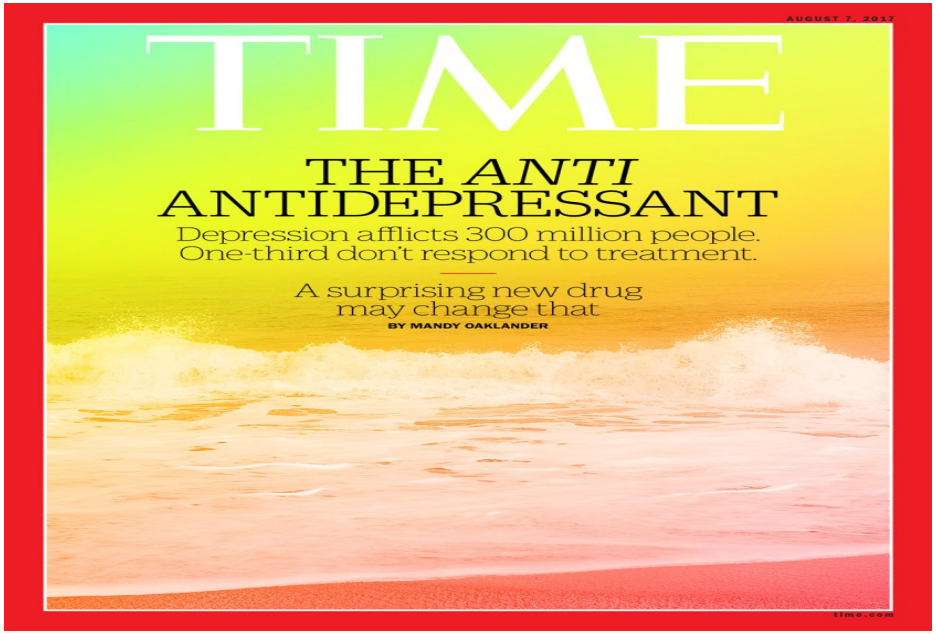
I Farmaci psicotropi

nella popolazione geriatrica



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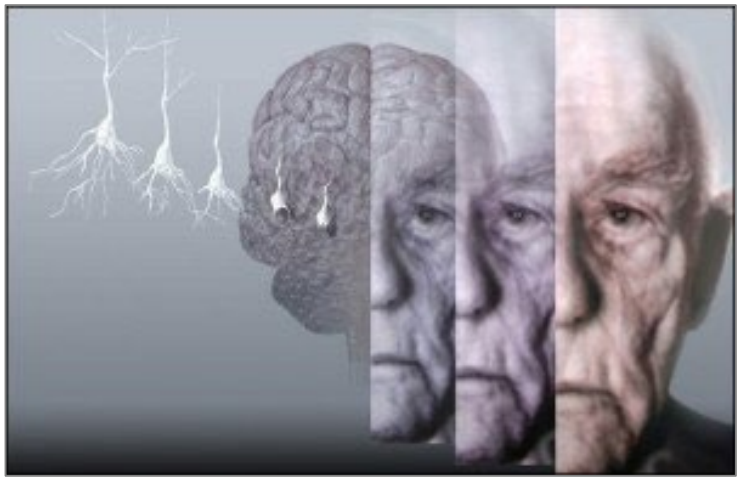
Psicofarmacologia nella popolazione geriatrica



- **Spesso pazienti anziani presentano comorbilità psichiatriche e mediche**
- **La politerapia solitamente è più regola che eccezione**
- **La politerapia espone i pazienti a problemi di safety**

Psicofarmacologia nella popolazione geriatrica: alcune considerazioni

- Farmacocinetica
- Farmacodinamica
- Cambiamenti fisiologici dell'invecchiamento
- Patologie fisiche
- Declino cognitivo
- Compliance
- Poli Farmacoterapia

Farmacocinetica

ASSORBIMENTO

↓ motilità gastrica and pH causa ↓ assorbimento e ritardo dell'effetto terapeutico

DISTRIBUZIONE

Maggior rapporto massa grassa/massa magra e minor acqua corporea e albumina causa:

- ↑ volume di distribuzione
- ↑ emivita (attenzione a farmaci lipofili come diazepam)
- ↓ di farmaco legato all'albumina quindi incremento della dose attiva

METABOLISMO

- Ridotto volume epatico ma in assenza di patologia nn si altera il metabolismo

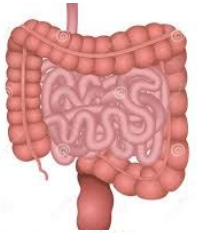
ESCREZIONE

- Perdita del 35% della funz renale dopo i 65 anni e del 50% dopo gli 80 anni.

Farmacodinamica

- Ridotto controllo della pressione e della temperatura

- I recettori sono più sensibili-→aumentata incidenza di effetti collaterali:



✓ farmaci che riducono la motilità GI (anti Ach e oppioidi)-→stitichezza

✓ farmaci che abbassano la pressione(diuretici, TCA)-→rischio cadute

- Più sensibili a BDZ

- Maggior rischio di effetti collaterali GRAVI :

agranulocitosi con clozapina, ictus con antipsicotici, sanguinamento con I

Non compliance nella popolazione geriatrica

- 40-70% non compliance
- 10% farmaci assunti prescritti per altre indicazioni
- 20% farmaci assunti senza prescrizione
- 40% interrompe la terapia precocemente

Potenziali rischi della polifarmacoterapia

JAMA Intern Med. 2017 Oct 1;177(10):1544. doi: 10.1001/jamainternmed.2017.4790.

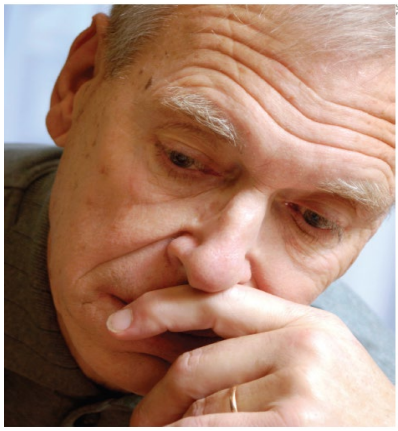
The Dangers of Polypharmacy in Elderly Patients.

Turgeon J[1,2], Michaud V[1,2], Steffen L[2].

- Effetti avversi e interazioni
- Non compliance o errori dovuti alla complessità dello schema farmacologico
- Ulteriori farmaci per trattare gli effetti avversi
- Difficoltà a tornare alla monoterapia
- Difficile discriminare efficacia di un farmaco quando co-somministrato con molti altri

Ridurre i rischi in psichiatria

The Maudsley
PRESCRIBING
GUIDELINES 10th Edition



- Usare il farmaco quando strettamente necessario
- Evitare, se possibile, alfa 1 bloccanti, anticolinergici, farmaci molto sedativi, con lunga emivita o potenti inibitori degli enzimi epatici
- Iniziare con una dose bassa e aumentare gradualmente
- Cercare di non trattare gli effetti collaterali con altri farmaci. Meglio sostituire con farmaci meglio tollerati
- Terapie più semplici possibili e idealmente monosomministrazione

Effetti indesiderati più frequenti nell'anziano

ANTICOLINERGICI

Deficit cognitivi
Confusione
Glaucoma
Ritenzione urinaria
Ileo paralitico

ANTIADRENERGICI

Ipotensione ortostatica
Cadute a terra
Fratture di femore

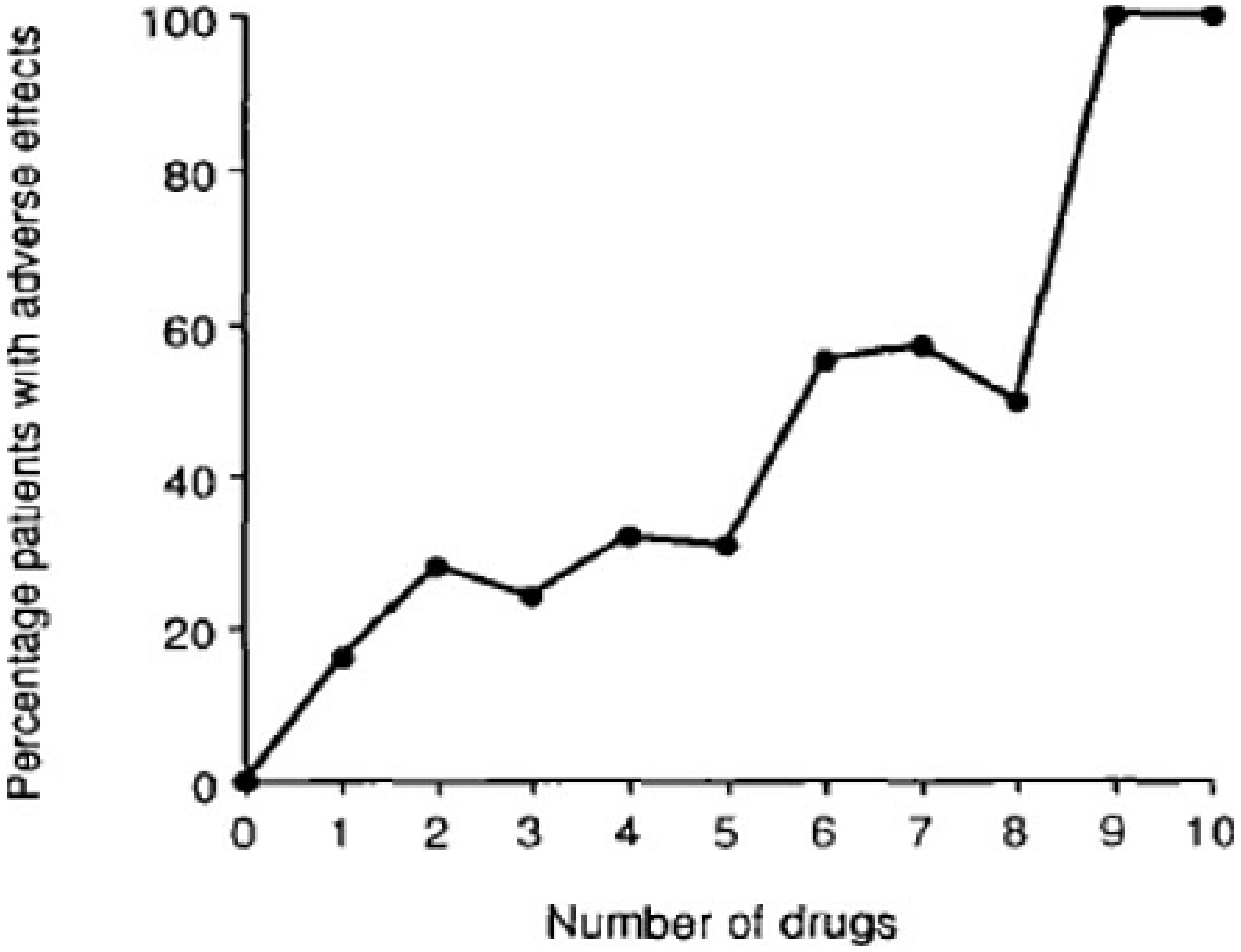
ANTISTAMINICI

Sedazione
Deficit coordinazione

CHINIDINOSIMILI

Blocchi di branca
Blocchi A-V
Aritmie ventricolari

Aumento del R di reazioni avverse all'aumentare del n. di farmaci assunti



Cresswell KM et al. British Medical Bulletin 2007; 83: 259-74

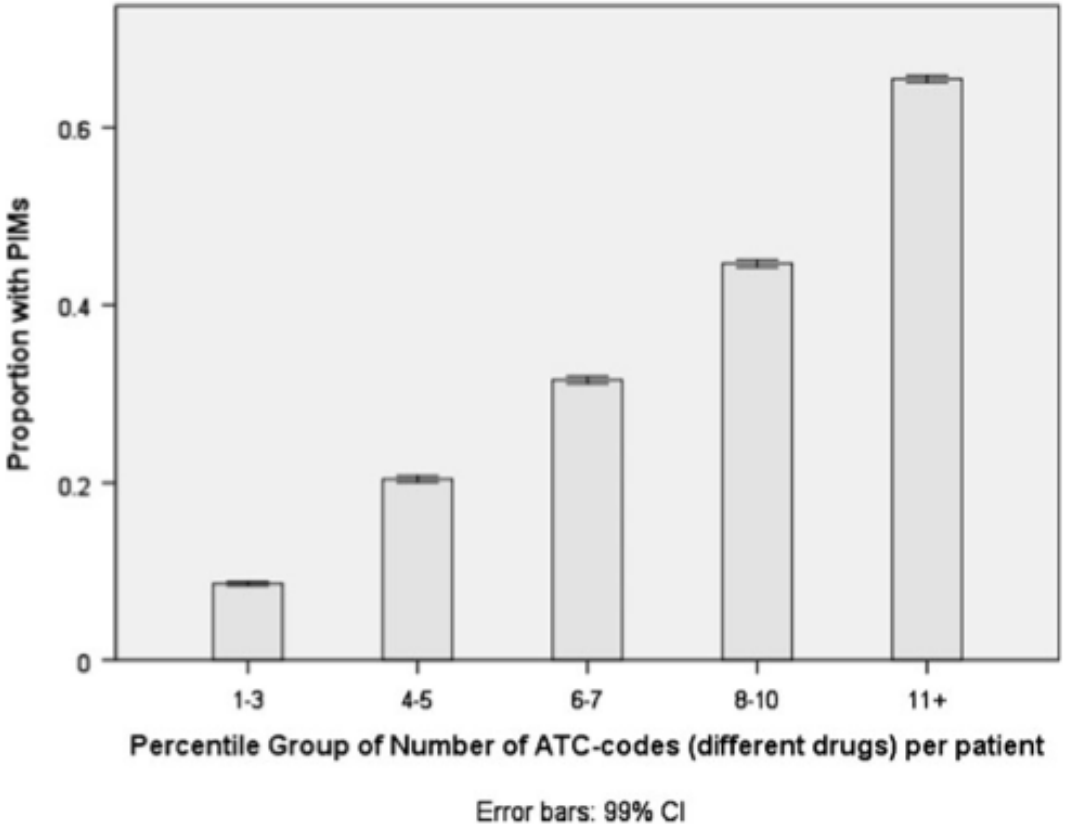
Eur J Clin Pharmacol
DOI 10.1007/s00228-012-1223-8

Received: 5 October 2011 / Accepted: 13 January 2012
© Springer-Verlag 2012

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Inappropriate prescribing for the elderly—a modern epidemic?

Gunhild Nyborg · Jørund Straand · Mette Brekke



Popolazione norvegese

- **>70 anni**
- **445.900 soggetti**
- **(88% popolazione)**
- **11.492.000 prescrizioni**
- **24540 prescrittori**

AGENZIA ITALIANA DEL FARMACO

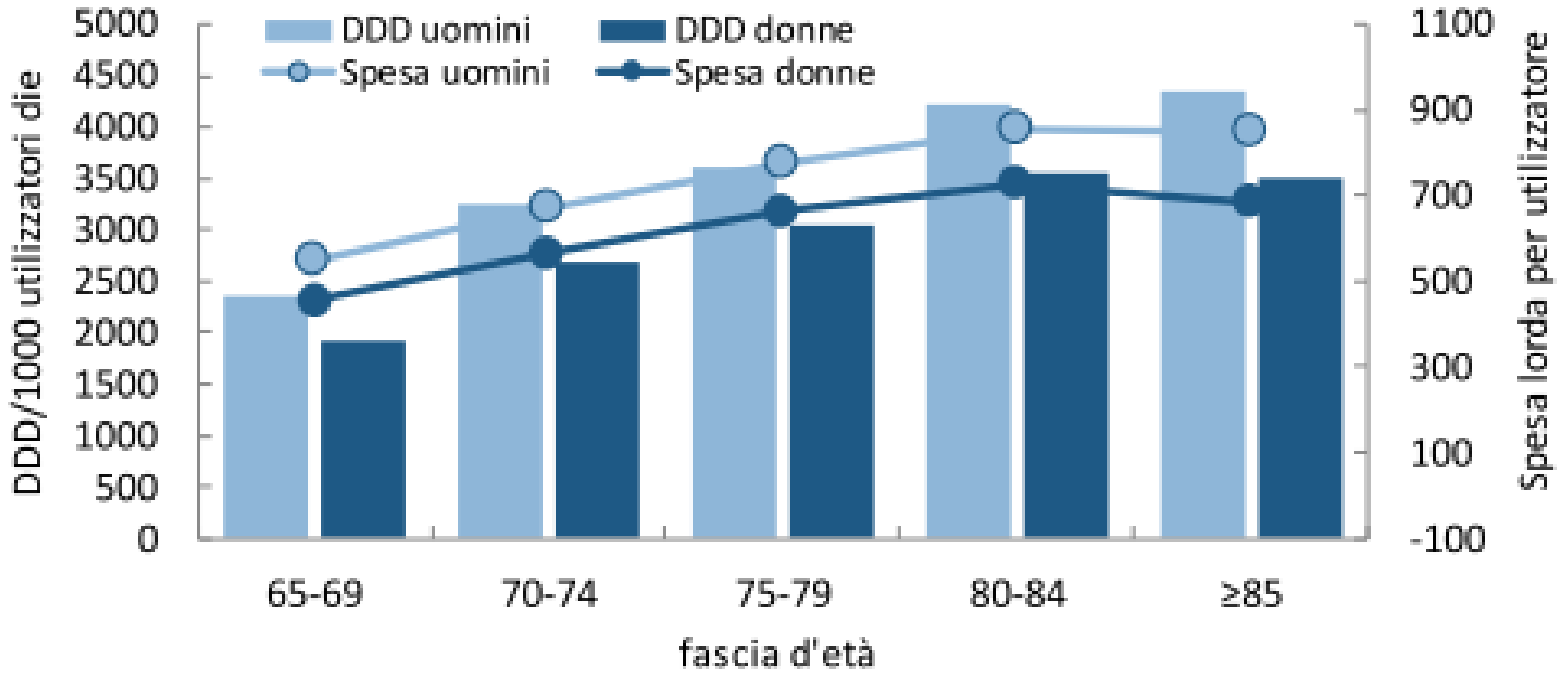
L'uso dei Farmaci in Italia

Rapporto Nazionale Anno 2018

OSSERVATORIO NAZIONALE SULL'IMPIEGO DEI MEDICINALI

- 98% degli anziani ha ricevuto almeno una prescrizione di un farmaco
- Andamento dosi e spesa aumenta conl'età fino alla fascia 80-84 per poi ridursi lievemente
- Differenze di genere: gli uomini i consumano e spendono di più

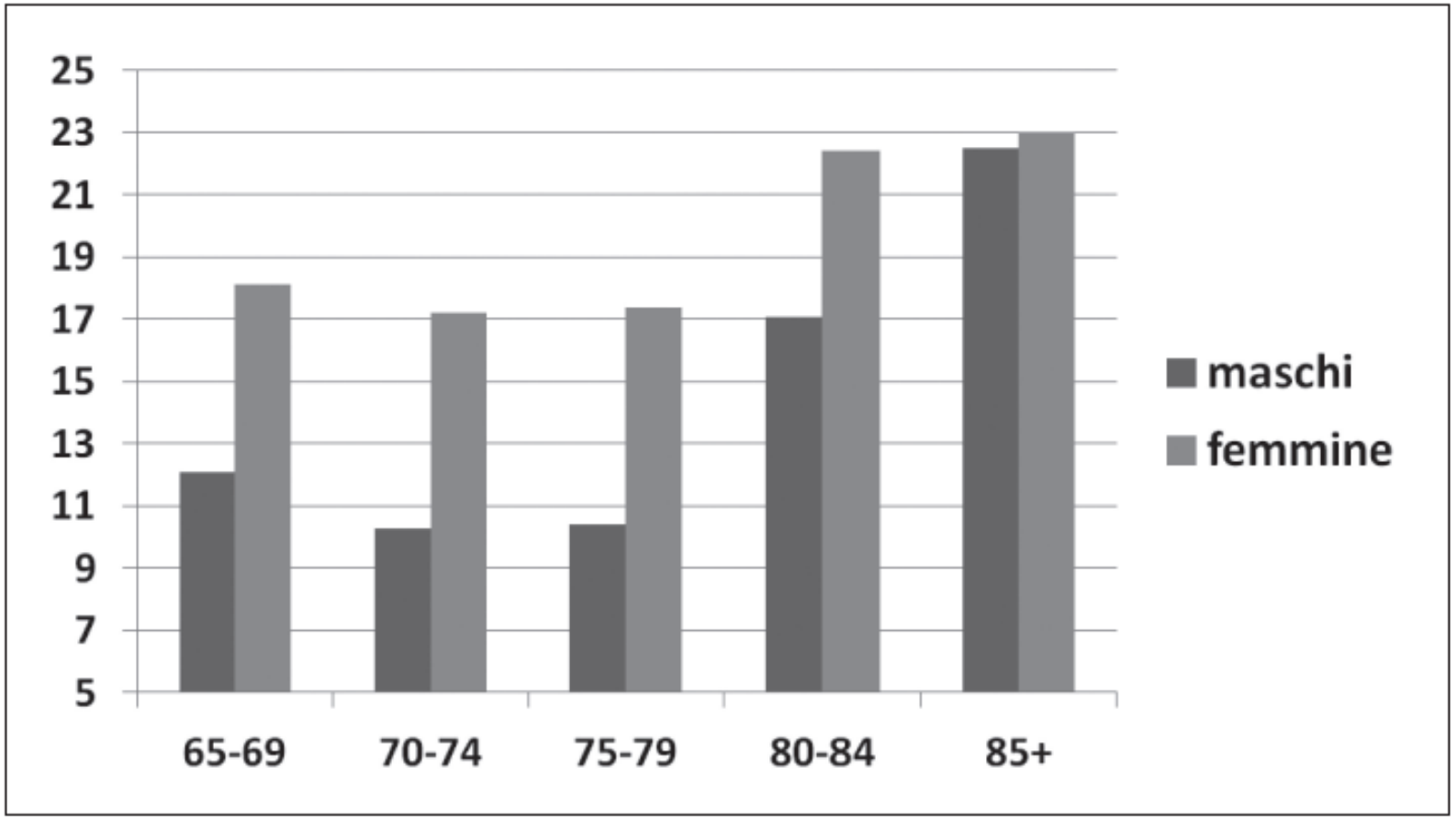
Andamento della prescrizione nella popolazione di età ≥65 anni (DDD/1000 utilizzatori die e spesa per utilizzatore) (2018)



OSSERVATORIO NAZIONALE SULL'IMPIEGO DEI MEDICINALI

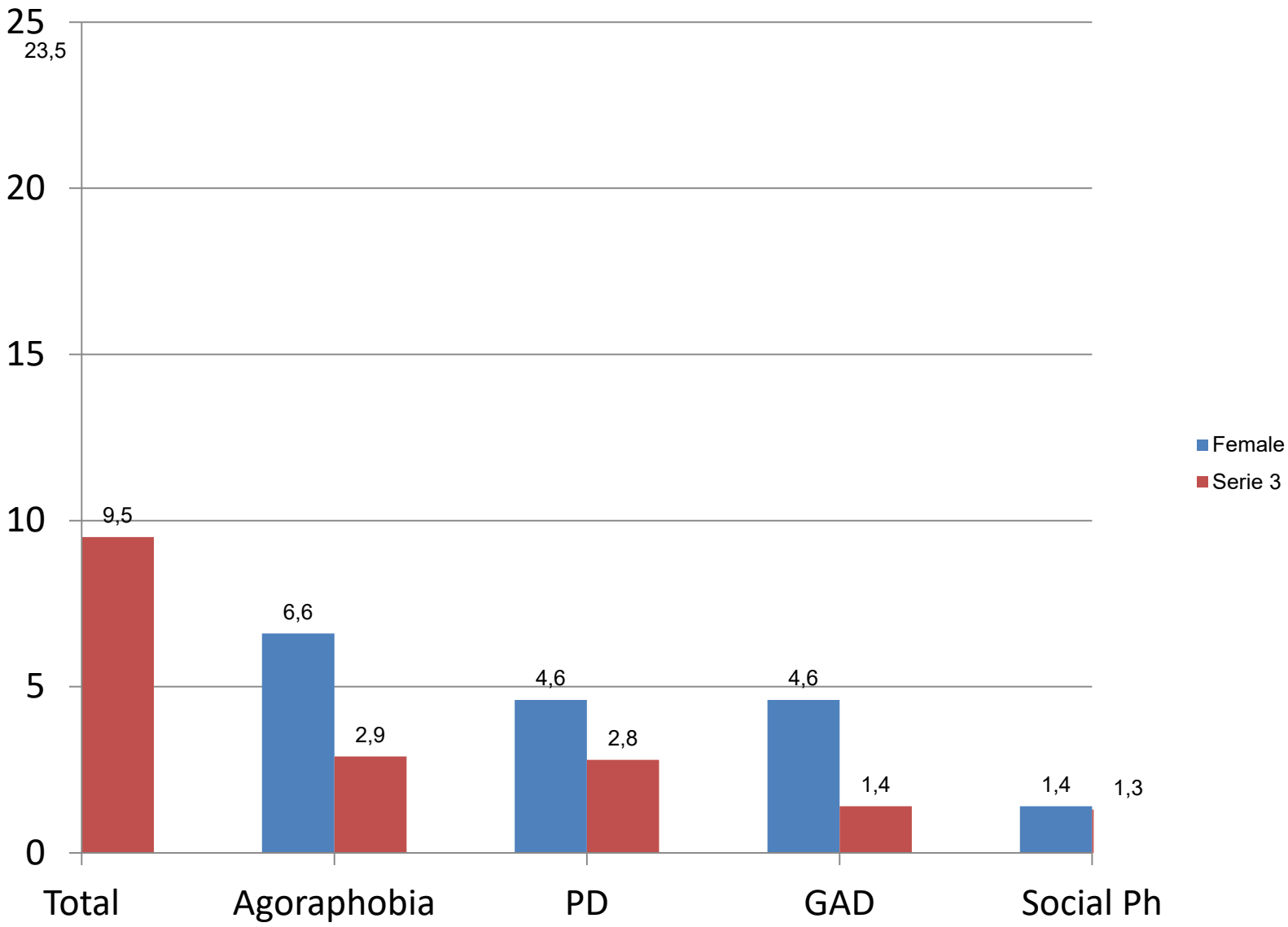
Categoria	Prevalenza d'uso (%)		
	Uomini	Donne	Totale
Antiulcera peptica e malattia da reflusso gastroesofageo	46,6	48,7	47,8
Antitrombotici	47,6	40,9	43,8
Sostanze modificatrici dei lipidi, non associate	36,9	32,9	34,6
Farmaci antiinfiammatori ed antireumatici non steroidei	29,0	35,7	32,8
Betabloccanti	30,1	31,0	30,6
Vitamine A e D, comprese le loro associazioni	12,0	40,9	28,3
Antibatterici beta-lattamici, penicilline	25,0	23,9	24,4
Antibatterici chinolonici	21,7	19,2	20,3
Ace inibitori non associati	21,5	16,8	18,8
Corticosteroidi sistemici, non associati	17,4	19,2	18,4
Calcio-antagonisti selettivi con preval.effetto vascolare	19,0	17,1	17,9
Diuretici ad azione diuretica maggiore	16,4	18,2	17,4
Antagonisti dell'angiotensina II, associazioni	15,1	17,7	16,6
Antagonisti dell'angiotensina II, non associati	15,5	15,9	15,7
Ipoglicemizzanti, escluse le insuline	17,8	13,5	15,4
Antidepressivi	10,4	19,0	15,3
Altri antibatterici beta-lattamici	14,7	14,7	14,7
Ace inibitori, associazioni	14,2	13,9	14,0

Prevalenza sintomi depressivi gravi in >65 stratificati per età e sesso



- Health and Retirement Study. (ref: Sonnega, A. Faul, J., Ofstedal, M.B., Langa, K., Phillips, J., & Weir, D. (2014). Cohort profile: the Health and Retirement Study (HRS)).

La prevalenza dei disturbi d'ansia nella popolazione anziana



Canuto et al., Am J Geriatr Psychiatry 2018:26(2):164-85

Interazioni farmacologiche degli antidepressivi

Alcuni farmaci possono inibire il metabolismo ossidativo dei farmaci metabolizzati dagli isoenzimi microsomiali epatici (citocromo P-450)

Esistono tra gli AD differenze significative nel grado di inibizione esercitato sui diversi citocromi

Antidepressivi: effetto di inibizione sugli isoenzimi del CYP P450

	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Citalopram	0	0	0	+	0
Escitalopram	0	0	0	0	0
Fluoxetina	+	++	+/++	+++	+/++
Fluvoxamina	+++	++	+++	+	++
Paroxetina	+	+	+	+++	+
Sertralina	0	+	0	+/++	+
Venlafaxina	0	0	0	+	+
Duloxetina	0	0	0	++	+
Mirtazapina	0	0	0	+	0
Reboxetina	0	0	0	+	+
Bupropione	0	0	0	++	0
Agomelatina	0	0	0	0/+	0
Vortioxetina	0	0	0	0	0

0 = inibizione minima o assente; + = inibizione lieve; ++ = inibizione moderata; +++ = inibizione elevata

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SSRIs

In general, SSRIs tend to be the most commonly prescribed antidepressants. NICE recommends that SSRIs should normally be used as first-line treatment for depression in all age groups.[9]

Given the high rates of polypharmacy in the elderly, drug interactions are an important consideration. SSRIs such as citalopram and escitalopram (along with non-SSRIs mirtazapine and venlafaxine) have minimal effect on the cytochrome P450 system and so have a reduced risk of pharmacokinetic interactions. By contrast, fluoxetine and paroxetine are strong inhibitors of CYP2D6 while sertraline has a moderate inhibitory effect.[22]

It is important to be aware of the anticholinergic side-effects of SSRIs, which include postural hypotension and sedation, though these are less common with SSRIs than with TCAs.[19]

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Hyponatraemia is a potentially serious adverse effect associated with use of SSRIs in the elderly, and has been reported with almost all SSRIs in addition to the serotonin and noradrenaline reuptake inhibitor (SNRI) venlafaxine.[23] Particular caution should be exercised when co-prescribing with a diuretic. Other risk factors for developing hyponatraemia include increasing age, female sex and previous hyponatraemia.[23] When prescribing in at-risk groups, monitoring of urea and electrolytes can be useful, in addition to being vigilant for clinical features such as lethargy, muscle cramps, anorexia and headaches. Mild hyponatraemia can often be asymptomatic.

Hyponatremia Associated with Selective Serotonin-Reuptake Inhibitors in Older Adults

Susan Jacob and Sarah A Spinler

- Incidenza: 0.5 - 32%
- Rischio >: età avanzata, sesso F, ridotto BMI, uso di diuretici, ridotta natriemia basale
- SSRI / SNRI / NARI / NaSSA / AP / CBZ / OxC
- Nausea, astenia, crampi, confusione, coma
- Insorgenza precoce; non dose-correlata; risoluzione alla sospensione

PRESCRIBING GUIDELINES

SSRIs are associated with a modestly increased risk of upper GI tract bleeding in older people.[24] Serotonin plays an important role in the maintenance of platelet function, and SSRIs may inhibit the reuptake of serotonin by platelet serotonin transporters, leading to a potential for serotonin depletion in platelets and subsequent tendency towards bleeding. NICE guidance recommend consideration should be given to co-prescribing gastroprotective medication in high-risk individuals.[9]

PRESCRIBING GUIDELINES

Although almost all psychotropics can affect the QT interval, citalopram and escitalopram are particularly associated with interval prolongation in comparison with other SSRIs.[25] QT inter-

Medicines and Healthcare products Regulatory Agency (MHRA) guidance issued in 2011 recommends reduced maximum daily doses – 20mg citalopram or 10mg escitalopram for people aged over 65 years – in addition to considering an ECG before commencing treatment for patients with a history of cardiac disease. Sertraline, by contrast, is among the safest SSRIs in the context of cardiac disease.[26]

The Maudsley

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Venlafaxina

- Se SSRI inefficaci
- Rischio ipertensione e iponatriemia nell'anziano

- Mirtazapina

- add on con altri antidepressivi
- Aumento appetito e sonnolenza, a volte un vantaggio nel pz anziano
- Scarsi effetti sulla sfera sessuale

Table Antidepressants and the elderly

	Anticholinergic side-effect (urinary retention, dry mouth, blurred vision, constipation)	*Postural hypotension*	*Sedation*
Older tricyclics[15]	Variable: moderate with nortriptyline, imipramine and dosulepin (dothiepin) Marked with others	All can cause postural hypotension Dosage titration is required	Variable: from minimal with imipramine to profound with trimipramine
SSRIs[15,16]	Dry mouth can be a problem with paroxetine	Much less of a problem, but an increased risk of falls is documented with SSRIs	Can be a problem with paroxetine and fluvoxamine Unlikely with the other SSRIs
Others[17,18]	Minimal with mirtazapine and venlafaxine Can be rarely a problem with reboxetine Duloxetine – few effects	Venlafaxine can cause hypotension at lower doses, but it can increase BP at higher doses, as can duloxetine	Mirtazapine, mianserin and trazodone are sedative Duloxetine – neutral effects

Int Clin Psychopharmacol. 2012 Jul;27(4):215-23. doi: 10.1097/YIC.0b013e3283542457.

A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder.

Katona C[1], Hansen T, Olsen CK.

- Età media 70,6
- Vortioxetina (P=0.001) e duloxetina mostrano significativo miglioramento HAM D dopo 8 settimane rispetto al placebo
- Maggior efficacia di vortioxetina vs placebo nelle funzioni cognitiv (velocità processazione, memoria verbale e di lavoro
- Drop out da effetti avversi 5.8% per vortioxetina, 9,9% per duloxetina, 2,8% per placebo
- Unico evento avverso con significativa incidenza con vortioxetina è la nausea 21,8% risp a placebo
- Maggior incidenza di nausea, xerostomia, stitichezza, iperidrosi e sonnolenza con duloxetina rispetto a placebo

CNS Spectr. 2017 Aug;22(4):348-362. doi: 10.1017/S1092852916000626. Epub 2016 Nov 21.

Efficacy, safety, and tolerability of vortioxetine for the treatment of major depressive disorder in patients aged 55 years or older.

Abstract

OBJECTIVE: These post hoc analyses evaluate the efficacy, safety, and tolerability of vortioxetine versus placebo in patients aged ≥55 years with major depressive disorder (MDD).

CONCLUSION: Vortioxetine 5-20 mg/day is efficacious and well tolerated in MDD patients aged ≥55 years, a group that is often comorbid with other conditions and treated with other medications.

TABLE 6. Most frequently reported (≥5% in any treatment group) treatment-emergent adverse events in patients aged ≥55 years by MedDRA preferred term (APTS)

MedDRA preferred term, patients, n (%)	Placebo (N = 561)	Vortioxetine 5 mg (n = 376)	Vortioxetine 10 mg (n = 259)	Vortioxetine 15 mg (n = 118)	Vortioxetine 20 mg (n = 194)	Vortioxetine all doses (N = 947)
Nausea	49 (8.7)	68 (18.1)	47 (18.1)	40 (33.9)	62 (32.0)	217 (22.9)
Headache	77 (13.7)	44 (11.7)	30 (11.6)	20 (16.9)	26 (13.4)	120 (12.7)
Diarrhea	33 (5.9)	21 (5.6)	14 (5.4)	13 (11.0)	14 (7.2)	62 (6.5)
Dizziness	42 (7.5)	24 (6.4)	13 (5.0)	10 (8.5)	10 (5.2)	57 (6.0)
Dry mouth	26 (4.6)	23 (6.1)	9 (3.5)	8 (6.8)	12 (6.2)	52 (5.5)
Constipation	17 (3.0)	14 (3.7)	10 (3.9)	8 (6.8)	10 (5.2)	42 (4.4)
Fatigue	17 (3.0)	17 (4.5)	7 (2.7)	6 (5.1)	3 (1.5)	33 (3.5)
Vomiting	6 (1.1)	7 (1.9)	8 (3.1)	8 (6.8)	8 (4.1)	31 (3.3)
Anxiety	8 (1.4)	3 (0.8)	3 (1.2)	6 (5.1)	0	12 (1.3)

The Journal of Prevention of Alzheimer's Disease - JPAD©
Volume 6, Number 3, 2019

Treatment Effects of Vortioxetine on Cognitive Functions in Mild Alzheimer's Disease Patients with Depressive Symptoms: A 12 Month, Open-Label, Observational Study

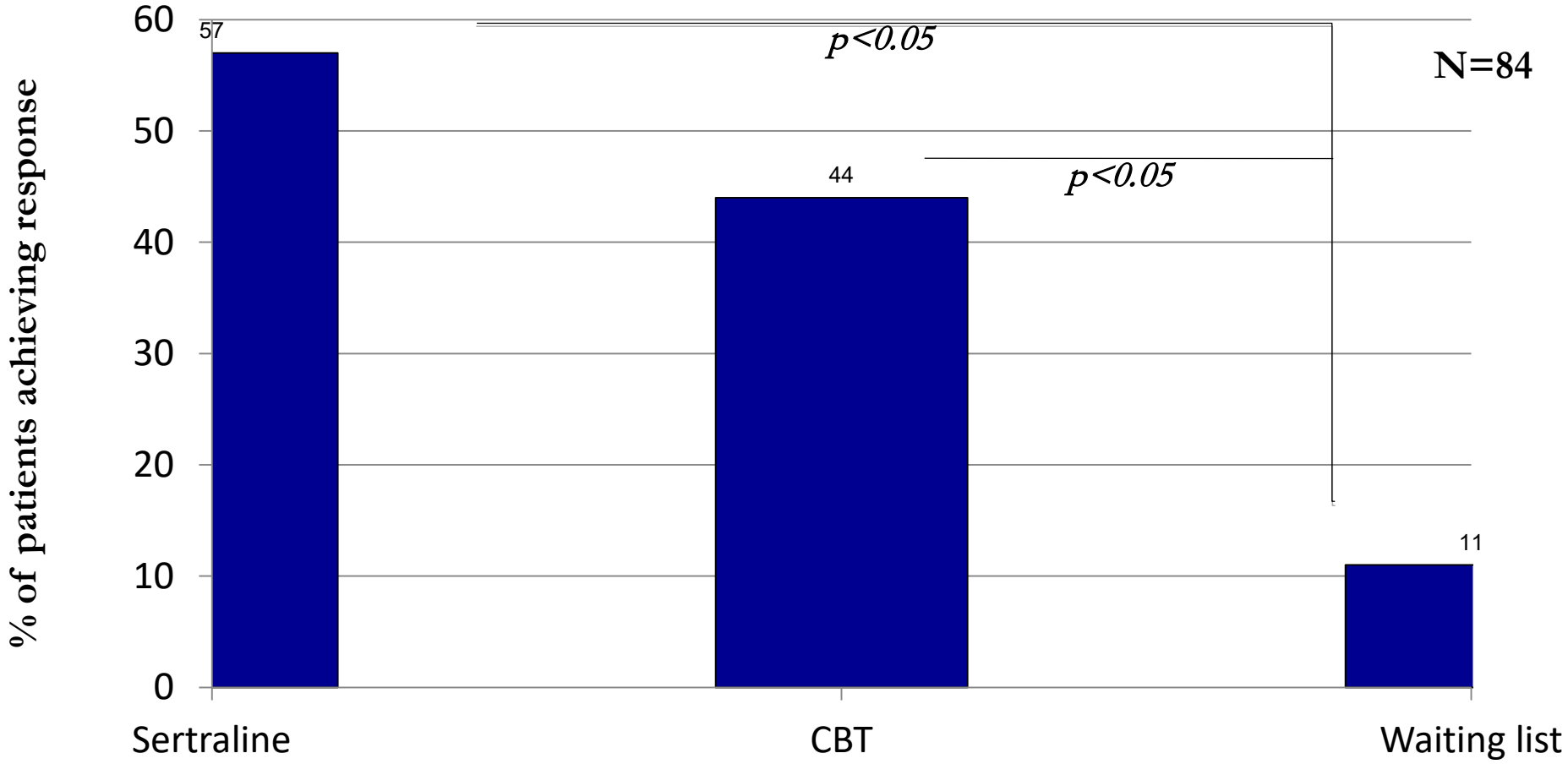
E. Cumbo, S. Cumbo, S. Torregrossa, D. Migliore

BACKGROUND/OBJECTIVES:depressive symptoms are common in Alzheimer's disease(AD). Aim of the study was to investigate the efficacy of vortioxetine compared with other conventional antidepressants on cognitive functions in AD patients with depressive symptoms.

PARTICIPANTS: 108(71 female, 37 male) AD patients with depression(mean age 76.7± 4.3).

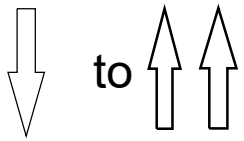
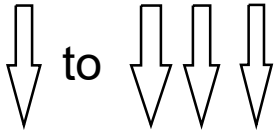
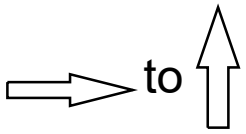
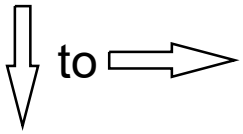
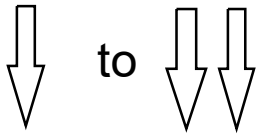
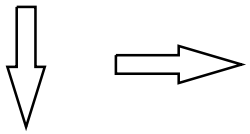
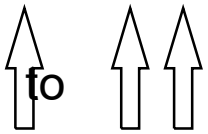
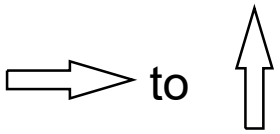
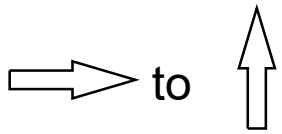
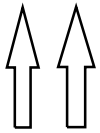
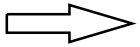
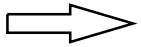
RESULTS: Statistically significant improvement vs. controls was observed for vortioxetine on most of the cognitive tests and showed significantly baseline-to-endpoint reduction in both HAM-D and Cornell total scores.The most commonly reported adverse events were nausea and headache for votioxetine; nausea in the control group.

Effectiveness of Cognitive–Behavioral Therapy and Sertraline versus a Waitlist Control Group for Anxiety Disorders in Older Adults



Schuurmans et al., Am J Geriatr Psychiatry 2006;14:255–63

Antidepressants : Sleep Effects

	Sleep Continuity	REM Sleep	SWS	Comments
Tricyclic				RLS
SSRI SNRI				Variable effects on insomnia; may ↑ RLS; ↓ apnea
Trazodone				Carry-over sedation
Mirtazapine				Weight increase, RLS

Augmentation treatment

- Sali di litio:
- è ancora una delle strategie terapeutiche più validate in add on per la depressione resistente
- Valida opzione anche nella popolazione adulta matura ma attenzione alla tossicità
- Antipsicotici atipici:
- Minori evidenze rispetto alla popolazione giovane e carsa tollerabilità

Int J Bipolar Disord. 2017 Dec;5(1):19. doi: 10.1186/s40345-017-0089-1. Epub 2017 Jul 9.

An observational study of 110 elderly lithium-treated patients followed up for 6 years with particular reference to renal function.

Bocchetta A[1,2], Cabras F[2], Pinna M[2], Poddighe A[3], Sardu C[4], Ardau R[1], Chillotti C[1], Del Zompo M[5,6].

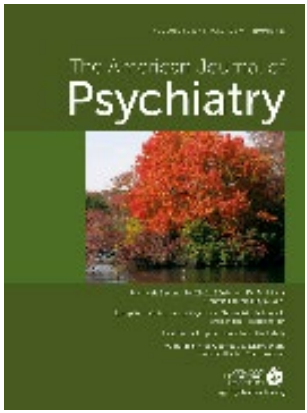
Abstract

BACKGROUND: Recent observational studies have focused on lithium treatment in the elderly, with particular reference to safety in terms of thyroid and renal functions. The purpose of this study was to compare the clinical characteristics of patients starting lithium treatment before (N = 79) or after (N = 31) the age of 65 years. Patients were followed up for 6 years with focus on renal function and prescription of levothyroxine and methimazole.

RESULTS: At baseline, median lithium serum concentration was 0.55 mmol/l. The estimated glomerular filtration rate was lower than 60 ml/min/1.73 m^2 in 43 (39%) patients. In a multiple regression analysis controlling for age and gender, we found a significant effect of duration of lithium treatment on estimated glomerular filtration rate (-0.85 ml/min/1.73 m^2 per year of prior exposure). The annual decline during follow-up was 2.3 ml/min/1.73 m^2. Two patients were prescribed levothyroxine, and two were prescribed methimazole for the first time during follow-up.

CONCLUSIONS: Median lithium serum concentration in this cohort of elderly patients with mainly bipolar disorders was lower than the therapeutic range indicated for younger adults. The decline in glomerular filtration rate may be accelerated by long-term lithium use. Thyroid and renal functions continue to require close monitoring throughout the course of lithium treatment. Trial registration NP/2013/3836. Registered 24 June 2013.

...non solo Depressione Resistente ma anche Disturbo Bipolare!



Editorials

Am J Psychiatry. 2017 Nov 1;174(11):1032-1033. doi: 10.1176/appi.ajp.2017.17070762.

Treatment of Bipolar Disorder in the Elderly.

Dunner DL[1].

"Acute manic episodes are not frequent among elderly patients. Certainly first manic episodes rarely occur in this age group and, if diagnosed, should raise the question of a medical cause for the syndrome. In my clinical experience, dating back several decades, it has been unusual to hospitalize patients with bipolar disorder for a recurrent manic episode. Although I have encountered patients who had a history of recurrent mania, my experience has been that if the illness is properly treated and stabilized, recurrences are not likely to be severe enough to require hospitalization and are more likely to be mild hypomanic episodes, which can be treated on an outpatient basis. We have come a long way since the 1960s in the development of appropriate mood-stabilizing agents, such as lithium and anticonvulsants, to prevent recurrent manic episodes in patients with bipolar disorder. The major clinical problem of bipolar patients continues to be treating depressive episodes, and this is also true for elderly bipolar patients."

Young RC, Mulsant BH, Sajatovic M, et al.Am J Psychiatry 2017

J Affect Disord. 2019 Aug 20;259:210-217. doi: 10.1016/j.jad.2019.08.056. [Epub ahead of print]

Psychiatric and physical outcomes of long-term use of lithium in older adults with bipolar disorder and major depressive disorder: A cross-sectional multicenter study.

Morlet E[1], Costemale-Lacoste JF[2], Poulet E[3], McMahon K[4], Hoertel N[5], Limosin F[5]; CSA Study Group.

OBJECTIVE: Although lithium is widely used in current practice to treat bipolar disorder (BD) and treatment-resistant major depressive disorder (MDD) among older adults, little is known about its efficacy and tolerability in this population, which is generally excluded from randomized clinical trials. The objective of this study was to evaluate the efficacy and tolerability of long-term use of lithium among older adults with BD and MDD.

METHOD: Data from the Cohort of individuals with Schizophrenia and mood disorders Aged 55 years or more (CSA) were used. Two groups of patients with BD and MDD were compared: those who were currently receiving lithium versus those who were not. The effects of lithium on psychiatric (i.e., depressive symptoms severity, perceived clinical severity, rates of psychiatric admissions in the past-year), geriatric (overall and cognitive functioning) and physical outcomes (i.e., rates of non-psychiatric medical comorbidities and general hospital admissions in the past-year) were evaluated. All analyses were adjusted for age, sex, duration of disorder, diagnosis, smoking status, alcohol use, and use of antipsychotics, antiepileptics or antidepressants.

RESULTS: Among the 281 older participants with BD or MDD, 15.7% were taking lithium for a mean duration of 12.5(SD = 11.6) years. Lithium use was associated with lower intensity of depressive symptoms, reduced perceived clinical global severity and lower benzodiazepine use (all $p < 0.05$), without being linked to greater rates of medical comorbidities, except for hypothyroidism.

LIMITATIONS: Data were cross-sectional and data on lifetime history of psychotropic medications was not assessed.

CONCLUSION: Our results suggest that long-term lithium use may be efficient and relatively well-tolerated in older adults with BD or treatment-resistant MDD.

Geriatr Psychol Neuropsychiatr Vieil. 2018 Mar 1;16(1):78-86. doi: 10.1684/pnv.2017.0718.

Neuroprotective effects of lithium: what are the implications in humans with neurodegenerative disorders?

Morlet É[1], Hozer F[2], Costemale-Lacoste JF[3].

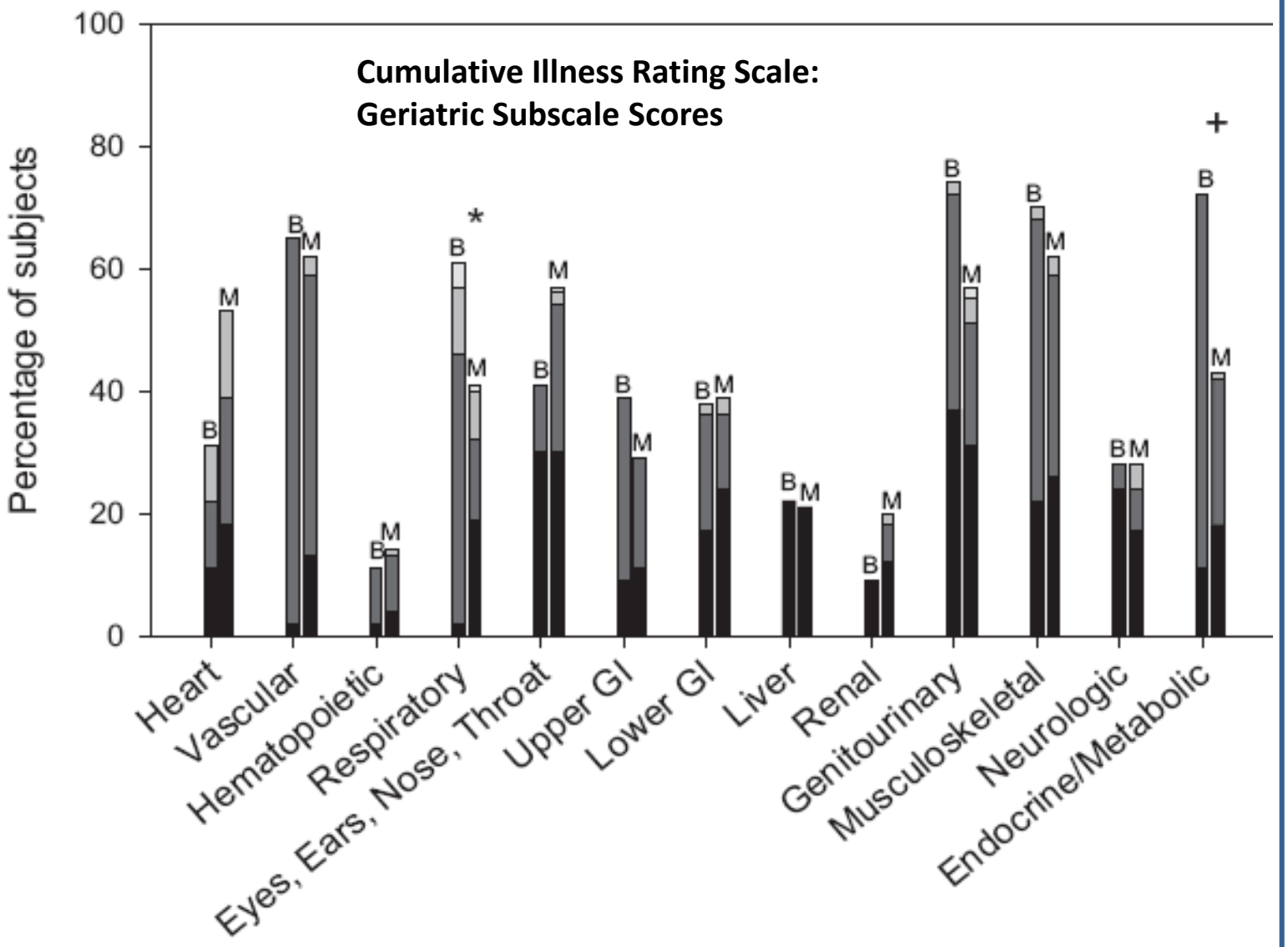
Abstract

Lithium is used as a first line treatment in bipolar disorder. The neuroprotective effects of lithium in this indication tend to be well known and are mediated by its action on two enzymes: glycogen synthase kinase-3 and inositol monophosphatase-1. Preclinical and clinical studies seek to evaluate the neuroprotective effect of lithium in neurodegenerative disorders. The aims of this literature review is to gather clinical studies that investigated the efficacy of lithium in neurodegenerative diseases, using a systematic method based on PubMed data. Results were found concerning Alzheimer's disease and related dementias, Huntington's disease, amyotrophic lateral sclerosis and spino-cerebellar ataxia. Lithium exposure showed a potential neuroprotective effect in studies on psychiatric populations with a lower prevalence of Alzheimer's disease in exposed patients. In patients with mild cognitive impairment, lithium would be associated with clinical improvement and a lower level of cerebrospinal phosphorylated tau protein. Lithium would allow at least a partial improvement in symptoms, including suicidal thoughts, in Huntington's disease. Despite several positive case reports and short studies, further controlled researches have failed to substantiate any positive effects of lithium exposure in amyotrophic lateral sclerosis. In spinocerebellar ataxia, introduction of lithium may be of benefits in terms of improvement of cerebellar symptoms. Large randomized controlled trials are required to asses the effect of early exposure lithium in these indications, based on reliable biological markers of disease.

- ✓ MILD COGNITIVE IMPAIRMENT
- ✓ HUNTINGTON'S DISEASE
- ✓ ATASSIA SPINOCEREBELLARE

- ✓ NO EFFECT IN SLA

Medical burden in late life Bipolar and Major Depressive Disorders



(B) Bipolar Disorder
(M) Major Depressive Disorder

* X^2=10.98, df=1, p=0.0009 , + X^2=17.34, df=1, p=0.0001 (ordinal logistic regression)
statistically significant after Bonferroni correction (P < 0.004)

Gildengers et al. Am J Ger Psychiatry 2008;16:3

BD: n=108

MDD: n=54

Litio: fattori di incremento dei livelli plasmatici

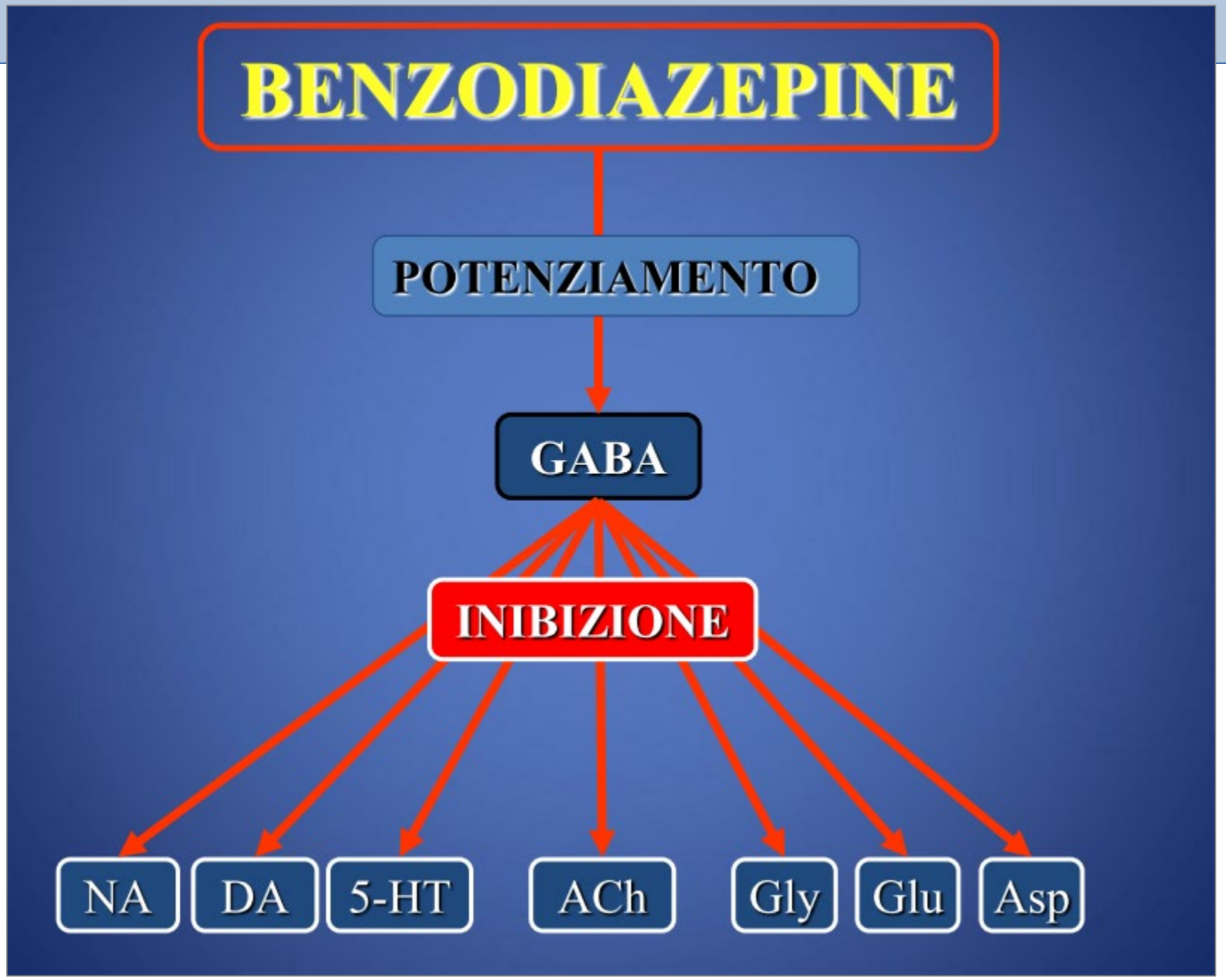
Modificazioni fisiologiche nella vecchiaia	↓ Volume distribuzione ↓ Clearance renale ↑ Emivita plasmatica (28-36 h)
Fattori di ulteriore riduzione della clearance	Ipertensione arteriosa Insufficenza cardiaca Disfunzioni renali Deficit di sodio
Interazioni farmacocinetiche	Diuretici tiazidici ACE inibitori FANS

Young et al, 2004; Sajatovic et al, 2005; Aziz et al, 2006

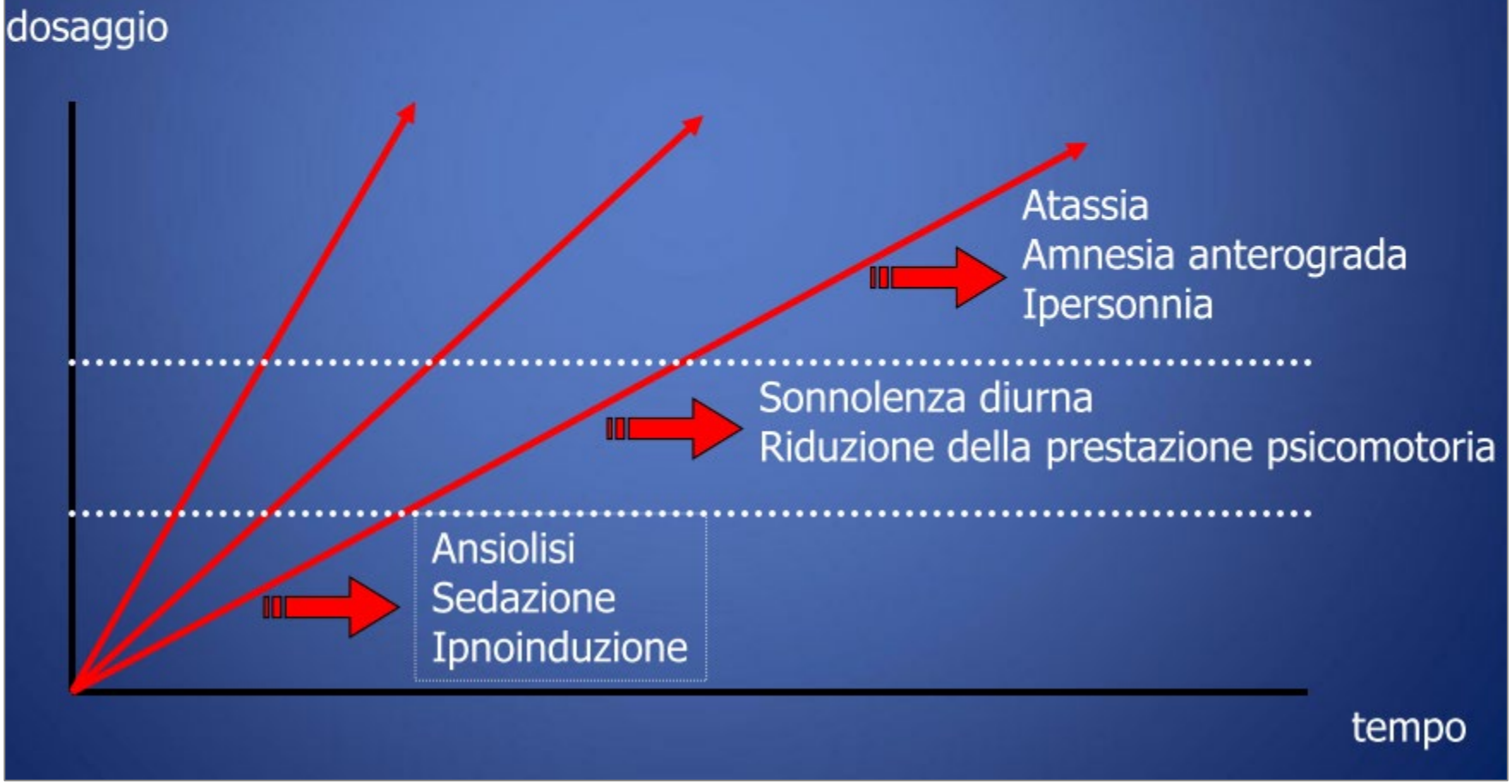
Valproato: Modificazioni Cinetiche negli Anziani

Processo cinetico	Modificazione legata all'età	Effetto
Distribuzione	↓ Albumina plasmatica	↑ 50% Quota libera (↑↑ con ASA)
Metabolismo	↓ Massa epatica ↓ Flusso ematico epatico ↓ Attività enzimi metabolizzanti	↑ Emivita plasmatica (16-20 h) ↓ 40% Clearance ↑ Concentrazioni di steady-state

Young et al, 2004; Fenn et al, 2006


BENZODIAZEPINE
POTENZIAMENTO
GABA
INIBIZIONE
NA
DA
5-HT
ACh
Gly
Glu
Asp

I disturbi secondari da trattamento con BDZ sono in funzione del dosaggio utilizzato e della sensibilità individuale. Nei casi di iperdosaggio relativo i disturbi secondari si manifestano con una progressione più o meno rapida in funzione del dosaggio utilizzato



Curr Psychiatry Rep (2016) 18:89
DOI 10.1007/s11920-016-0727-9

ANXIETY DISORDERS (A PELISSOLO, SECTION EDITOR)

Benzodiazepine Misuse in the Elderly: Risk Factors, Consequences, and Management

Guillaume Airagnes[1,2,3] · Antoine Pelissolo[4] · Mélanie Lavallée[5,6,7] · Martine Flament[8] · Frédéric Limosin[1,2,9]

Abstract

Benzodiazepine (BZD) inappropriate use (i.e., misuse and overuse) is a worldwide public health problem. Despite current knowledge about increased sensitivity to side effects in the elderly, that should lead to more caution, only a third of BZD prescriptions in this age group are considered appropriate. The most frequent inadequate situations are excessive duration and/or dosage of a medical prescription or self-medication, especially in a context where it would be contraindicated, e.g., long-acting BZD in the elderly. Polypharmacy and comorbidities are major risk factors. Consequences of BZD inappropriate use are falls, delirium and other cognitive dysfunction, acute respiratory failure, car accidents, dependence, and withdrawal symptoms. An emerging concern is a potentially increased risk of dementia. Contrary to most clinicians' belief, discontinuation of chronic BZD use in elderly patients is feasible, with adequate psychotherapeutic or pharmacological strategies, and can lead to long-term abstinence. Brief cognitive therapy mostly relies

Sleep Med. 2012 Aug;13(7):893-7. doi: 10.1016/j.sleep.2011.12.014. Epub 2012 Jun 14.

What is the point of guidelines? Benzodiazepine and z-hypnotic use by an elderly population.

Neutel CI[1], Skurtveit S, Berg C.

Tra i 60 e 70 anni l'esposizione a fattori di rischio per condotte d'abuso cambiano significativamente e.g. dallo stress lavorativo al pensionamento.

Aumenta la prevalenza di disturbi del sonno e deficit cognitivi spesso correlati a prescrizioni inappropriate di BDZ o BDZ simili.

CRITERI PER PRESCRIZIONE INAPPROPRIATA:

- durata del trattamento > di 30 settimane
- tot > 300 assunzioni giornaliere/anno
-uso della BDZ come ipnoinducente, trattamento del delirium

(Numerose linee guida e.g. Beers' criteria)

Fattori di rischio **individuali** associati ad uso inadeguato BDZ come ipnoinduttori

- **Genere F**
- **Prescrittori multipli**
- **Polifarmacoterapia**
- **Dolore cronico**
- **Disabilità fisica/ridotta mobilità**
- **Scadimento cognitivo**
- **Ritiro sociale**
- **Ideazione suicidaria**

- **Rischio di morte se associato a oppiacei**

Kuerbis et al 2014

Conseguenze dell'uso inadeguato:

- **CADUTE**
- **DELIRIUM**
- **INSUFFICIENZA RESPIRATORIA**
- **ALTERAZIONI NEUROPSICOLOGICHE**

Kuerbis et al 2014

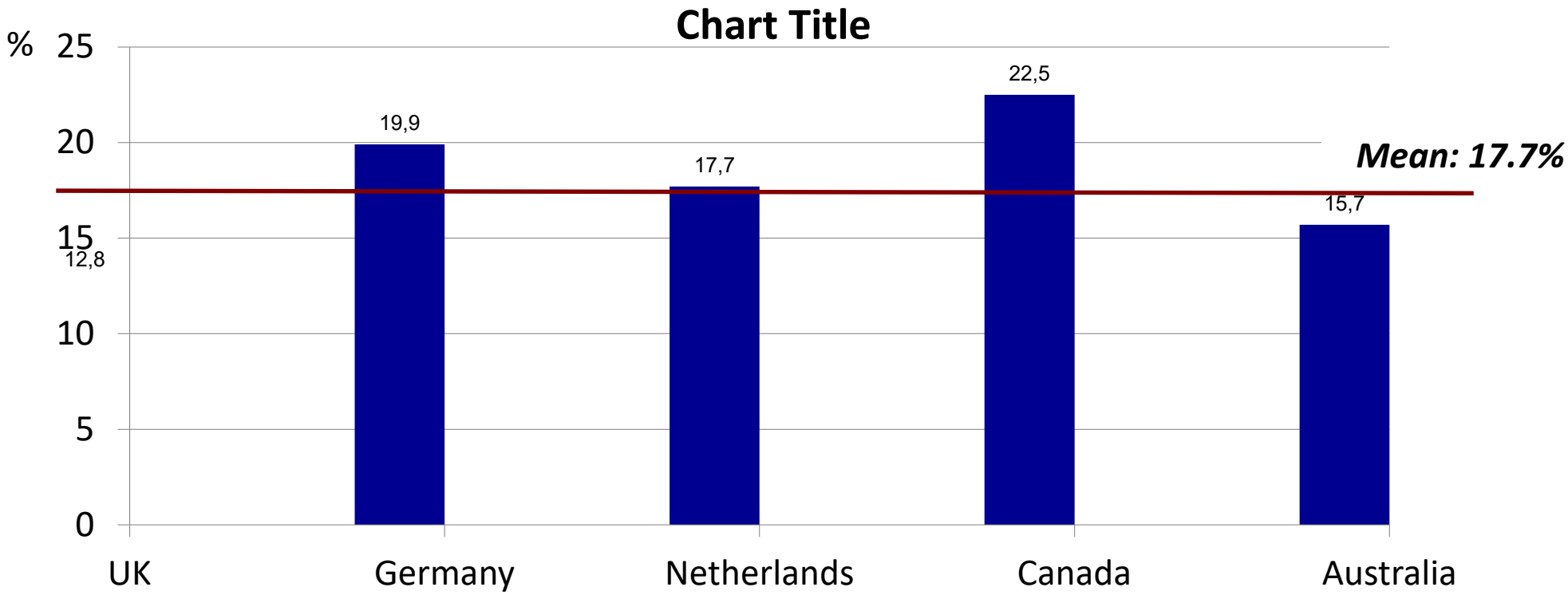
Medical Management of Benzodiazepine Misuse in the Elderly

Clinicians often refrain from planning BZD or BZD-related hypnotic's withdrawal in the elderly, considering that the risk of withdrawal exceeds the risk of keeping a treatment to which the patient can be strongly addicted.

It is also well-known that any factor that impairs the usual homeostasis could enhance the risk of delirium in the elderly Before starting to reduce dosage, several authors recommend to first switch all BZDs for diazepam, which has a relatively long half-life and is available in various formulations and dosages However, oxazepam could be a better choice in case of liver insufficiency

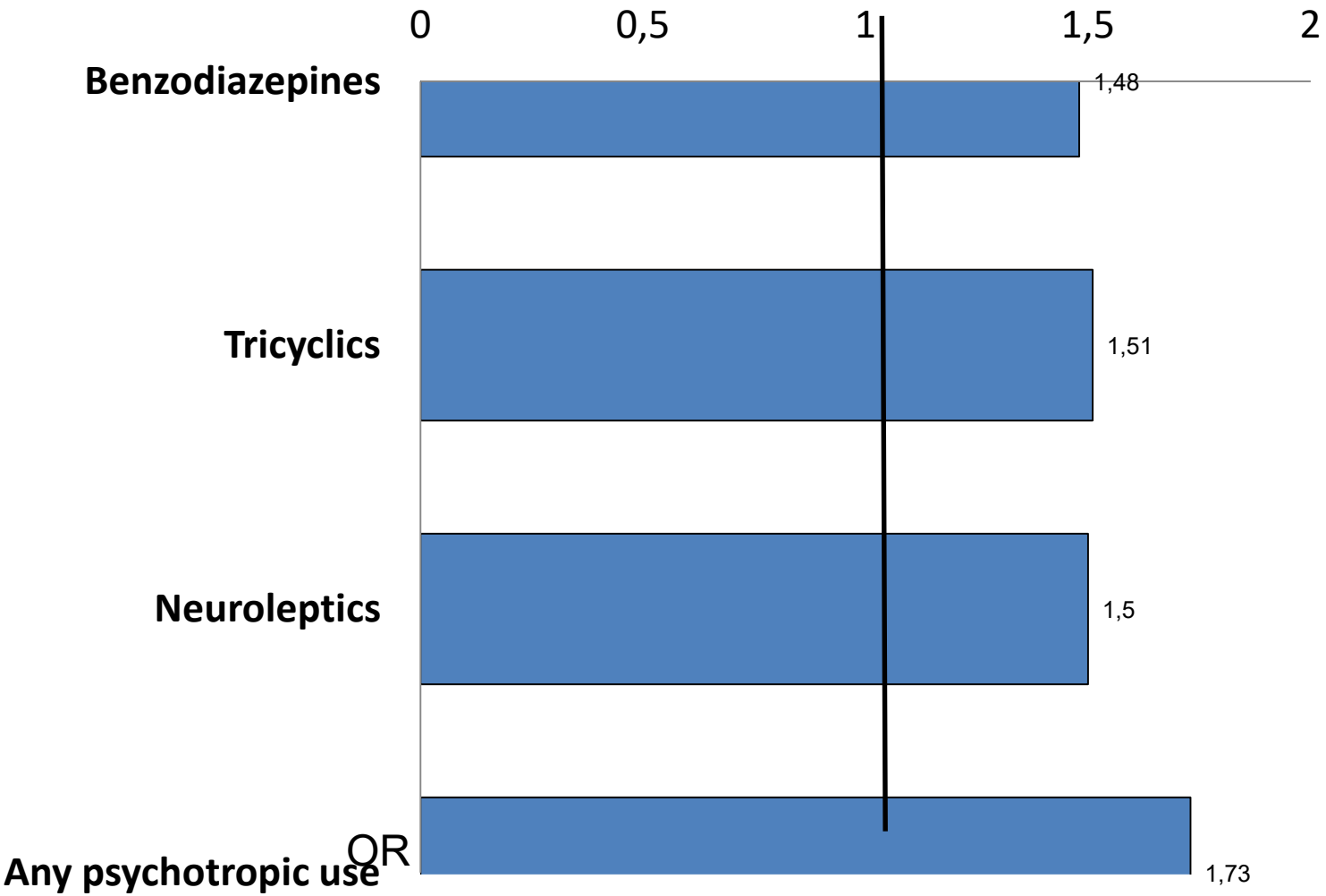
Curr Psychiatry Rep 2016

Survey of benzodiazepine usage in elderly population



Dell'Osso and Lader. Eur Psychiatry 2013;28(1):7-20

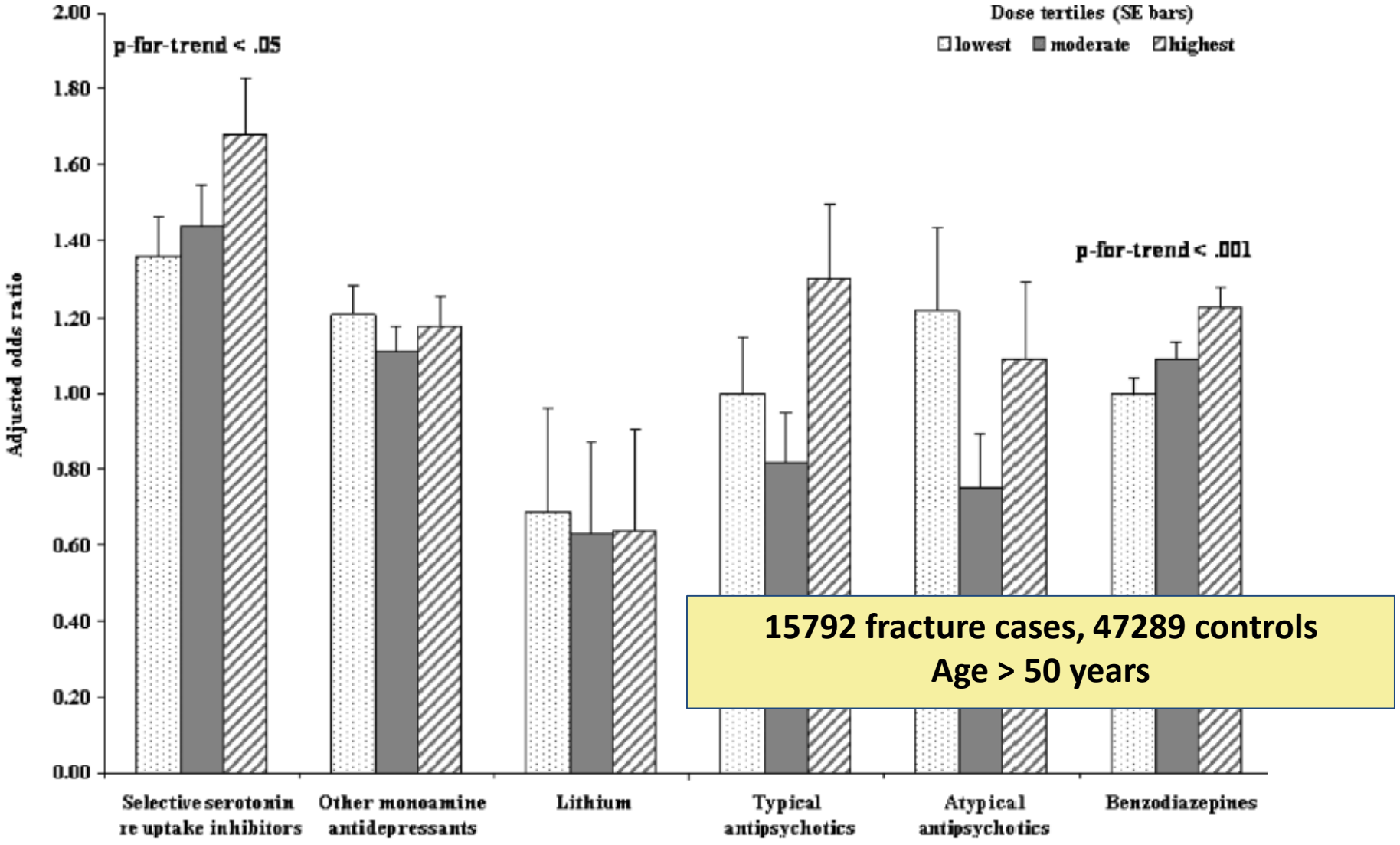
Drugs and falls in older people: a systematic review and meta-analysis



40 studies, patients >60 years old

Leipzig et al., J Am Ger Soc

Fracture risk from psychotropic medications a population-based analysis



15792 fracture cases, 47289 controls
Age > 50 years

Bolton et al., J Clin Psychopharmacol 2008;28:384-91

Antipsicotici

Antipsicotici tipici o di prima generazione

- **Fenotiazine**
  - clorpromazina
- **Butirrofenoni**
  - aloperidolo
- **Tioxanteni**
- **Benzamidi sostituite**

Antipsicotici atipici o di seconda generazione

- **Clozapina**
- **Risperidone**
- **Olanzapina**
- **Quetiapina**
- **Amisulpride**
- **Aripiprazolo**
- **Paliperidone**
- **Ziprasidone**
- **Lurasidone**
- **Cariprazina**

Curr Psychiatry Rep. 2015 Feb;17(2):1. doi: 10.1007/s11920-014-0542-0.

Late-life psychosis: diagnosis and treatment.

Reinhardt MM[1], Cohen CI.

Harv Rev Psychiatry. 2015 Sep-Oct;23(5):354-67. doi: 10.1097/HRP.0000000000000068.

Psychosis in Later Life: A Review and Update.

Colijn MA[1], Nitta BH, Grossberg GT.

Argomento poco rappresentato nella letteratura scientifica internazionale

E' stato calcolato che soltanto l'1% circa della letteratura sulla schizofrenia è dedicato alla popolazione anziana

Cohen CI et al., *Lancet Psychiatry*, 2015

Schizophr Bull. 2018 Oct 19. doi: 10.1093/schbul/sby147. [Epub ahead of print]

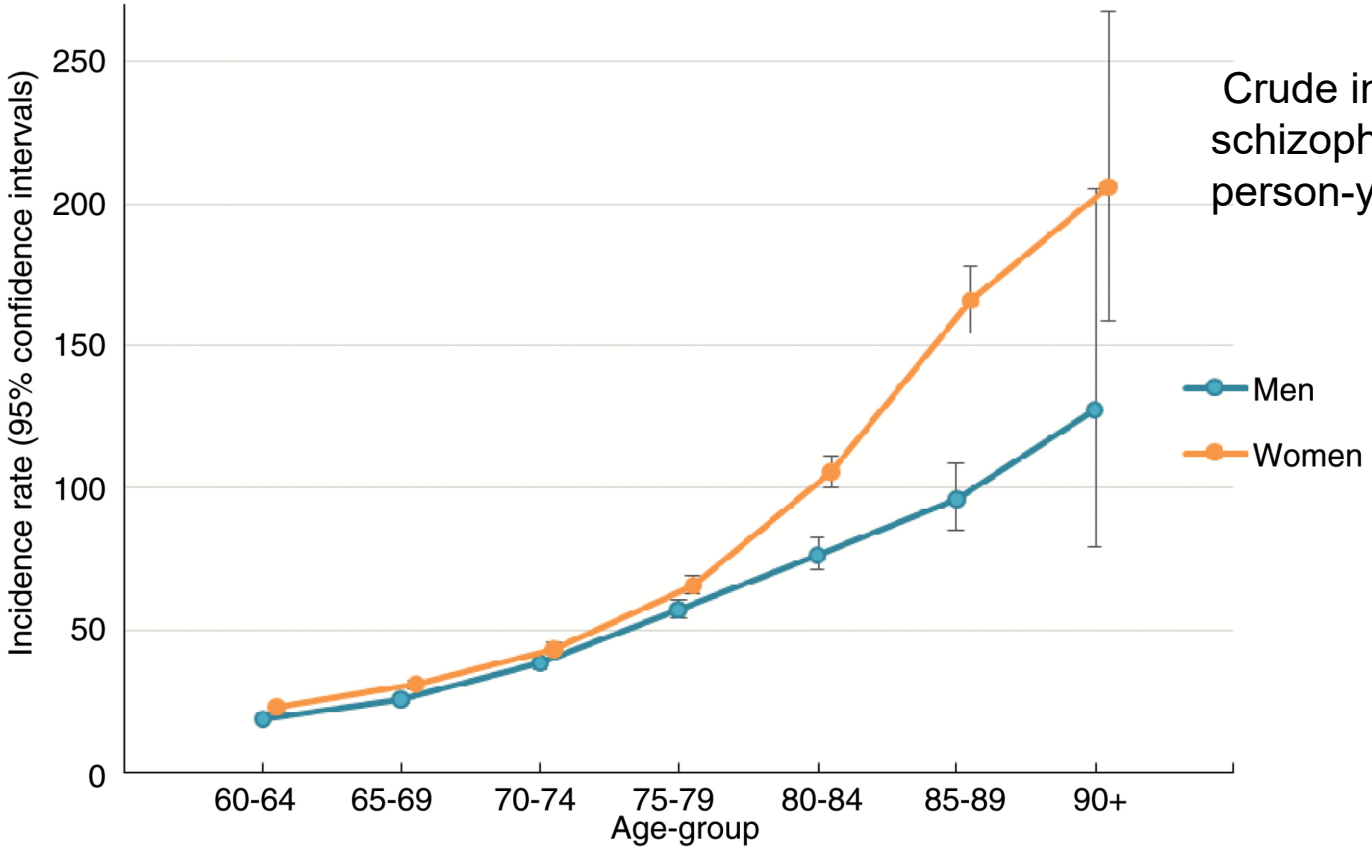
The Incidence of Nonaffective, Nonorganic Psychotic Disorders in Older People: A Population-based Cohort Study of 3 Million People in Sweden.

Stafford J[1], Howard R[1], Dalman C[2], Kirkbride JB[1].

Abstract

BACKGROUND: There are limited data on the epidemiology of very late-onset schizophrenia-like psychosis (VLOSLP) and how this relates to potential risk factors including migration, sensory impairment, traumatic life events, and social isolation.

INTERPRETATION: We identified a substantial burden of psychosis incidence in old age, with a higher preponderance in women and most migrant groups. Life course exposure to environmental factors including markers of deprivation, isolation, and adversity were associated with VLOSLP risk.



Crude incidence rates of very late-onset schizophrenia-like psychosis per 100 000 person-years at-risk by age .

Alto impatto socio-economico:

La schizofrenia rappresenta la **terza causa**,
tra tutti i disturbi psichiatrici e da uso di sostanze,
di **anni trascorsi con disabilità** oltre i 60 anni.

La spesa per persona in questa popolazione supera quella di molte altre condizioni mediche e psichiatriche.

Whiteford HA et al., *Lancet*, 2013

Epidemiologia: qualche dato...

Tuttavia, l'incremento demografico mondiale e l'invecchiamento della popolazione occidentale modificano molto il quadro…

A livello mondiale il numero di persone con più di 60 anni di età sarà **RADDOPPIATO da oggi al 2050**

United States Census Bureau, *International Database*, 2013

Epidemiologia: qualche dato...

Si stima quindi che nel 2050 saranno oltre a

10 milioni

i pazienti affetti da schizofrenia con più di 55 anni

inoltre…

I pazienti con più di 55 anni di età rappresenteranno circa

UN QUARTO

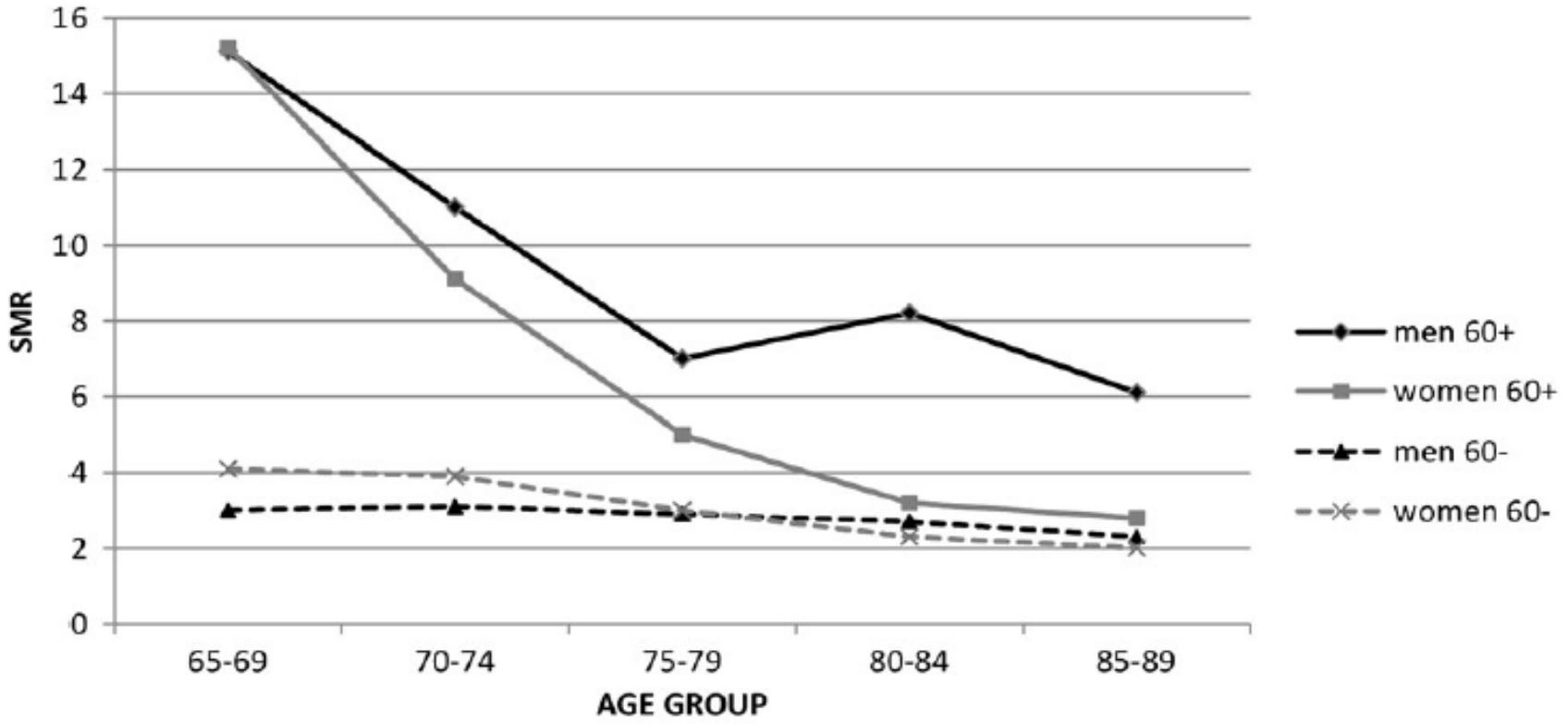
del totale dei pazienti affetti da schizofrenia

GIÀ NEL 2025

Cohen CI et al., *Psychiatric Clinics of North America*, 2018

VERY-LATE-ONSET SCHIZOPHRENIA

Aumentata mortalità



1. line: SMRm+(x=number of cases),SMRw+(x); 2. line: SMRm-(x),SMRw-(x)
15.1(16),15.2(7) / 11.0(36),9.1(65) / 7.0(69),5.0(123) / 8.2(52) 3.2(125) / 6.1(6),2.8(4)
3.0(161),4.1(139) / 3.1(458),3.9(575) / 2.9(467),3.0(742) / 2.7(202),2.3(478) / 2.3(28),2.0(121)

Talaslahti et al., *Internation Journal of Geriatric Psychiatry*, 2014

LATE-ONSET spesso secondario...

Metabolic

- Vitamin B_{12} deficiency
- Folate deficiency
- Electrolyte abnormalities
  - Sodium
  - Potassium
  - Calcium
  - Magnesium
- Acute intermittent porphyria
- Hepatic encephalopathy
- Uremic encephalopathy
- Other nutritional deficiencies
- Anoxia/hypoxia
- Hypercarbia

Infections

- Meningitides
- Encephalitides (e.g., herpes, etc.)
- Neurosyphilis
- HIV/AIDS
- Pneumonia

Endocrine

- Hypo-/hyperthyroidism
- Adrenal disease
- Hypo-/hypoglycemia
- Hypo-/hyperparathyroidism

Neurological

- Parkinson's disease
- Epilepsy
  - Temporal lobe epilepsy
  - Grand mal
  - Non-convulsive status epilepticus
- Subdural hematoma
- Cerebrovascular events
- Huntington's disease
- Multiple sclerosis
- Amyotrophic lateral sclerosis

- Tumors
  - Temporal lobe—auditory hallucinations
  - Occipital lobe—visual hallucinations
  - Limbic—delusions
  - Hypothalamus—delusions
- Limbic encephalitides
- Autoimmune[reference]
  - Paraneoplastic syndromes
  - Systemic lupus erythematosis
  - Vasculitides
- Sleep disorders (narcolepsy)

Brunelle S et al., 2012

LATE-ONSET spesso secondario...

INTOSSICAZIONI

- Alcohol
- Cannabis
- Phencyclidine
- Other hallucinogens
- Inhalants

- Sedatives, hypnotics, or anxiolytics
- Stimulants (inclusive of amphetamine-type substances cocaine, or other unspecified stimulants)
- Other/unknown substances

FARMACI

- Antiparkinson drugs
- Anticholinergic drugs
- Cimetidine
- Digoxin
- Antiarrhythmic drugs
- Corticosteroids
- Interferon

Brunelle S et al., 2012

LATE-ONSET...

delirium

Prevalenza che arriva a **50%** negli anziani ospedalizzati

Si caratterizza per una durata **BREVE**

Allucinazioni: 40-70%
Deliri: 25-79%

Inouye SK et al., *Lancet*, 2014

LATE-ONSET... demenza

Ora **DISTURBI NEUROCOGNITIVI**

Allucinazioni: 4-76% (mediana 23%)
Deliri: 16-70% (mediana 37%)

Prevalenza di sintomi psicotici varia nel tempo: 20% nelle fasi precoci, 50% verso il 3°-4° anno di malattia

Ostling S et al., *Journal of Geriatric Psychiatry and Neurology*, 2011

Farmacoterapia

Curr Geri Rep (2015) 4:290–300
DOI 10.1007/s13670-015-0149-2

GERIATRIC PSYCHIATRY (GT GROSSBERG, SECTION EDITOR)

Current Concepts in the Diagnosis and Treatment of Schizophrenia in Later Life

Ahsan Y. Khan[1] · William Redden[1] · Muhammad Ovais[1] · George T. Grossberg[1]

Farmacoterapia

Table 1 Recommended doses of atypical antipsychotics in elderly patients

Oral antipsychotic	Starting dose (mg/day)	Maximum dose (mg/day)
Risperidone	0.25–0.5	2–3
Clozapine	6.25	50–100
Olanzapine	1–5	5–15
Quetipine	12.5–25	100–200
Ziprasidone	20	80–160
Aripipzole	2.5–5	10–15
Asenapine	No dose adjustment appears to be	Necessary in older patients
Iloperidone	Limited or no data evaluating the	Effectiveness and safety in elderly
Lurasidone	No dose adjustment appears to be	Necessary in older patients
Depot antipsychotics		
Risperdal Consta	25 mg, 37.5 mg or 50 mg IM every 2 weeks (dosing for otherwise healthy elderly patients is the same as for healthy adults)	Max dose: 50 mg IM every 2 weeks
Invega Sustena:	Schizophrenia: day 1: 234 mg IM Day 2: 156 mg IM Clinical experience has not identified differences in responses between the elderly and young adults. Adjust dose based on renal function	39–234 mg monthly maintenance dose Monthly maximum dose: 234 mg
Olanzapine Pamoate (Zyprexa Relprevv)	1st 8 weeks: Target oral olanzapine dose: 10 mg/day-Zyprexa Relprevv dose: 210 mg/2 weeks, 405 mg/4 weeks 15 mg/day olanzapine-Zyprexa Relprevv dose: 300 mg/2 weeks 20 mg/day olanzapine-Zyprexa Relprevv-300 mg/2 weeks	Maintenance dose: After 1st 8 weeks: 150 mg/2 weeks or 300 mg/4 weeks. 210 mg/2 weeks or 405 mg/4 weeks. 300 mg/2 weeks

Khan AY et al., *Current Geriatric Reports*, 2015

Farmacoterapia

Basandosi anche sulla mole di letteratura esistente per ciascuna molecola sia per efficacia che per collateralità:

Prima Linea: Risperidone

Seconda linea: Quetiapina, Olanzapina, Aripiprazolo

Cohen CI et al., *Psychiatric Clinics of North America*, 2018

Farmacoterapia

Iniziare con un dosaggio basso e titolarlo molto lentamente.

Dose iniziale: Un quarto della dose tipica in un adulto

Dose di mantenimento: Da **un terzo** a **metà** della dose tipica in un adulto

Cohen CI et al., *Psychiatric Clinics of North America*, 2018

Farmacoterapia

Rivalutare e ridurre la terapia nei pazienti stabili.

Nei pazienti stabili, una riduzione del dosaggio si accompagna ad un minor rischio di effetti collaterali e ad un miglioramento dei parametri di gravità del disturbo stesso.
Questo è probabilmente legato al diverso livello di **occupazione dei recettori D2/3** necessario per ottenere effetti clinici rilevabili:

Nei pazienti adulti: **65-80%**
Nei pazienti anziani: **50-60%**

Graff-Guerrero A et al., *JAMA Psychiatry*, 2015

Farmacoterapia

Trattare anche i sintomi depressivi.

Nel paziente anziano con schizofrenia si preferisce l'impiego di **SSRI**.
Un recente studio controllato suggerisce l'impiego di

citalopram

nel trattamento della depressione subsindromica nei pazienti di mezz'età ed anziani affetti da schizofrenia.

Zisook S et al., *Journal of Clinical Psychiatry*, 2009

Farmacoterapia

Altre raccomandazioni utili…

- When treating patients with **EPS** use **quetiapine** first and **olanzapine** or **aripiprazole** second.
- Use **quetiapine** or **olanzapine** in patients with **prolactin-related disorders**.
- **Avoid clozapine** and **ziprasidone** in patients with **congestive heart failure.**
- **Avoid clozapine** and **olanzapine** in patients who are already **obese** and have **uncontrolled diabetes** or **hyperlipidemia.**

Khan AY et al., *Current Geriatric Reports*, 2015

Farmacoterapia

Come precauzione generale, risulta utile monitorare:

- Pressione sanguigna, sia per ipertensione che per ipotensione
- Livelli plasmatici di glucosio
- Aumento ponderale
- ECG e quadro cardiaco
- Emocromo per funzione midollare
- Funzione epatica
- Funzione renale

Khan AY et al., *Current Geriatric Reports*, 2015

Farmacoterapia

Take home message

- Minima dose efficace
- Evitare stratificazioni teraputiche
- Corretto inquadramento diagnostico
- Maggior sensibilità agli effetti collaterali
- Frequente comorbidità


PER GLI EFFETTI COLLATERALI DELL'ULTIMO FARMACO CHE LE HO DATO PRENDA QUEST'ALTRO. SE POI CI FOSSERO INTERAZIONI LE DARO' UN ALTRO FARMACO ANCORA CHE EVITI CONSEGUENZE...
NON POTREI AVERE INDIETRO IL MIO PRIMO DISTURBO?