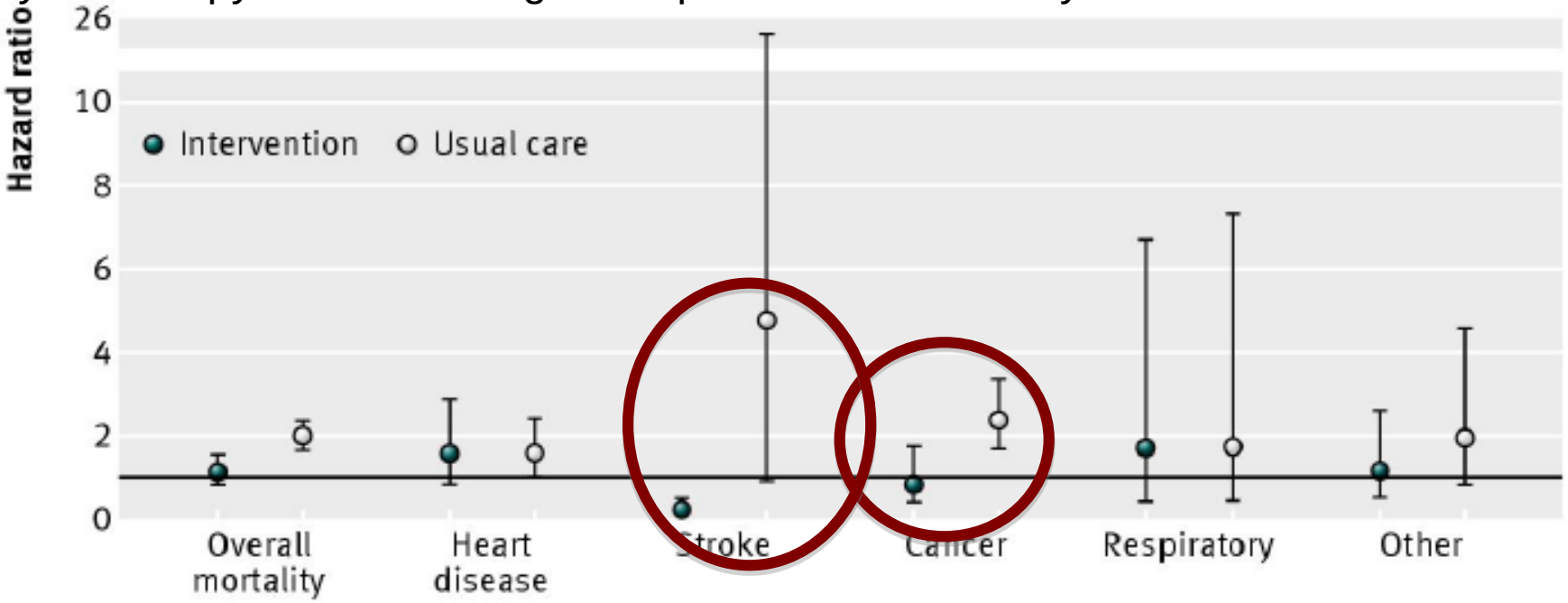
311 elderly patients (mean age 72 years) assigned to duloxetine 60 mg (n=207)
Or placebo (n=104) for 8 weeks ina double blind study



Raskin J, Am J Psychiatry 2007

Long term effect of depression care management on mortality in older adults: follow-up of cluster randomized clinical trial in primary care

1226 participants (PROSPECT); depression care manager woth PCP, offering psychotherapy and increasing antidepressant dose for 2 years

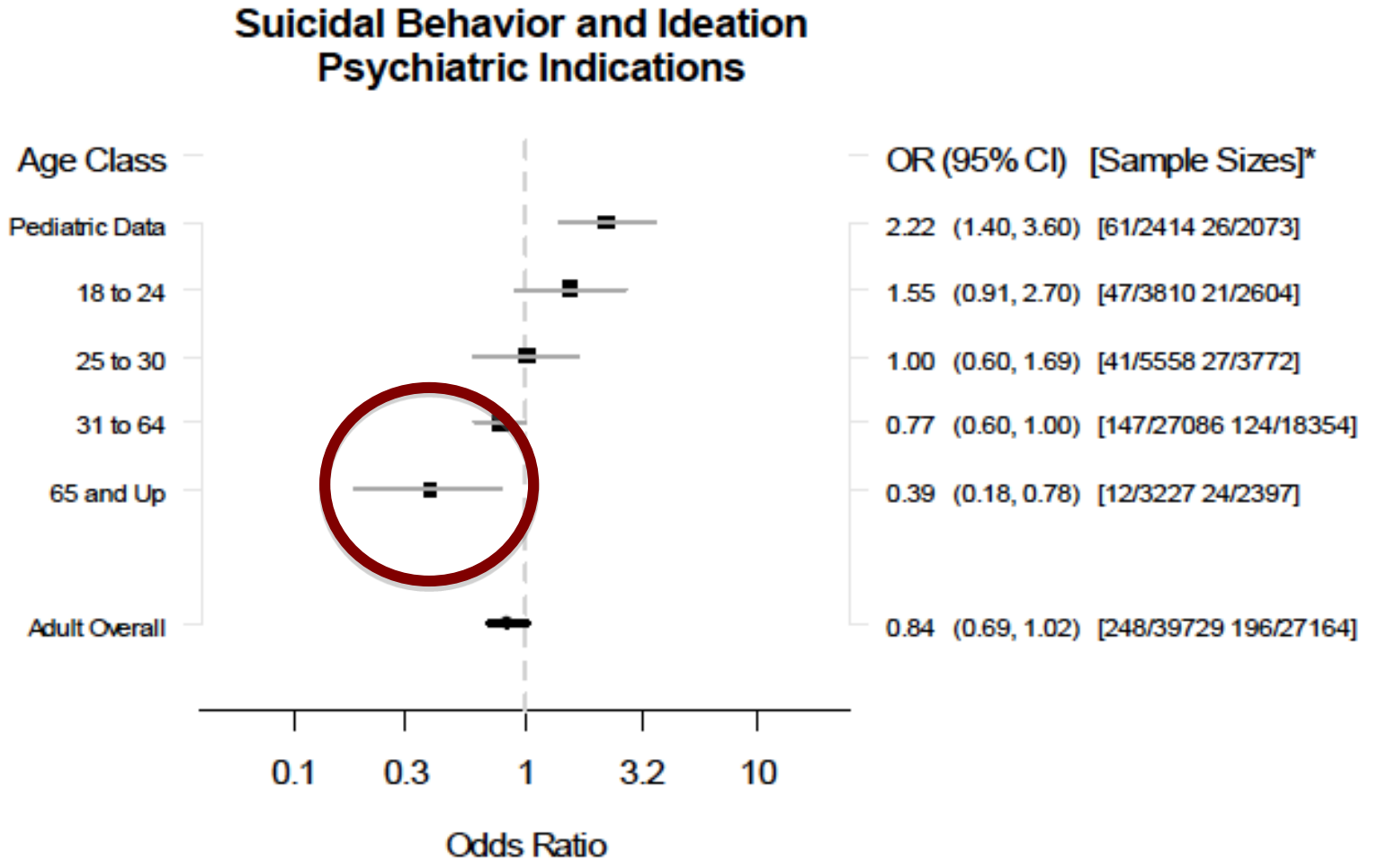


No of deaths

Major depression	79	68	27	15	5	4	15	26	12	5	18	17
No depression	95	95	28	30	8	3	25	31	11	10	21	21

Gallo R, et al, BMJ 2013

Clinical review: relationship between antidepressant drugs and suicidality in adults 2006.



Administration USFaD: www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-FDA.pdf [Last accessed 22 May 2015.

Efficacy of antidepressants for late-life depression: a meta-analysis and meta-regression of placebo-controlled randomized trials

- 74 RCTs (20,572 participants) included in the review. Of these, 15 trials (4,756 patients) were based on patients with depression in later life.
- The effect of antidepressants in older later life depression was not significantly different to placebo (RR 1.13, 95% CI 0.93 to 1.37), but there was significant heterogeneity ($p<0.002$). Response rates showed that the number-needed-to-treat was six for studies of adults, eight for later life depression and 21 for older later life depression.
- CONCLUSIONS: The present meta-analysis suggests that antidepressants are efficacious in late-life MDD, but significant study heterogeneity suggests that other factors may contribute to these findings

Tedeschini E, J Clin Psychiatry 2011

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Tedeschini E, J Clin Psychiatry 2011

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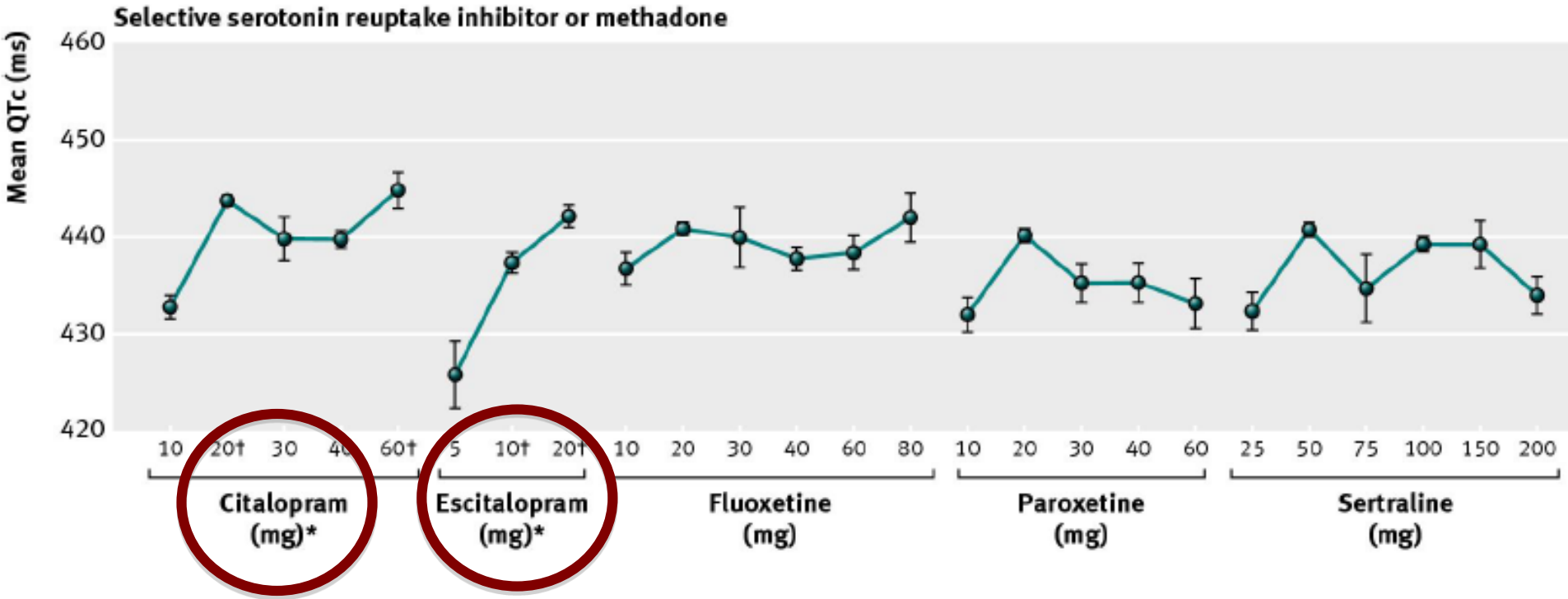
Aspects involved in the psychopharmacological response in the elderly

- Psychosocial and stigma
- Pharmacokinetics and pharmacodynamics
  - Changes affecting distribution (↓weigth, body size, muscle mass and body water, ↑body fat)
  - ↓ plasma albumin may ↑plasma-free concentrations of SSRI
  - Long-half life antidepressants (e.g. fluoxetine) are not recommended; SIADH may be frequent
- Loss of neurons in the cortex, locus coeruleus, and hippocampus increase sedative effects
- Reduced sensitivity of baroreceptors facilitate hypotensive effects
- Loss of cholinergic transmission in CNS increases sensitivity to anticholinergic effects (i.e., delirium)

QT interval and antidepressant use: a cross sectional study of electronic health records

Castro V M et al



BMJ

BMJ 2013;346:f288 doi: 10.1136/bmj.f288 (Published 29 January 2013)

Characteristics, prevalence, risk factors, and underlying mechanism of hyponatremia in elderly patients treated with antidepressants

- Cross-sectional study (March 2007-April 2009) with prospectively collected data.
- Patients older than 60 years, using antidepressants,
- 345 patients included. **The prevalence of hyponatremia as an AR-AD was 9.3%**.
- Risk factors: history of hyponatremia (adjusted OR 11.17, 95%CI 2.56-40.41), weight<60 kg (adjusted OR 3.47, 95%CI 1.19-10.13), and psychosis (adjusted OR 3.62, 95%CI 1.12-11.73).

Mannesse CK, Maturitas 2013

Fall risk-increasing drugs and hip fracture in elderly

Table 2 Risk of hip fracture in patients using FRIDs

Drugs/group of drugs	Model A	Model B	Model C	Model D
Cardiovascular drugs	*Odds ratio (95% CI)*	*Odds ratio (95% CI)*	*Odds ratio (95% CI)*	*Odds ratio (95% CI)*
Vasodilators used in cardiac diseases	1.14 (0.96-1.35)	0.99 (0.83-1.18)	1.02 (0.85-1.21)	0.89 (0.74-1.06)
Antihypertensive agents	0.99 (0.37-2.67)	1.12 (0.41-3.02)	1.29 (0.47-3.49)	1.26 (0.46-3.42)
Diuretics	1.35* (1.17-1.56)	1.10 (0.95-1.27)	1.07 (0.92-1.23)	0.97 (0.84-1.12)
Beta-blocking agents	0.96 (0.83-1.11)	1.01 (0.88-1.16)	1.01 (0.88-1.17)	0.92 (0.80-1.07)
Calcium channel blockers	0.82* (0.68-0.98)	0.87 (0.73-1.05)	0.88 (0.73-1.05)	0.83 (0.69-1.00)
Renin-angiotensin system inhibitors	0.89 (0.77-1.04)	0.99 (0.85-1.16)	1.02 (0.87-1.19)	0.93 (0.79-1.09)
Psychotropic drugs				
Opioids	2.03* (1.75-2.36)	1.83* (1.57-2.13)	1.76* (1.51-2.05)	1.56* (1.34–1.82)
Dopaminergic agents	1.88* (1.31-2.67)	1.96* (1.37-2.81)	1.99* (1.39-2.84)	1.78* (1.24-2.55)
Antipsychotics excluding lithium	1.80* (1.35-2.39)	1.42* (1.06-1.89)	1.37* (1.03-1.84)	1.31 (0.98-1.75)
Anxiolytics	1.75* (1.49-2.06)	1.48* (1.25-1.74)	1.41* (1.19-1.66)	1.31* (1.11-1.54)
Hypnotics and sedatives	1.75* (1.51-2.02)	1.48* (1.28-1.71)	1.42* (1.22-1.64)	1.31* (1.13-1.52)
Antidepressants	2.08* (1.78-2.43)	1.88* (1.61-2.20)	1.79* (1.53-2.10)	1.66* (1.42-1.95)

Thorell *et al. BMC Geriatrics* 2014, **14**:131
http://www.biomedcentral.com/1471-2318/14/131

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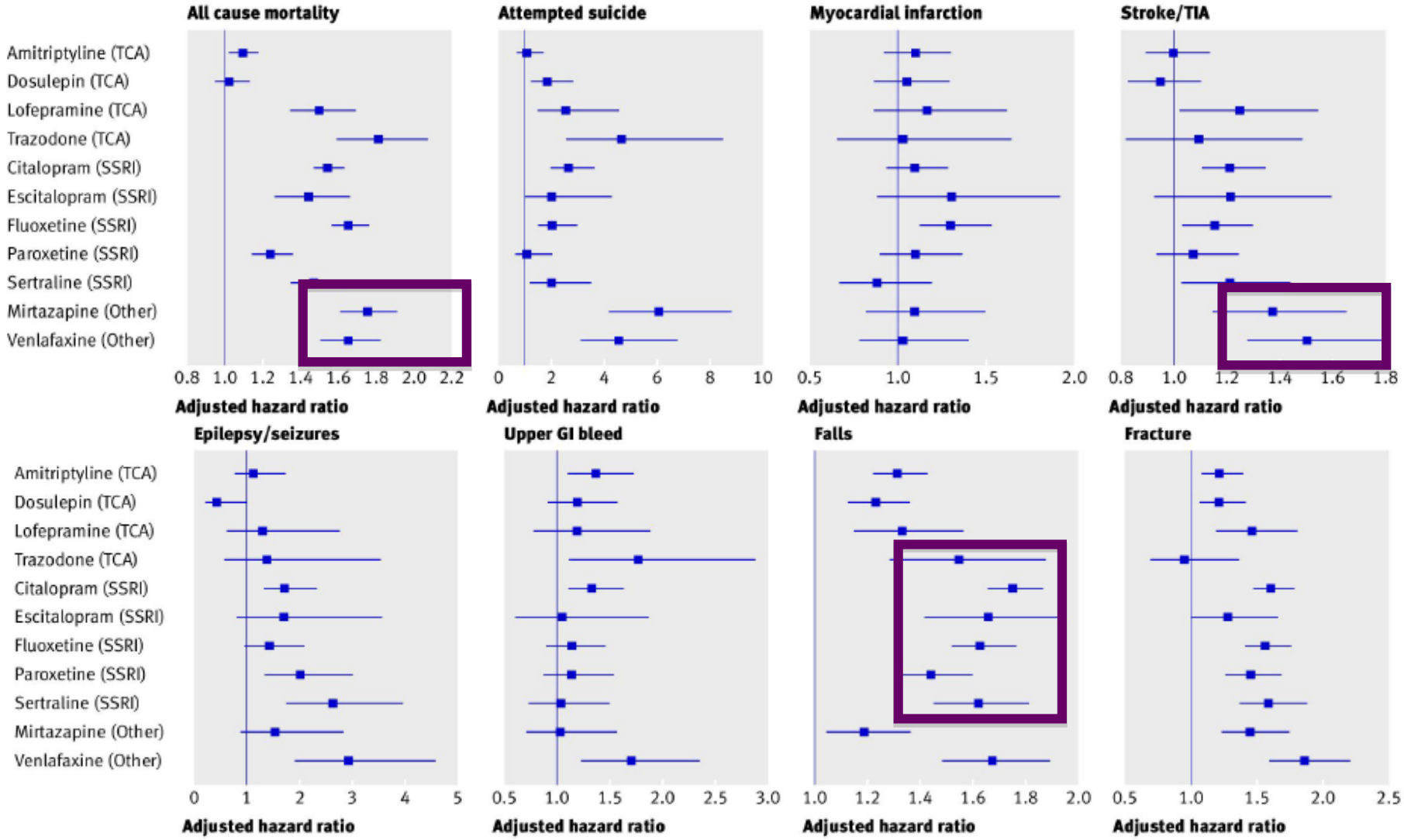
Antidepressant use and risk of adverse outcomes in older people: population based cohort study



Coupland C, et al BMJ 2011

Comparative Efficacy and Safety of Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors in Older Adults: A Network Meta-Analysis

Kristian Thorlund, PhD, MSc,[*†‡] *Eric Druyts, MSc,*[‡§] *Ping Wu, MBChB, MSc,*[‡] *Chakrapani Balijepalli, MD, PhD,*[‡] *Denis Keohane, MD,*[‖] *and Edward Mills, PhD, MSc*[*‡]

- 15 RCT comparing SSRIs or SNRIs with placebo or another active antidepressant. The eligible population included individuals aged 60 and older with a primary diagnosis of MDD.
- RCTs had to assess the active interventions for at least 6 weeks.
- For efficacy, partial response to treatment (defined as ≥50% reduction in HDRS) score or MADRS score from baseline.

J Am Geriatr Soc 2015

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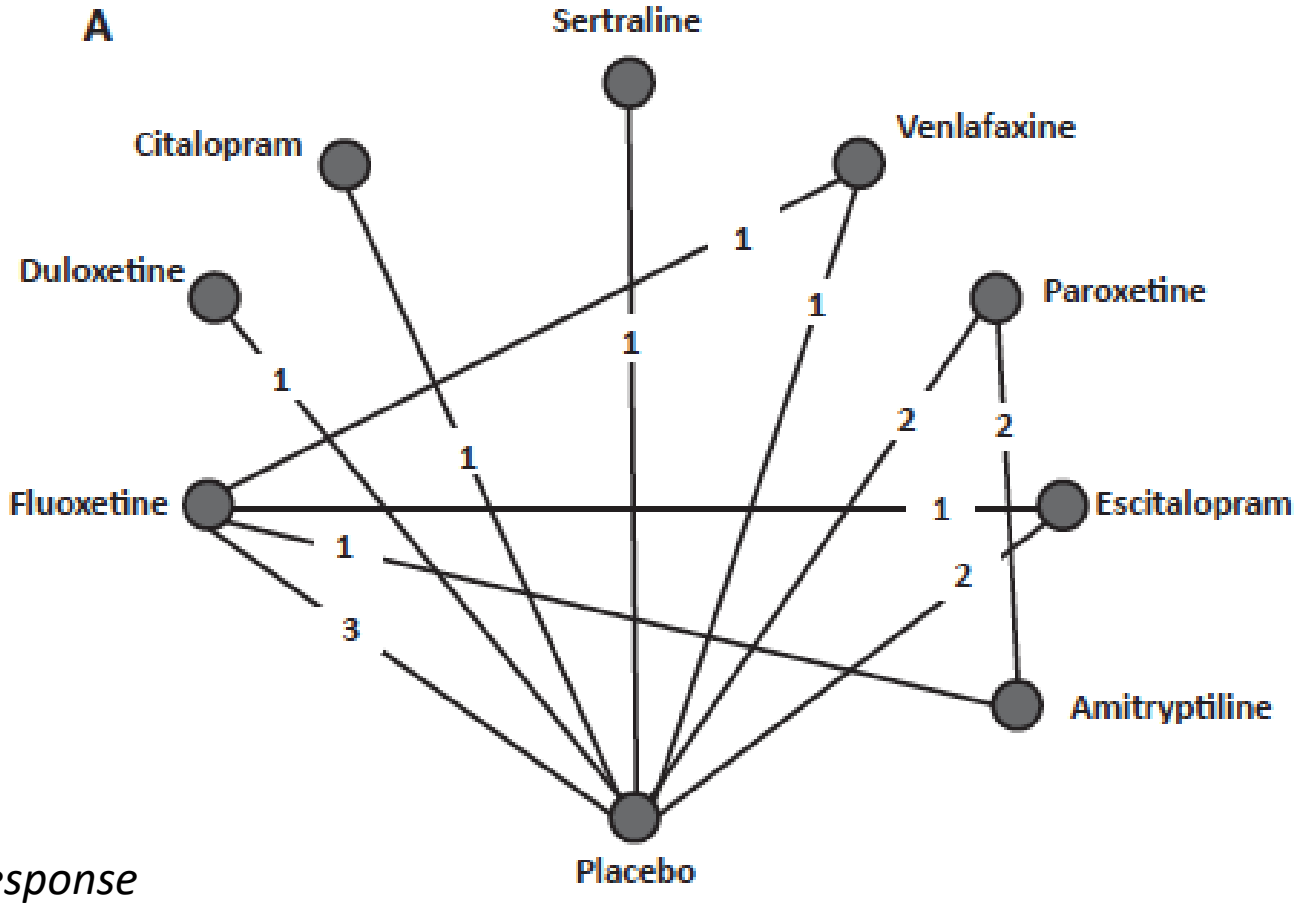

Partial response

2015

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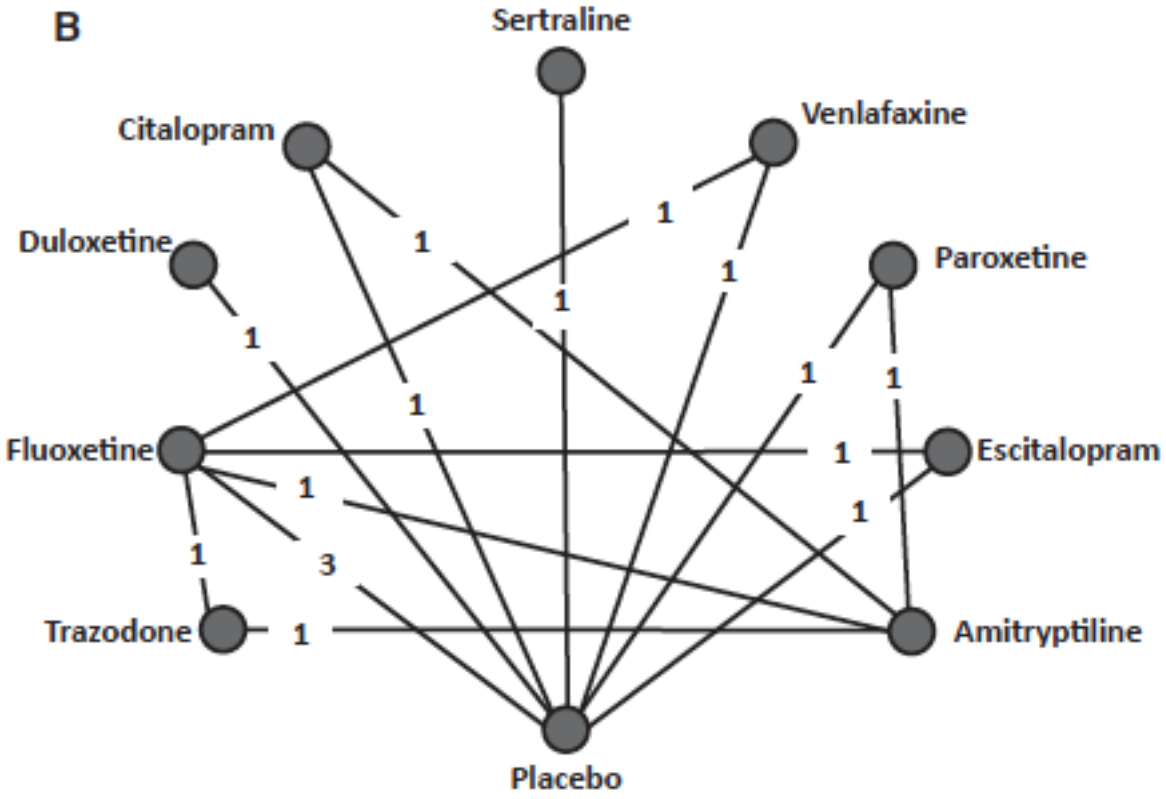

Dizziness

J Am Geriatr Soc 2015

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Sertraline (RR = 1.28), paroxetine (RR = 1.48), and duloxetine (RR = 1.62) significantly better than placebo.

For dizziness, duloxetine (RR = 3.18) and venlafaxine (RR = 2.94) worse than placebo.

Hierarchy of safety associated with the different antidepressants, although there appears to be a dearth of reporting of safety outcomes.

Table 2. Relative Risks and 95% ors and Serotonin-Norepinephrine Reupt

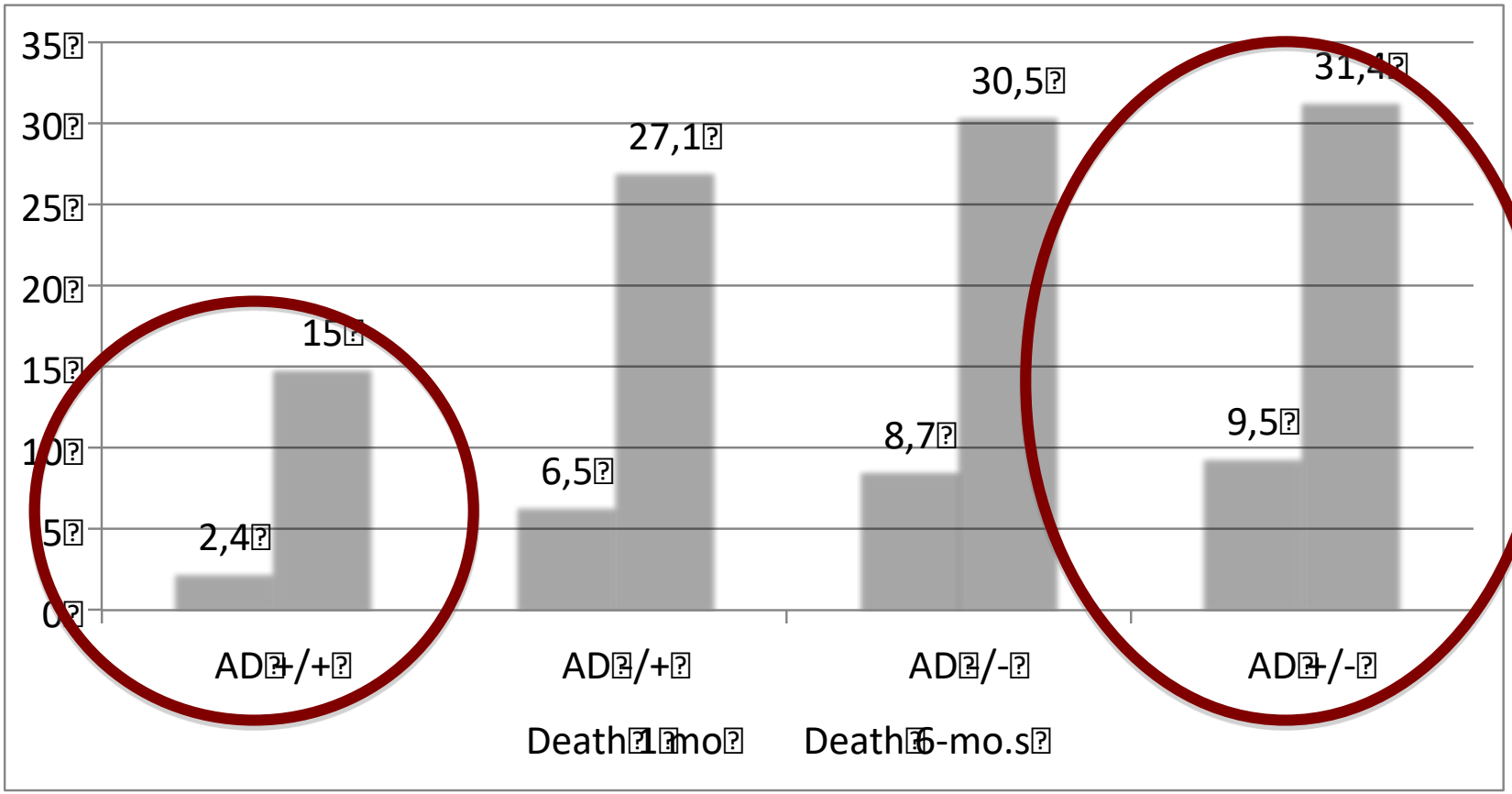
Medication	Sertraline	Venl	alopram
Placebo	1.28 (1.07–1.51)	1.21 (0	.99–1.41)
Sertraline		0.95 (0	.73–1.19)
Venlafaxine			.72–1.40)
Citalopram			.77–1.75)
Paroxetine			.63–0.99)
Duloxetine			.55–0.98)
Fluoxetine			.91–1.34)

J Am Geriatr Soc 2015

Clinical features and outcomes of 1351 patients admitted to a Geriatric Unit (March 8, 2013 to Aug 25, 2014)

	+/+ (n=167)	+/- (n=105)	-/+ (n=107)	-/- (n=972)	p
Age (yrs)	83.2±6.3	83.8±5.1	84.5±6.7	84.2±6.8	0.24
Females, n (%)	47 (70.1)	32 (76.2)	29 (60.4)	269 (58.5)	0.05
Charlson Index	2.6±2.2	2.5±2.1	2.5±2.1	2.9±2.2	0.51
Dementia	15 (9.0)	63 (60)	34 (31.8)	289 (29.7)	< 0.001
MNA-SF	8.5±2.9	7.4±3.2	8.1±2.9	8.9±3.2	< 0.001
Albumin, gr	3.4±0.6	3.3±0.5	3.4±0.5	3.3±0.5	0.04
MMSE	20.5±6.9	13.4±7.6	18.3±7.6	19.6±8.2	< 0.001
Delirium	59 (35.3)	74 (50.5)	56 (52.3)	356 (36.3)	< 0.001
BDZ pre-admis	53 (31.7)	30 (28.6)	35 (32.7)	154 (15.8)	< 0.001

Proportion of patients who died at 1 and 6 months (1351 patients) according to AD prescription



P = 0.003 at 1 month

P = 0.001 at 6 months

Factors predicting AD withdrawal at discharge from AGU (378 pts)

	OR	95% IC	p
Age	1.0	0.9 – 1.1	
Gender female	0.9	0.5 – 1.5	
Delirium on admission	**0.4**	**0.2 – 0.6**	**.000**
ADL score=0 (pre-admission)	0.8	0.3 – 1.8	
ADL score=1-5 (pre-admission)	0.9	0.4 – 1.8	
ADL score=6 (pre-admission)	ref		
Malnutrition	0.7	0.4 – 1.2	
Dementia	**0.5**	**0.2 – 0.8**	**.004**

Multiple logistic regression analysis (enter method)

Conclusioni

- La scelta di utilizzare antidepressivi nell'anziano con multimorbilità non è facile e deve tenere conto di numerose variabili
- Allo stato attuale non vi sono chiare indicazioni sul tipo di antidepressivo indicato per questa categoria di soggetti
- La scelta di sospendere (o prescrivere) antidepressivi dovrebbe tenere in considerazione sia la prognosi dell'individuo che alcune condizioni di salute associate (quali ad esempio demenza e delirium)