


U.P.I.A.
 Unione Provinciale
 Istituti per Anziani

**Corso di Aggiornamento
 Medici RSA/RSD in Formazione
 27 ottobre 2023**

LA TERAPIA DELLA DEPRESSIONE NELL'ANZIANO FRAGILE

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 Clinica San Francesco, Verona





Clinical characteristics of Late-Life Depression (LLD)

- Occurring in individuals aged ≥ 60
- **Early-Onset (EOD)** or **Late-Onset (LOD, after 60)**
- High incidence of chronic illness
- Cognitive dysfunction
- Disability
- Poor prognosis
 - ✓ Risk of mortality 2x
 - ✓ Risk of suicide 3.5x



Naismith et al. Progress in Neurobiology 98 (2012) 99–143
 Weisenbach & Kumar. Curr Psychiatry Rep (2014) 16:463

Late-Life Depression (LLD): multiple underlying pathophysiologies.

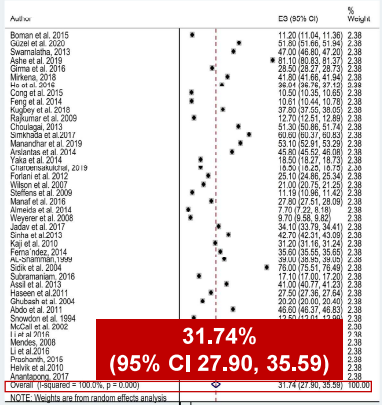


- **Early-Onset Depression (EOD):** long-term illness-specific effects:
 - ✓ lifetime n° and severity of episodes
 - ✓ overall longer duration of illness
- **Late-Onset Depression (LOD):**
 - ✓ underlying possible brain changes
 - ✓ potential role of underlying prodromal neurodegenerative disease
- **Impact on:** longitudinal course, response to treatment, new interventions

Naismith et al. Progress in Neurobiology 98 (2012) 99–143

Prevalence of depression among old age: a systematic review and meta-analysis

- N 42 studies
- n = 57.486 elders



31.74%
 (95% CI 27.90, 35.59)

Zenebe et al. Annals of General Psychiatry (2021) 20:55

The Depression Iceberg



Major Depressive Disorder (DSM-5)

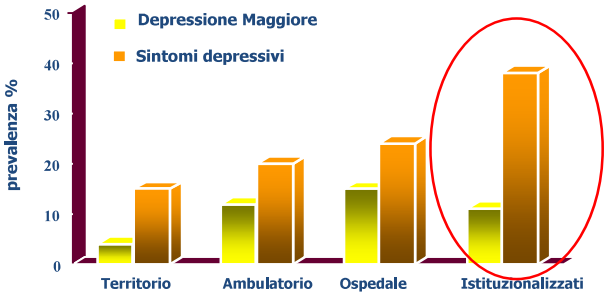
- 5/9 sx – 2 weeks

Common in Older Adults

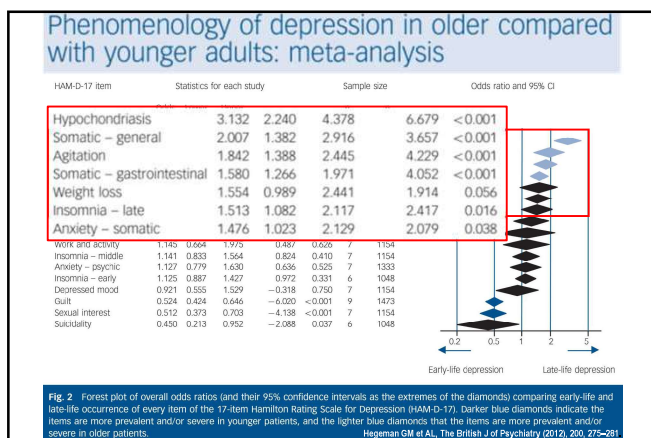
- ✓ Subsyndromal depression:
- ✓ Minor depression
 - 2-4/9 sx – 2 weeks
- ✓ Recurrent brief depression
- ✓ Subsyndromal depression

APA, Diagnostic and statistic manual of mental disorders (5° ed.), AP Publishing, 2013

Depressione nell'Anziano: Prevalenza



Mulsant and Ganguli, J Clin Psychiatry, 1999



JAMDA 14 (2013) 392–397

JAMDA
journal homepage: www.jamda.com

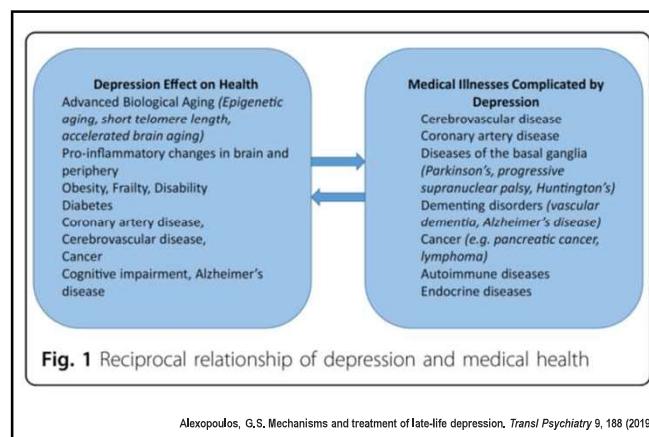
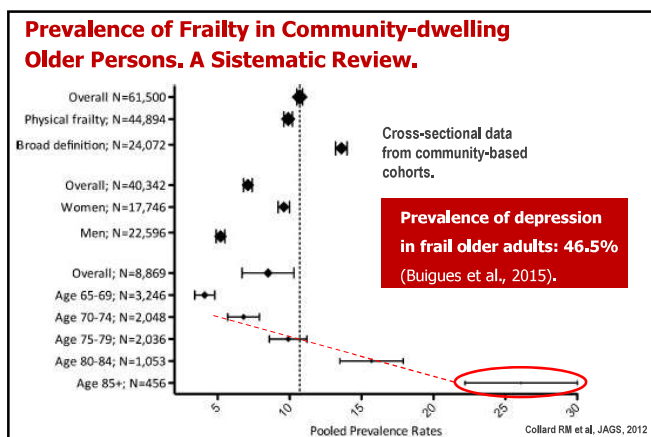
ELSEVIER

Special Article

Frailty Consensus: A Call to Action

John E. Morley MB, BCh^{a,*}, Bruno Vellas MD^{b,c}, G. Abellan van Kan MD^{b,c}, Stefan D. Anker MD, PhD^{d,e}, Iuergen M. Bauer MD, PhD^f, Roberto Bernabei MD^g, Matteo Cesari MD, PhD^{b,c}, W.C. Chumlea PhD^h, Wolfram Doeberer MD, PhD^{d,i}, Jonathan Evans MD^j, Linda P. Fried MD, MPH^k, Jack M. Guralnik MD, PhD^l, Paul R. Katz MD, CMD^m, Theodore K. Malmstrom PhD^{a,n}, Roger J. McCarter PhD^o,

"...A medical syndrome with multiple causes and contributors, that is characterized by diminished strength, endurance, and reduced physiologic function, and increases an individual's vulnerability for developing increased dependency and/or death..."



Depression: Indications for Treatment

- **Severity of mood depression and/or anhedonia**
- **Concomitant psychotic symptoms**
- **"Suicidality"**
- **Psychomotor agitation or retardation**
- **Episode lasting at least 2 weeks**
- **Sleep and/or eating disorders**
- **Symptoms worse in the morning**
- **Reduced performance and autonomy**

Depression in Alzheimer's Disease: what's useful for diagnosis?

- If worse in the morning, very useful for the diagnosis.
- Guilt and suicidal thoughts uncommon, but strong indicators.
- Self-deprecating statements ('I am a dummy' or 'I am no good').
- Short lived symptoms, but frequently recurrent.
- **Irritability, worry, or fear more than frank sadness.**
- **Patients stay to themselves, talk less, with a lower volume.**
- **Face towards the wall, refusal of food and/or medicaments.**

Late stages

Lyketsos & Lee, 2004, Dement Ger Cogn Disord, 17, 55-64

Evoluzione dei Farmaci Antidepressivi

1950	1960	1970	1980	1990
Fenelzina	Imipramina	Maprotilina	Fluoxetina	Nefazodone
Isocarbossazide	Cloimpramina	Amoxapina	Sertralina	Mirtazapina
Tranilcipromina	Nortriptilina	Mianserina	Paroxetina	Venlafaxina
	Amitriptilina	Trazodone	Fluvoxamina	Tianeptina
	Desipramina		Citalopram	Reboxetina
			Bupropione	Milnacipran
			Moclobemide	
2000	2008-2010	2014	2019	
Escitalopram	Agomelatina	Vortioxetina	Esketamina	
Duloxetina	Desvenlafaxina			

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Antidepressants

- TCAs
- SSRIs
- SNRIs
- SARI
- Multimodal ADs
- S-Ketamine

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The Ideal Antidepressant for the Older Adults

- Antidepressant efficacy
- Simple and predictable kinetics
- Safety and tolerability
- No drug-drug interactions

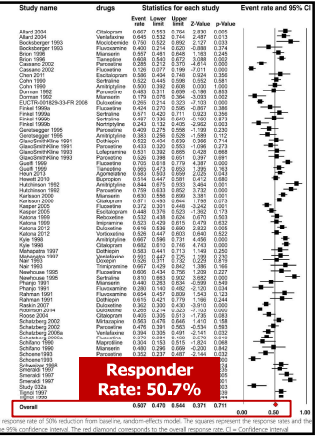
- **Antidepressant efficacy**
- **Simple and predictable kinetics**
- **Safety and tolerability**
- **No drug-drug interactions**

How well do elderly patients with MDD respond to ADs: a systematic review and single-group meta-analysis.

- **N: 44 studies, 6373 patients**
- **≥ 50% ↓ on the HAM-D: 50.7%**
- **Better response to treatment for pts. in AD-controlled trials compared to PBO-controlled trials (selection bias).**

Study name **drugs** **Statistics for each study** **Event rate and 95% CI**

Study name	drugs	K	n	OR	95% CI	Z-Value	P-Value
Alex 1984	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Alex 2004	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 1993	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 1998	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2000	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2002	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2004	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
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Balazs 2008	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2010	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2012	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2014	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2016	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2018	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2020	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2022	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2024	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2026	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2028	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2030	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2032	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2034	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2036	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2038	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2040	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2042	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2044	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2046	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2048	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2050	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2052	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2054	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2056	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2058	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2060	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2062	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2064	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2066	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2068	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2070	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2072	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2074	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2076	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2078	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2080	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2082	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2084	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balazs 2086	Fluoxetine	1	10	0.85	0.47-1.52	0.07	0.48
Balaz							



Antidepressants, Older Adults and Evidence-Based Medicine (EBM)



- **Inclusion criteria generally not «real world» oriented:**
 - ✓ No late-onset depression
 - ✓ No «vascular depression»
 - ✓ Psychotic depression: scarcity of data
 - ✓ No complex comorbidity/politherapy
 - ✓ **Frailty as specific inclusion criterion: no data**

Mallery et al. BMC Geriatrics (2019) 19:306



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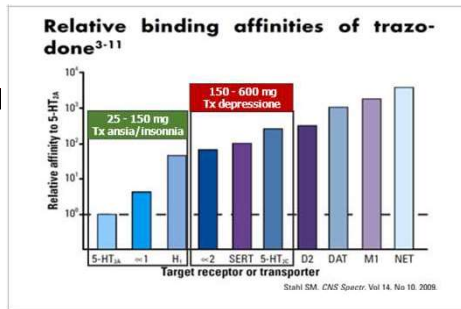
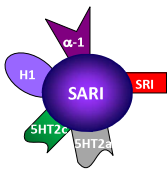
Mallery et al. BMC Geriatrics (2019) 19:306

Antidepressants: Efficacy on Specific Domains (I)

- TCAs
- SSRIs
- SNRIs
- **SARI**
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Serotonin Receptor Antagonists and Reuptake Inhibitors (SARI): Trazodone.

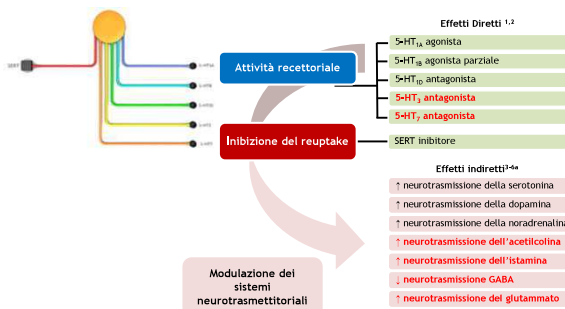


Mod. Da: Stahl S. M. (2008), *Essential Psychopharmacology*, Cambridge University Press

Antidepressants: Efficacy on Specific Domains (II)

- TCAs
- SSRIs
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- **Multimodal ADs**
- S-Ketamine

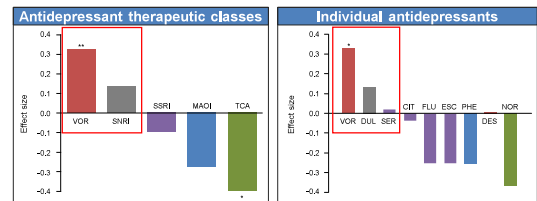
Vortioxetina: Antidepressivo ad Azione Multimodale



¹In the forebrain; GABA-gamma-aminobutyric acid

¹ Bang-Andersen et al. *J Med Chem* 2011;54:2299-2321;
² Westrich et al. *Poster at FMAAD 2012*;
³ Mark et al. *Poster at ECNP 2011*; ⁴ Mark et al. *Poster at SOBP 2011*;
⁵ Peltonen et al. *Poster at ECNP 2012*; ⁶ Mark et al. *Poster at APA 2013*

Antidepressants and changes in cognitive dysfunction measured by the Digit Symbol Substitution Test (DSST): a Network Meta-Analysis

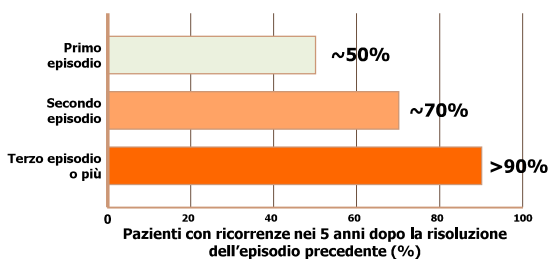


*p<0.05; **p<0.01 vs placebo

DSST: Executive function, working memory, processing speed

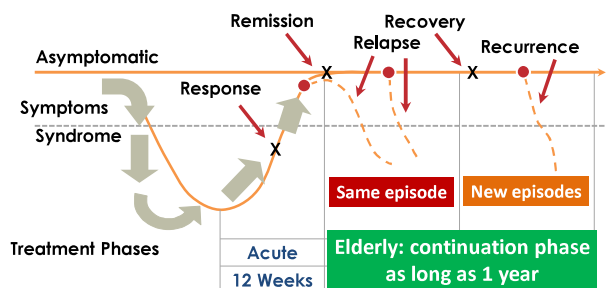
VOR, vortioxetine; SNRI, serotonin-noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant; DUL, duloxetine; SER, sertraline; CIT, citalopram; FLU, fluoxetine; ESC, escitalopram; PHE, phenelzine; DES, desipramine; NOR, nortriptyline
 Baune BT et al. *Int J Neuropsychopharmacol* 2018;21:97-107

La ricorrenza diventa più probabile dopo ogni episodio depressivo

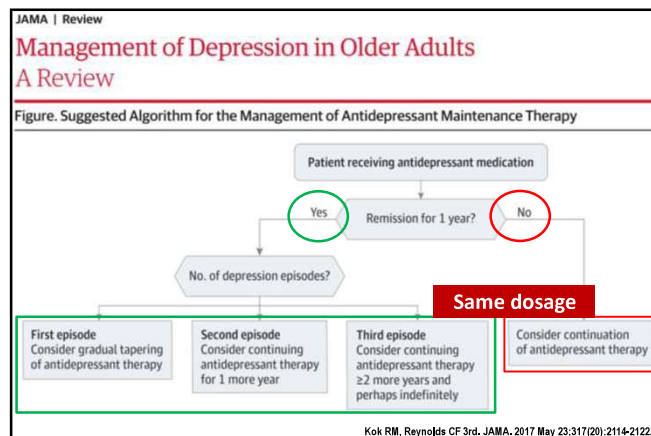
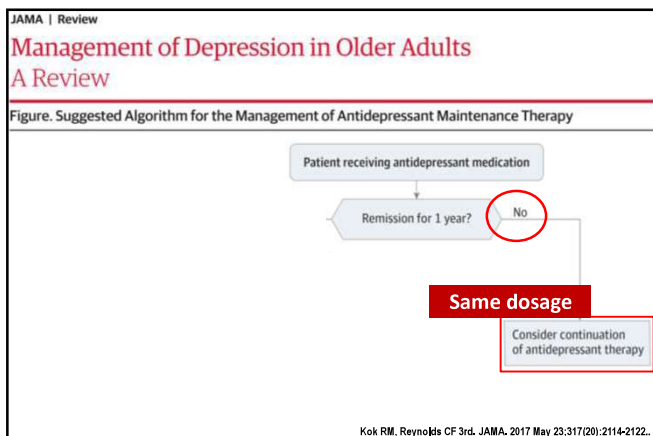


Keller. *J Clin Psychiatry* 1999; 60(Suppl 17):41-45.

Treating Depression is a Long-Term Enterprise



Kupfer DJ. *J Clin Psychiatry*. 1991;52(suppl):28-34.



Antidepressants in Alzheimer's Disease: Duration of Treatment

- Standard guidelines for late-life depression do not apply (1 year - >> lifetime)
- No maintenance or discontinuation studies
- The progression of dementia can lead to the loss of the neurobiological substrate of depression
- Gradual withdrawal * of antidepressants after 6 months - 1 year from the response

* ≤ 25% per week

Lyketsos CG & Lee HB, 2004, Dement Ger Cogn Disord, 17, 55-64

The Ideal Antidepressant for the Older Adults

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The Ideal Antidepressant for the Older Adults

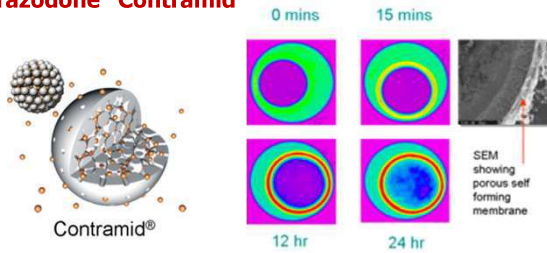
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Trazodone a rilascio immediato FARMACOCINETICA (100 mg)

	C _{MAX}	T _{max}	T _½	AUC
TZD IR, adulto giovane	1.2 µg/ml (dose singola)	1 h	6.6 h	7.3 µg/ml/h
TZD IR, anziano	1.6 µg/ml (dose singola) 2 µg/ml (dose ripetuta)	1.5 h	9-11 h	17 µg/ml/h

„Trazodone“, prescribing information, 2014

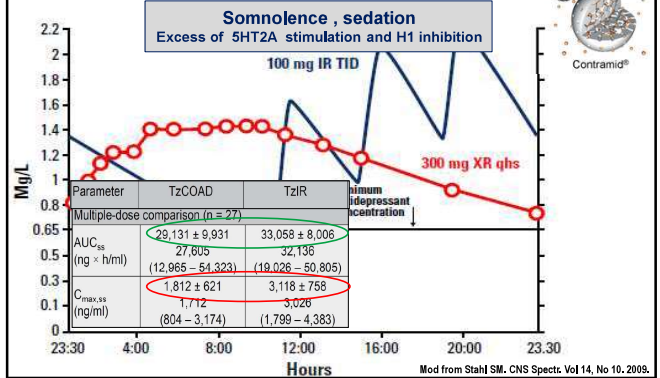
Trazodone "Contramid"



Contramid® è una matrice di amido ad alto contenuto di amilosio reticolato modificato, con incorporate le molecole di trazodone. La figura mostra la RMN allo stato solido di una compressa rotonda di Contramid (rosa) immersa in acqua (verde).

Entro 15 minuti la struttura esterna di Contramid si riorganizza per formare una nuova membrana di controllo del rilascio comprendente catene di amido reticolate (giallo >> rosso). Questa membrana rimane intatta e uniforme per almeno 24 ore garantendo il rilascio di ordine zero del farmaco dalla compressa.

Comparison of Concentrations of Trazodone IR and Trazodone COAD (Contramid)



Evidence from the scientific literature about age-related reduction in systemic clearance of antidepressants

Renal clearance may be impaired with age; avoid use in creatinine clearance < 30 ml/minute

N/A= None Available;

Other Antidepressants

Bupropion	Yes
Mirtazapine	N/A
Nefazodone	N/A
Methylphenidate	N/A
Trazodone	Yes
Vilazodone	N/A
SNRI	
Desvenlafaxine	Yes
Duloxetine	N/A
Venlafaxine	Yes
SSRI	
Citalopram	Yes
Escitalopram	Yes
Fluoxetine	N/A
Paroxetine	N/A
Sertraline	Yes

Tetracyclines

Amoxapine	N/A
Maprotiline	No
Trimipramine	N/A
TCA	
Amitriptyline	Yes
Desipramine	No
Doxepin	Yes
Imipramine	Yes
Nortriptyline	Yes
† men only	

Boyce RD, Am J Geriatr Pharmacother. 2012 April; 10(2): 139–150.

Farmaco	Ambito di dosaggio
Citalopram	20 mg (↑ QTc)
Escitalopram	10 mg (↑ QTc)
Fluoxetina	20 - 60 mg
Fluvoxamina	50 - 300 mg - RCP: anziani?
Paroxetina	20 - 40 mg
Sertralina	50 - 200 mg
Mirtazapina	30 - 45 mg
Venlafaxina	75 - 225 mg ↓↓ dose con ↓↓ Creatinina Cl.
Duloxetina	60 - 120 mg
Bupropione	150 mg - dose raccomandata
Trazodone	75 - 300 mg ↓↓ dose nei pazienti molto anziani
Vortioxetina	5-10 mg

AD di II GEN: buona tollerabilità – in genere dosaggi simili agli adulti giovani, salvo CrCl molto ridotta/ patologie d'organo.

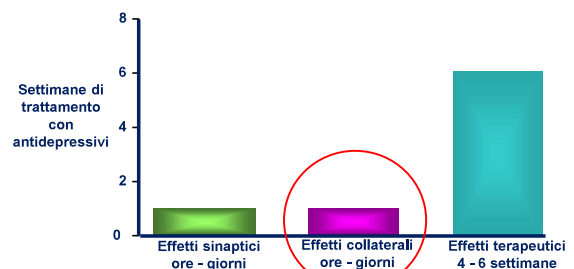
Consigliata per tutti i composti una titolazione iniziale.

Mod da: Biggio G et AL, Rivista Società Italiana di Medicina Generale N.1 2017 1

The Ideal Antidepressant for the Older Adults

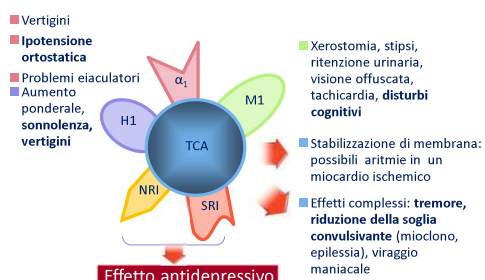
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DINAMICA TEMPORALE DEGLI EFFETTI DEGLI ANTIDEPRESSIVI



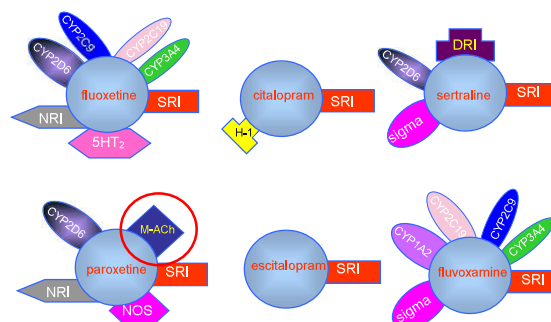
Mod. Da: Stahl S. M. (2008). Essential Psychopharmacology, Cambridge University Press

Antidepressivi Triciclici: Profilo Farmacodinamico ed Effetti Clinici



Preferibili le amine secondarie (NORTRIPTILINA, DESIPRAMINA) per un miglior profilo di tollerabilità (anticolinergica, antiadrenergica, antistaminica)

SSRI's: Pharmacodynamic Profile



Mod. Da: Stahl, S. M. (2008), Essential Psychopharmacology, Cambridge University Press

Relation Between Delirium and Anticholinergic Drug Burden in a Cohort of Hospitalized Older Patients

- Retrospective, cross-sectional study - 477 older pts. in AGU*.
- Delirium: 151 pts. (31.7%).**
- 377 pts (79.0%): at least one anticholinergic drug.
- Pts. with delirium had a **higher anticholinergic burden** than those without delirium.
- Dose - effect relationship, cumulative effect.**

Table 2 Anticholinergic medications most commonly prescribed according to the Anticholinergic Cognitive Burden (ACB) scale

Drugs	ACB score	Delirium, n (%)	No delirium, n (%)
Furosemide	1	59 (39.1)	144 (44.2)
Quetiapine	3	24 (15.9)	10 (3.1)
Trazodone	1	18 (11.9)	7 (2.1)
Digoxin	1	16 (10.6)	20 (6.1)
Haloperidol	1	12 (7.9)	12 (3.7)
Warfarin	1	9 (6.0)	31 (9.5)
Promazine	3	9 (6.0)	4 (1.2)
Fentanyl	1	6 (4.0)	4 (1.2)
Alprazolam	1	5 (3.3)	10 (3.1)
Paroxetine	3	5 (3.3)	-
Isosorbide	1	5 (3.3)	18 (5.5)
Atenolol	1	4 (2.6)	15 (4.6)
Metoprolol	1	4 (2.6)	5 (1.5)
Olanzapine	3	4 (2.6)	-
Prednisone	1	3 (2.0)	11 (3.4)
Nifedipine	1	2 (1.3)	6 (1.8)



*Acute Geriatric Unit

Pasina L et al, Drugs & Aging (2019) 36:85-91

SSRI / SNRI negli Anziani: Caveats

- Jitteriness syndrome* (attivazione precoce)
- Apatia da SSRI (15 – 80 %)
- Prolungamento QTc (CIT, ESC)
- Sindrome da sospensione (0 – 60 %)
- Iponatriemia /SIADH (0.5 – 32%)
- Effetti extrapiramidali (≤ 1/1000)**
- Fenomeni di sanguinamento (23/10.000)**

Jacob & Spinler, Ann Pharmacother, 2006, 40, 1618-22; Yuan et al, Am J Med, 2006, 119, 719-727; Schillevoort et al, J Clin Psychopharm, 2002, 17, 75-79; Wongparakan et al, Ann Gen Psychiatry, 2007, 6, 7; Boyer & Shannon, NEJM, 2005, 352; Hartikainen et al, J Gerontol, 2007, 62, 10, 1172-1181.

Citalopram News – Ottobre 2011

NOTA INFORMATIVA IMPORTANTE CONCORDATA CON LE AUTORITÀ REGOLATORIE EUROPEE E L'AGENZIA ITALIANA DEL FARMACO (AIFA)

- Citalopram è associato ad un prolungamento dose dipendente dell'intervallo QT
- La dose massima di citalopram è ora di 40 mg al giorno
- Per i pazienti anziani...la dose massima viene ridotta a 20 mg al giorno**
- Citalopram è **controindicato** per i pazienti affetti da un noto prolungamento del QT o da sindrome congenita del QT lungo
- L'utilizzo di Citalopram è **controindicato** in associazione ad altri farmaci noti per prolungare l'intervallo QT

Escitalopram: Scheda tecnica

- Per i pazienti anziani...la dose massima viene ridotta a 10 mg al giorno**
- Stesse controindicazioni che Citalopram

Hyponatremia* Associated with Psychotropic Drugs in Older Adults.

- Incidence: 0.5 - 32%**
- Risk >:** older age, female gender, decreased BMI, thiazide diuretics, decreased baseline sodium
- SSRIs / SNRIs / NARIs / NaSSA / APs / CBZ:**
- Nausea, asthenia, cramps, confusion > coma**
- Early onset; not dose-related; resolves after discontinuation**
- 5-HT_{1c}, 5-HT₂ stimulation**
 - ✓ hypothalamic: SIADH
 - ✓ kidney: concentration deficit

*Serum levels < 135 mmol/L

Jacob & Spinler, Ann Pharmacother, 2006 Sep;40(9):1618-22, Epub 2006 Aug 8.

Association of Antidepressant Use With Drug-Related Extrapyramidal Symptoms - A Pharmacoepidemiological Study

- N: 3,838 subjects with EPS
- 38,380 age-matched controls

EPS: rate ratios vs. controls

- Excluded:
 - ✓ primary Parkinson disease
 - ✓ Tx with levodopa, ropinirole, pramipexole, domperidone, metoclopramide, entacapone, benztropine, selegiline, rasagiline, diphenhydramine, trihexyphenidyl, FGAs, SGAs and TCAs.

- **Duloxetine: 5.68 (95% CI: 4.29–7.53)**
- **Mirtazapine: 3.78 (95% CI: 1.71–8.32)**
- **Citalopram: 3.47 (95% CI: 2.68–4.50)**
- **Escitalopram: 3.23 (95% CI: 2.44–4.26)**
- **Paroxetine: 3.07 (95% CI: 2.15–4.40)**
- **Sertraline: 2.57 (95% CI: 2.02–3.28)**
- **Venlafaxine: 2.37 (95% CI: 1.71–3.29)**
- **Bupropion: 2.31 (95% CI: 1.67–3.21)**
- **Fluoxetine: 2.03 (95% CI: 1.48–2.78)**

Guo MY et al. J Clin Psychopharmacol. 2018 Aug;38(4):349-356.

Additive Risk of Gastrointestinal Bleeding With Concomitant SSRIs, NSAIDs, and Acid-Suppressing Agents (7/12 studies)

Table 2. Additive Risk of Gastrointestinal Bleed With Concomitant SSRIs, NSAIDs, and Acid-Suppressing Agents. 16-1327-29

Study	SSRI ^a	SSRI + PPI ^a	NSAIDs ^a	SSRI + NSAIDs ^a	SSRI + NSAID + PPI ^a
Anglin et al. ¹² 2014	1.66 (1.44-1.92)	NR	2.8 (2.2-3.56)	4.25 (2.82-6.42)	NR
Loke et al. ¹⁰ 2008	2.36 (1.44-3.85)	NR	3.16 (2.40-4.18)	6.33 (3.40-11.8)	NR
Oka et al. ¹³ 2014	1.73 (0.65-2.82)	NR	2.55 (1.51-2.59)	4.02 (2.89-5.15)	NR
Dall et al. ²⁷ 2009	1.67 (1.46-1.92)	0.96 (0.5-1.82)	NR	8.0 (4.8-13)	NR
Targownik et al. ²⁸ 2009	1.43 (1.09-1.89)	0.56 (0.24-1.3)	NR	3.17 (2.01-5.0)	0.93 (0.29-3.03)
de Abajo and Garcia-Rodriguez ²⁹ 2008	1.8 (1.1-2.9)	1.3 (0.5-3.3)	NR	9.1 (4.8-17.3)	1.1 (0.3-3.4) ^b
Jiang et al. ¹¹ 2015	1.55 (1.35-1.78)	0.81 (0.43-1.53)	NR	10.9 (7.3-16.2)	0.98 (0.51-1.88) ^b

Abbreviations: NR, not reported; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor.

^aReported as OR (95% CI).

^bPPIs were grouped with other acid-suppressing medications.

- **SSRIs increase risk of bleeding by 1.16 - 2.36-fold.**
- **Risk is synergistic between SSRIs and NSAIDs; OR: 3.17-10.9.**
- **Acid-reducing medications may mitigate risk of GIB in chronic NSAIDs and SSRI users; OR: 0.98-1.1.**

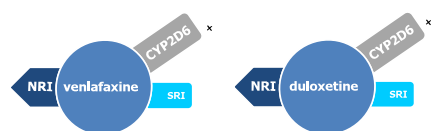
Bixby AL et al. Annals of Pharmacotherapy 2019, Vol. 53(2) 186-194

Clinical Management of Bleeding Risk With Antidepressants

- **ADs with low or no affinity for the 5-HT transporter: bupropion or mirtazapine.**
- **Patient history and response to prior ADs.**
- **Educate the patient about risk and signs/symptoms of bleeding.**
- **GIB: R/B must be weighed before discontinuing and an acids suppressing agent may be added.**
- **Avoid unnecessary NSAID use.**

Bixby AL et al. Annals of Pharmacotherapy 2019, Vol. 53(2) 186-194

SNRI: profilo farmacodinamico



	K _i (nM)	
	Serotonin	Noradrenaline
Duloxetine	0.8 ± 0.01	7.5 ± 0.3
Venlafaxine	82 ± 3	2483 ± 43

Mod. Da: Stahl S. M. (2008), Essential Psychopharmacology, Cambridge University Press

VENLAFAXINE: CARDIOVASCULAR EFFECTS

Parameter	Effect in Healthy Individuals
Heart Rate	Possible increase
Arterial Blood Pressure	Dose-related increase (3 -13%)
Intra-Cardiac Conduction	Possible QRS prolongation

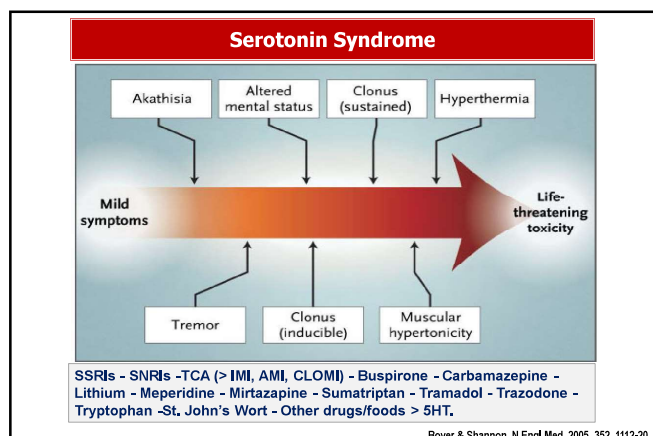
DULOXETINE: CARDIOVASCULAR EFFECTS

Parameter	Effect in Healthy Individuals
Heart Rate	Possible increase
Arterial Blood Pressure	No effect
Intra-Cardiac Conduction	No effect

Khawaja IS, Feinstein RE. Heart Dis. 2003 Mar-Apr;5(2):153-60; Mago R et al. Expert Rev Neurother. 2014 May;14(5):539-51

The Ideal Antidepressant for the Older Adults

- Antidepressant efficacy
- Simple and predictable kinetics
- Safety and tolerability
- **No drug-drug interactions**



Antidepressants and CYP-450 Isoenzymes Inhibition

Antidepressants	Major elimination pathway	Other elimination pathways	Inhibitory effect on CYP isoenzyme
SSRI			
Citalopram	CYP2C19	CYP3A4, CYP2D6	CYP1A2, CYP2B6, CYP2C19, CYP2D6
Escitalopram	CYP2C19	CYP3A4, CYP2D6	CYP1A2, CYP2B6, CYP2C19, CYP2D6
Fluoxetine	CYP2D6	CYP3A4, CYP2C19, CYP3A4	CYP2C8, CYP2C9, CYP2C19, CYP3A4
Fluvoxamine	CYP1A2	CYP2D6	CYP1A2, CYP2C19, CYP2C9, CYP3A4
Paroxetine	CYP2D6	CYP3A4	CYP2C8, CYP2C9, CYP2C19, CYP3A4
Sertraline	CYP2D6	CYP2C19, CYP2C9, CYP3A4, CYP2D6	CYP2C8, CYP2C9, CYP2C19, CYP3A4
SNRI			
Desvenlafaxine	CYP2D6	UGT, CYP3A4	None
Duloxetine	CYP2D6	CYP2D6	CYP2D6*
Levomilnacipran	CYP2D6	CYP3A4, CYP2C8, CYP2C19, CYP2D6, CYP2J2, UGT	None
Milnacipran	CYP2D6	CYP3A4	CYP3A4
Venlafaxine (active metabolite desvenlafaxine)	CYP2D6	CYP3A4	CYP2D6, CYP3A4
Others			
Agomelatine	CYP1A2	CYP2C9, CYP2C19	None
Escitalopram (active metabolite hydroxypropion)	CYP2D6	CYP2C8, CYP2C9	CYP2D6*
Floleupine	CYP2D6, CYP3A4	CYP1A2, UGT	None
Reboxetine	CYP3A4	CYP2C19, CYP2D6, carboxylesterase	None
Vilazodone	CYP3A4	CYP3A4, CYP2C19, CYP2C9, CYP2D6, CYP2C8, CYP2C9	CYP2C8
Vortioxetine	CYP2D6	CYP2D6, CYP2C8, CYP2D6	None

Notes: *Potent; †Moderate; ‡Underestimated; no symbol: weak. Data from Flockhart¹⁰, Gelberg et al.¹¹ and Spina et al.¹²
Abbreviations: CYP, cytochrome P450; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin-reuptake inhibitor; UGT, uridine diphosphate glucosyltransferases.

Low Y et al. Neuropsychiatric Disease and Treatment 2018;14:567-580

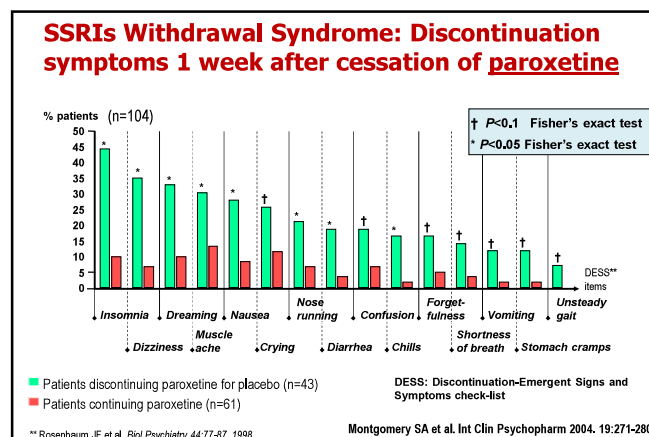
Discontinuation Symptoms of Antidepressants (SSRIs/ SNRIs)

- Dizziness, incoordination
- Flulike symptoms
- GI distress
- Sleep disturbance

- Paresthesia—"electric shocks"
- Confusion, disorientation
- Agitation

- Symptoms develop within 48 hours of discontinuation
- Symptoms may last up to 10 to 14 days
- Risk is higher if drug is taken for more than 1 month
- Agents with longer half-life protect against symptom emergence

De Vane L., 2000, VOL. 6, NO. 2, SUP. THE AMERICAN JOURNAL OF MANAGED CARE



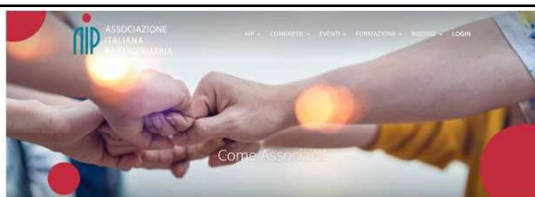
Antidepressant Discontinuation Syndrome: Risk Factors and Prevention

- Short elimination half-life (> paroxetine)
- High anticholinergic activity (> TCAs, paroxetine)
- Abrupt discontinuation of treatment
- Prevention: gradual tapering
 - ✓ 25% per week
 - ✓ 25% per month (in high risk patients)

Wilson E, Lader M. Ther Adv Psychopharmacol. 2015 Dec;5(6):357-68.
Keks et al. Aust Prescri. 2016 Jun;39(3):75-83.
Ogle NR, Akkerman SR. J Pharm Pract. 2013 Aug;26(4):389-96.

Key Messages

- Depression more common in frail older people.
- ADs are generally efficacious.
- EBM: frailty as an exclusion criterion. Safety/ tolerability: inter- and intraclass heterogeneity.
- Elderly more at risk: higher exposure/ sensitivity, somatic comorbidities and drug interactions.
- Pay attention to CV, anticholinergic, extrapyramidal effects.



Iscrizioni anno 2023

Iscriviti per usufruire degli esclusivi vantaggi che l'**Associazione Italiana di Psicogeriatría** riserva ai propri membri associati, come:

• Accesso alla rivista quadrimestrale "Psicogeriatría" online e relativi supplementi

• Accesso ai materiali dei Congressi e dei Corsi Nazionali

• Significativo sconto sulla quota di iscrizione al Congresso Nazionale

<https://www.psicogeriatría.it>