La politerapia nell'anziano tra evidenze (poche) e incertezze (tante)

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

ALESSANDRO NOBILI

Esperienze di farmacovigilanza: interazioni, rischio di abuso, eventi avversi e appropriatezza in ambito geriatrico e politerapico

Pavia, 20 Settembre 2013

Summary

- Le nuove sfide in sanità
- Multimorbilità e politerapia
- Limiti delle linee guida
- I rischi
- Una nuova pratica prescrittiva
- Strumenti, modelli, evidenze

INVECCHIAMENTO, CRONICITA', MULTIMORBILTA' E POLITERAPIA: LE NUOVE SFIDE DEL TERZO MILLENNIO?

Multiple diseases and polypharmacy in the elderly: challenges for the internist of the third millennium

Alessandro Nobili[1], Silvio Garattini[1], Pier Mannuccio Mannucci[2]

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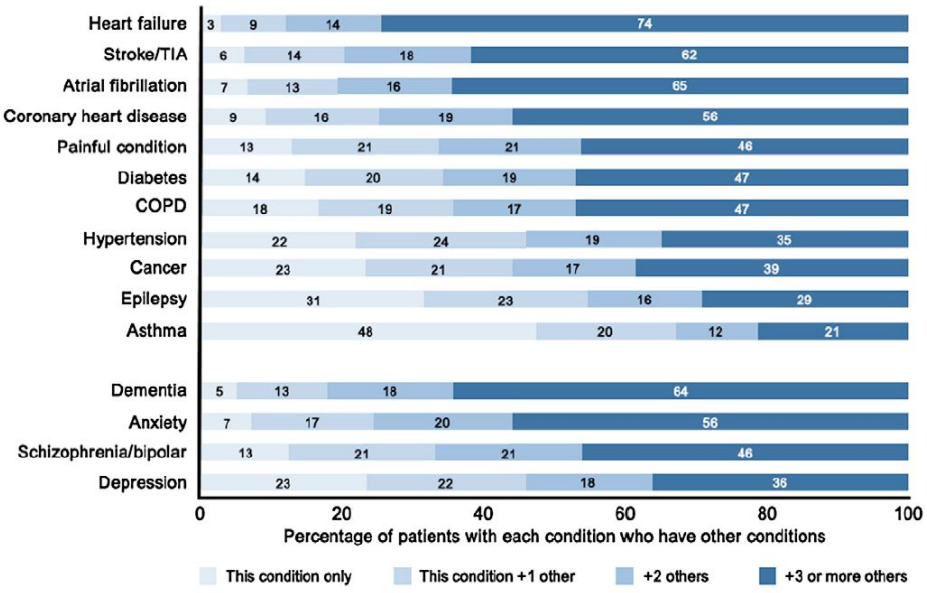
Abstract

The pattern of patients admitted to internal medicine wards has dramatically changed in the last 20–30 years. Elderly people are now the most rapidly growing proportion of the patient population in the majority of Western countries, and aging seldom comes alone, often being accompanied by chronic diseases, comorbidity, disability, frailty, and social isolation. Multiple diseases and multimorbidity inevitably lead to the use of multiple drugs, a condition known as polypharmacy. Over the last 20–30 years, problems related to aging, multimorbidity, and polypharmacy have become a prominent issue in global healthcare. This review discusses how internists might tackle these new challenges of the aging population. They are called to play a primary role in promoting a new, integrated, and comprehensive approach to the care of elderly people, which should incorporate age-related issues into routine clinical practice and decisions. The development of new approaches in the frame of undergraduate and postgraduate training and of clinical research is essential to improve and implement suitable strategies meant to evaluate and manage frail elderly patients with chronic diseases, comorbidity, and polypharmacy.

Journal of Comorbidity 2011;1:28–44

Figure 4. Number of patient whose 'primary diagnosis' is associated with other diseases – reproduced from [8], with permission.



Journal of Evaluation in Clinical Practice 2012 doi:10.1111/j.1365-2753.2012.01882.x

INVECCHIAMENTO, FRAGILITA', DISABILITA'

In Italia nel 2004-2005 le persone con disabilità di età superiore a 6 anni che vivono in famiglia sono circa 2.600.000 (4,8% della popolazione di 6 anni e più che vive in famiglia), **oltre 2 milioni hanno più di 65 anni** e di questi più della metà (circa **1.200.000) ha più di 80 anni**.

INVECCHIAMENTO

↓

MULTIMORBILITA'

↓

FRAGILITA'

↓

OSPEDALIZZAZIONE

↓

DISABILITA'

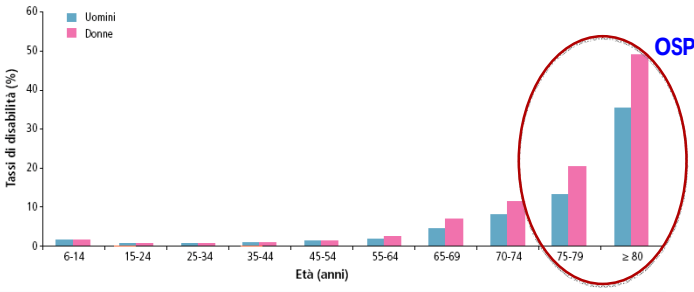


Figura 1.9 Tassi di disabilità per cento persone di 6 anni e più che vivono in famiglia per classe di età e sesso (anni 2004-2005). Fonte: Istat, 2005.

Dati Istat, 2010

The End of the Disease Era

Mary E. Tinetti, MD, Terri Fried, MD

The time has come to abandon disease as the focus of medical care. The changed spectrum of health, the complex interplay of biological and nonbiological factors, the aging population, and the interindividual variability in health priorities render medical care that is centered on the diagnosis and treatment of individual diseases at best out of date and at worst harmful. A primary focus on disease may inadvertently lead to undertreatment, overtreatment, or mistreatment. The numerous strategies that have evolved to address the limitations of the disease model, although laudable, are offered only to a select subset of persons and often further fragment care. Clinical decision making for all patients should be predicated on the attainment of individual goals and the identification and treatment of all modifiable biological and nonbiological factors, rather than solely on the diagnosis, treatment, or prevention of individual diseases. Anticipated arguments against a more integrated and individualized approach range from concerns about medicalization of life problems to "this is nothing new" and "resources would be better spent determining the underlying biological mechanisms." The perception that the disease model is "truth" rather than a previously useful model will be a barrier as well. Notwithstanding these barriers, medical care must evolve to meet the health care needs of patients in the 21st century. **Am J Med. 2004;116:179–185.**

Il prof. dott. Guido Tersilli primario della clinica Villa Celeste convenzionata con le Mutue
1969

Am J Med 2004;116:179-85

Clinical Practice Guidelines and Quality of Care for Older Patients With Multiple Comorbid Diseases

Implications for Pay for Performance

Obiettivo. Valutare l'applicabilità di linee guida al trattamento di pazienti anziani con polipatologie.

Donna di 79 anni:

- ipertensione arteriosa
- diabete mellito
- osteoartrite
- osteporosi
- BPCO

Disease and Medication
Hypertension
Hydrochlorothiazide
Lisinopril
Diabetes mellitus
Glyburide
Metformin
Enteric-coated aspirin
Lovastatin
Osteoarthritis
Naproxen
Omeprazole
Osteoporosis
Alendronate
Calcium plus vitamin D
Chronic obstructive pulmonary disease
Ipratropium
Albuterol

12 farmaci: con quale benefico/rischio globale?

Conclusioni. L'aderenza alle **linee guida** in pazienti con **polipatologie** può portare ad **eventi avversi indesiderati** e ad un utilizzo **inappropriato** di alcuni farmaci. Ciò può avere quindi una ricaduta sulla "qualità di vita di questi pazienti..

Boyd CM, et al. JAMA 2005;294:716-24

Potenziali limiti delle linee guida nel paziente anziano

- Secondo le LG questa paziente dovrebbe assumere **12 farmaci** [19 dosi]/giorno (costo di circa 5.000 dollari/anno!)
- **8/9 LG** (ipertensione, scompenso cardiaco, angina, fibrillazione atrial, ipercolesterolemia, diabete, osteoartrosi, BPCO, osteoporosi) **non quantificano** il beneficio tenendo conto del paziente (es. **apettativa di vita**)
- **5/9** non prendono in considerazione la **comorbidità**
- Non sono prese in considerazione le **ADR** e le **DDI**
- Non sono prese in considerazione la **compliance**, le **attività del paziente** e la **praticabilità qutotidiana**

Boyd, CM, et al. JAMA 2005;294:716-24.

Table 4. Potential Treatment Interactions for a Hypothetical 79-Year-Old Woman with 5 Chronic Diseases

Type of Disease	Medications With Potential Interactions	Type of Interaction: Medication and Other Disease	Type of Interaction: Medications for Different Diseases	Type of Interaction: Medication and Food
Hypertension	Hydrochlorothiazide, lisinopril	Diabetes: diuretics increase serum glucose and lipids*	Diabetes medications: hydrochlorothiazide may decrease effectiveness of glyburide	NA
Diabetes	Glyburide, metformin, aspirin, and atorvastatin	NA	Osteoarthritis medications: NSAIDs plus aspirin increase risk of bleeding Diabetes medications: glyburide plus aspirin may increase the risk of hypoglycemia; aspirin may decrease effectiveness of lisinopril	Aspirin plus alcohol: increased risk of gastrointestinal tract bleeding Atorvastatin plus grapefruit juice: muscle pain, weakness Glyburide plus alcohol: low blood sugar, flushing, rapid breathing, tachycardia Metformin plus alcohol: extreme weakness and heavy breathing Metformin plus any type of food: medication absorption decreased
Osteoarthritis	NSAIDs	Hypertension: NSAIDs: raise blood pressure†; NSAIDs plus hypertension increase risk of renal failure	Diabetes medications: NSAIDs in combination with aspirin increase risk of bleeding Hypertension medications: NSAIDs decrease efficacy of diuretics	NA
Osteoporosis	Calcium, alendronate	NA	Diabetes medications: calcium may decrease efficacy of aspirin; asprin plus alendronate can cause upset stomach Osteoporosis medications: calcium may lower serum alendronate level	Alendronate plus calcium: take on empty stomach (>2 h from last meal) Alendronate: avoid orange juice Calcium plus oxalic acid (spinach and rhubarb) or phytic (bran and whole cereals): eating these foods may decrease amount of calcium absorbed (>2 h from last meal)
Chronic obstructive pulmonary disease	Short-acting β-agonists	NA	NA	NA

Abbreviations: NA, no interaction is known; NSAIDs, nonsteroidal anti-inflammatory druge.
*Thiazide-type diuretics may worsen hyperglycemia, but effect thought to be small and not associated with increased incidence of cardiovascular events.
†This interaction is noted to be particularly relevant for individuals with diabetes; no recommendation for treatment is given.

Boyd C, et al. JAMA 2005;294:716-724

La rappresentatività degli anziani nei clinical trial

Solo un **piccolo numero di RCT** forniscono **informazioni specifiche sui diversi gruppi di età**, e ciò non è migliorato nel tempo:

The Persistent Exclusion of Older Patients From Ongoing Clinical Trials Regarding Heart Failure

Antonio Cherubini, MD, PhD; Joaquim Oristrell, MD, PhD; Xavier Pla, MD; Carmelinda Ruggiero, MD, PhD; Roberta Ferretti, MD; Germán Diestre, MD; A. Mark Clarfield, MD, FRCPC; Peter Crome, MD, DSc; Cees Hertogh, MD, PhD; Vita Lesauskaite, MD, PhD; Gabriel-Ioan Prada, MD, PhD; Katarzyna Szczerbinska, MD, PhD; Eva Topinkova, MD, PhD; Judith Sinclair-Cohen, BSD; David Edbrooke, MD, FRCA; Gary H. Mills, MD, PhD

Background: Much clinical research of relevance to elderly patients examines individuals who are younger than those who have the disease in question. A good example is heart failure. Therefore, we investigated the extent of exclusion of older individuals in ongoing clinical trials regarding heart failure.

Methods: In the context of the Increasing the PaRticipation of the ElDerly in Clinical Trials (PREDICT) study, data from ongoing clinical trials regarding heart failure were extracted from the World Health Organization Clinical Trials Registry Platform on December 1, 2008. Main outcome measures were the proportion of trials excluding patients by an arbitrary upper age limit or by other exclusion criteria that might indirectly cause limited recruitment of older individuals. We classified exclusion criteria into 2 categories: justified or poorly justified.

Results: Among 251 trials investigating treatments for heart failure, 64 (25.5%) excluded patients by an arbitrary upper age limit. Such exclusion was significantly more common in trials conducted in the European Union than in the United States (31/96 [32.3%] vs 17/105 [16.2%]; $P = .007$) and in drug trials sponsored by public institutions vs those by private entities (21/59 [35.6%] vs 5/36 [13.9%]; $P = .02$). Overall, 109 trials (43.4%) on heart failure had 1 or more poorly justified exclusion criteria that could limit the inclusion of older individuals. A similar proportion of clinical trials with poorly justified exclusion criteria was found in pharmacologic and nonpharmacologic trials.

Conclusion: Despite the recommendations of national and international regulatory agencies, exclusion of older individuals from ongoing trials regarding heart failure continues to be widespread.

Arch Intern Med. 2011;171(6):550-556

29% nel periodo 1985-1989

18% nel periodo 1990-1994

21% nel periodo 1995-1999

(Heiat A, Arch Intern Med 2002;162:1682)

Il **26%** degli RCT che studiano farmaci per lo scompenso cardiaci escludono gli anziani

Aspetti differenziali tra pazienti con scompenso cardiaco arruolati nei RCT e osservati in comunità

(Tavazzi, Ital Heart J Suppl 2000;1:1038)

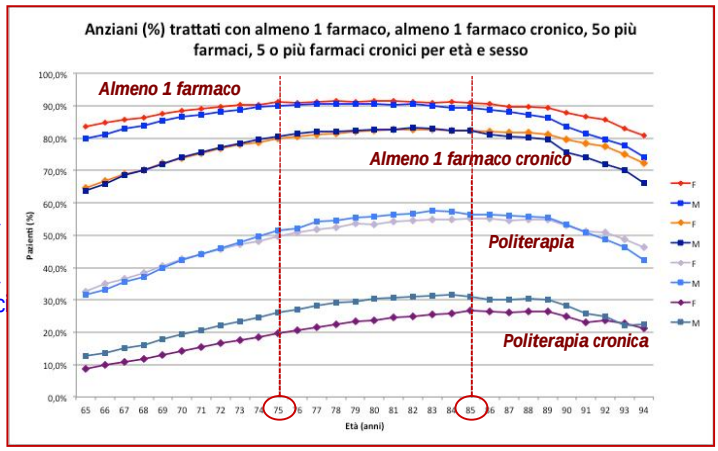
Caratteristiche	RCT	Comunità
Età media	60-65	75-80
Sesso (M/F)	4/1	1/1
FE > 40%	Criterio di esclusione	Molto frequente
CI instabile	Criterio di esclusione	Frequente
Creatinina >2-2.5 mg	Criterio di esclusione	17-43%
FA	20%	40%
Patologie concomitanti	Criterio di esclusione	Molto frequente
Dose target	Spesso raggiunta	Spesso più bassa
Compliance	Ottimale	Scarsa
Durata del trattamento	1-3 anni	Tutta la vita

Diverse popolazioni: la politerapia

I cambiamenti in relazione all'età

Dati 2005

- **88%** almeno 1 farmaco
- **76%** almeno un farmaco cronico*
- **46%** in politerapia (≥5 farmaci)
- **20%** in politerapia cronica (≥5 farmaci cronici)



* Farmaco cronico (almeno 4 confezioni nel corso di un anno)

Nobili A, et al. Pharmacoepidemiology and Drug Safety, 2011; 20: 488–496

Politerapia: un fenomeno in crescita

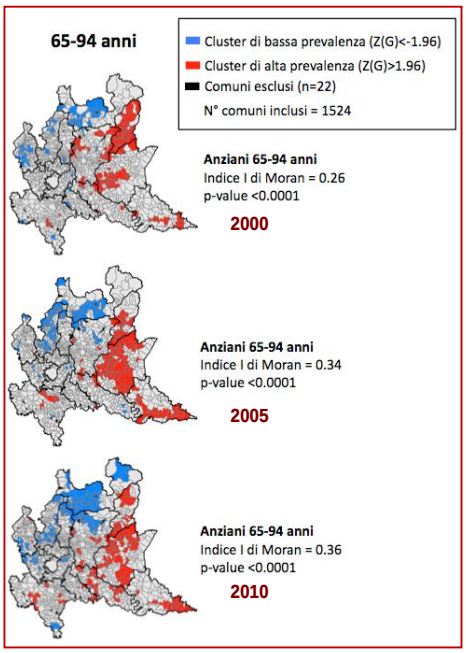
	n 2000	%	n 2010	%
Total population of Lombardy Region	9 256 127	100	10 155 949	100
Elderly (65-94 years)*	1 557 560	17.0	1 930 855	19.0
Age, mean (± SD)	75.1 (± 6.9)		76.1 (± 6.8)	
Female	941 106	60.4	1 113 400	57.7
Male	616 454	39.6	817 455	42.3
Age groups:				
65-74	916 651	58.9	1 030 775	53.4
75-84	480 381	30.8	692 414	35.9
85-94	160 528	10.3	207 666	10.7
No drug	187 764	12.0	185 683	9.7
At least one drug	1 369 796	88.0	1 745 172	90.3
At least one chronic drug‡	1 148 741	73.8	1 581 059	82.0
Polypharmacy (≥ 5 drugs)§	666 125	42.8	1 018 413	52.7
Chronic polypharmacy (≥ 5 chronic drugs)**	231 672	14.9	551 170	28.5
Total prescriptions to the elderly	21 439 913		43 877 720	
Total packages to the elderly	47 376 354		84 729 502	
Total active substances to the elderly	979		1142	
Number of prescriptions/person/year, mean (±SD)	13.9 (± 14.8)		22.8 (± 21.8)	
Number of packages/person/year, mean (±SD)	34.6 (± 32.4)		48.5 (± 42.2)	
Number of active substances/person/year, mean (±SD)	4.6 (± 4.0)		4.4 (± 5.6)	

Mappare la politerapia cronica come proxy di multimorbilita'

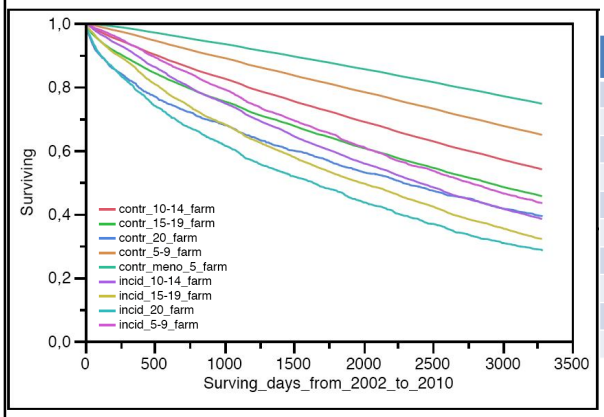
La politerapia cronica è stata definita come l'assunzione contemporanea di 5 o più farmaci in un mese per almeno 6 mesi (consecutivi o no) nell'arco dell'anno considerato

- La **prevalenza** di anziani in politerapia cronica è aumentata drasticamente passando da **1.3%** nel 2000, a **3.3%** nel 2005, fino a **7.1%** nel 2010
- L'aumento maggiore della percentuale di anziani in politerapia cronica si riscontra nella **classe di età 80-84 anni** (15.2 – 22.0%).
- Vi è solo una parziale correlazione tra gli anziani in politerapia cronica e quelli ospedalizzati.

Convegno SIGG, Milano 2012

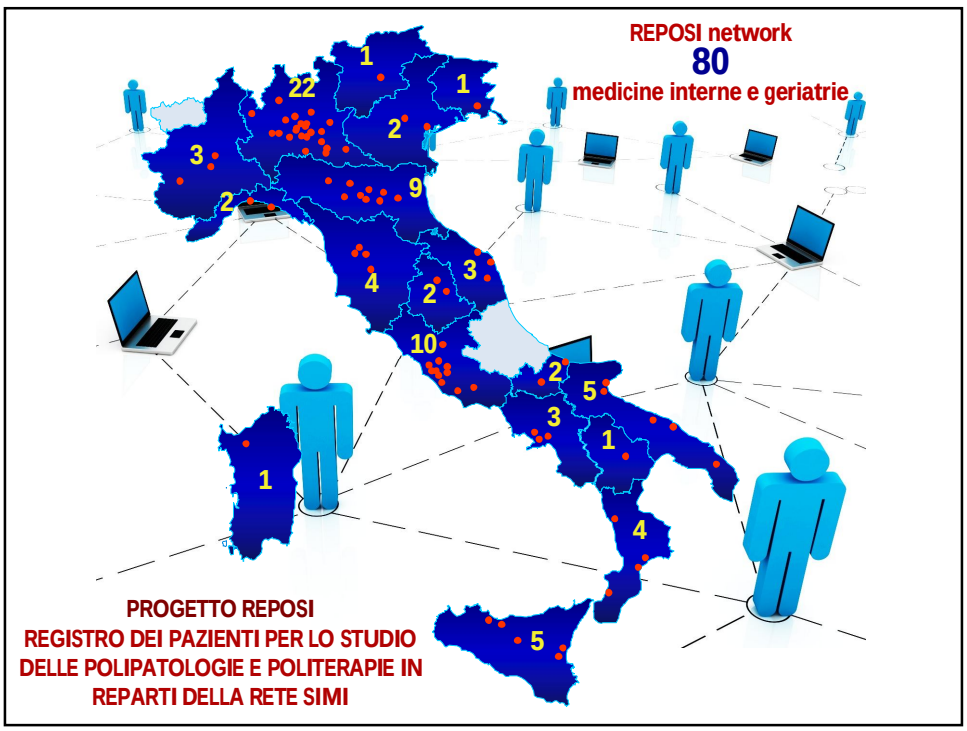


Ten years mortality for incident chronic polypharmacy elderly and controls in 2001 by number of overall drugs



Group, N of drugs	Number	Mean (days)	SE	Delta (days)
Overall		2766.3	0.74	
C < 5		**2894.9**	**0.89**	**Ref.**
C 5-9		2700.8	1.31	194,1
C 10-14		2447.0	3.02	447,9
C 15-19		2208.2	8.75	686,7
C >=20		1976.0	29.53	918,9
P 5-9		2252.5	16.70	642,4
P 10-14		2113.0	9.13	781,9
P 15-19		1916.3	10.84	978,6
P >=20		1733.4	27.36	1161,5

C = Controls
P = Polypharmacy
Ref. = Reference group
SE = Standard Error



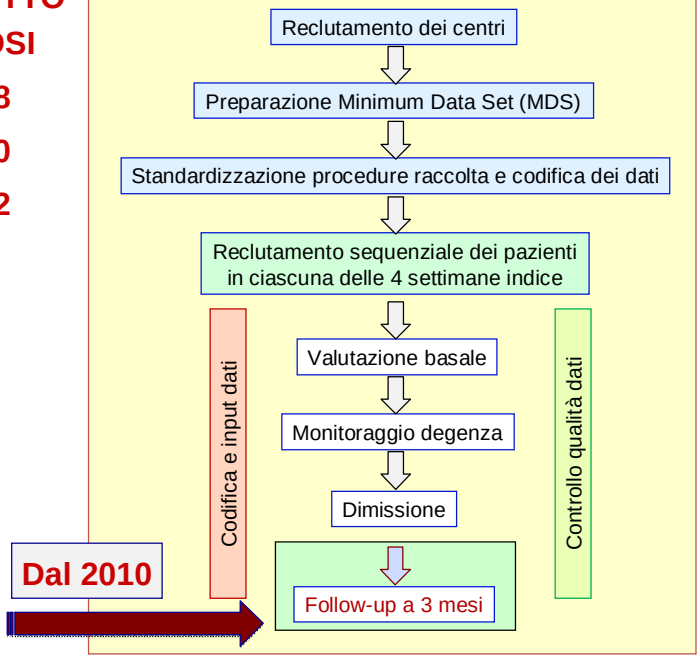
PROGETTO REPOSI

2008

2010

2012

Flow chart dello studio



Characteristics of patients enrolled in REPOSI 2010

Variables	N=1380
Females	697 (51%)
Age (mean±sd)	79±7
Older than 80 years	640 (46%)
Clinical and social frailty	1090 (79%)
BMI (mean±sd)	26±5
Underweight (BMI<18.5)	52 (4%)
Pts with bladder catheter at admission	312 (23%)
Mean (±sd) number of diagnosis at admission	6±2
Pts with 5 of more diagnosis at admission	891 (65%)
CIRS-Comorbidity Index (mean±sd)	3.0±1.7
CIRS-Severity Index (mean±sd)	1.6±0.3
Short Blessed Test (SBT) (mean±sd)	9.9±8.2
SBT (score=10-28) severe cognitive impairment	637 (48%)
Barthel Index (BI) (mean±sd)	76.8±30.7
BI (score=0-49) complete or severe dependence	266 (19%)

Characteristics of patients enrolled in REPOSI 2010

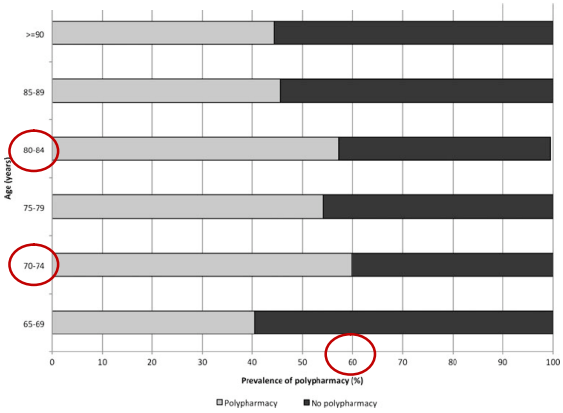
Variables	N=1380
Pts with at least one drug at admission	1348 (98%)
Mean (±sd) number of drugs at admission	5.4±2.7
Pts with 5 of more drugs at admission	805 (60%)
Pts with at least one inappropriate drug at admission	423 (31%)
In hospital serious adverse clinical events (mean±sd)	1.6±0.9
Pts with at least one in hospital serious ACE	477(35%)
Duration of hospital stay (mean±sd)	10.8±8.2
Discharged at home	1159 (84%)
Discharged in critical condition	19 (1%)
Transferred	120 (9%)
In hospital mortality	50 (4%)

Eur J Clin Pharmacol (2011) 67:507–519
DOI 10.1007/s00228-010-0977-0

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Polypharmacy, length of hospital stay, and in-hospital mortality among elderly patients in internal medicine wards. The REPOSI study

The prevalence of polypharmacy was **highest at ages 70-74 and 80-84 years**, with nearly 60% of patients in polypharmacy.



Eur J Clin Pharmacol (2011) 67:507–519

In-Hospital Death and Adverse Clinical Events in Elderly Patients According to Disease Clustering: The REPOSI Study

A. Marengoni,[1] F. Bonometti,[1] A. Nobili,[2] M. Tettamanti,[2] F. Salerno,[3] S. Corra,[4] A. Iorio,[5] M. Marcucci,[5] P.M. Mannucci,[6] for the Italian Society of Internal Medicine (SIMI) Investigators*

Clusters including HF, and either CRF or COPD, and CRF and anemia had a significant association with **in hospital death**.
The cluster including **HF and CRF** was also associated with **AEs.**
The effect of both HF and CRF on in-hospital death was additive.

Knowledge of the relationship among co-occurring diseases may help developing strategies to improve clinical practice and preventive interventions.

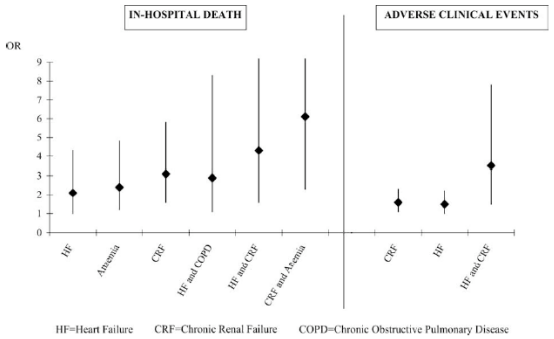


FIG. 2. Odds ratio (OR) and 95% confidence intervals for in-hospital death and adverse clinical events during hospitalization due to different clusters of diseases. Models adjusted for age, gender, education, number of drugs, and severe dependency. HF, Heart failure; CRF, chronic renal failure; COPD, chronic obstructive pulmonary disease.

REJUVENATION RESEARCH 2010; 13: 469-475.

European Journal of Internal Medicine 22 (2011) 597–602

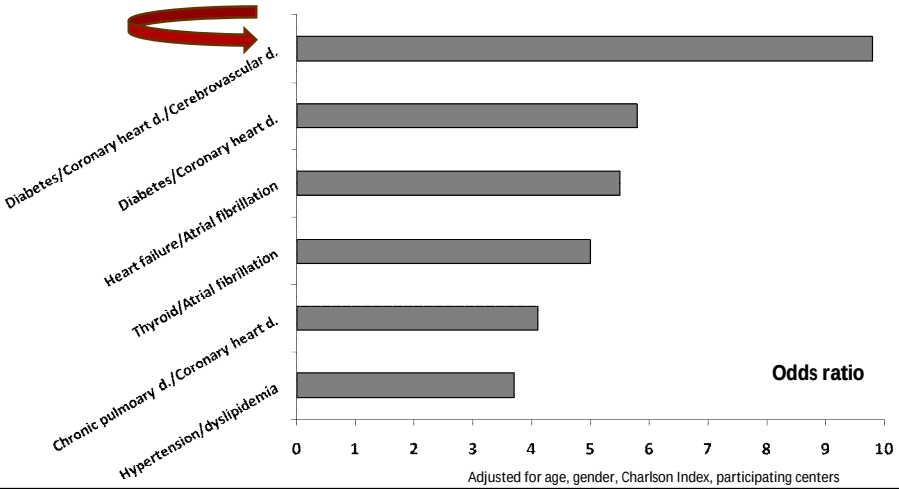
Contents lists available at SciVerse ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Association between clusters of diseases and polypharmacy in hospitalized elderly patients: Results from the REPOSI study



Risk factors for hospital readmission of elderly patients

Carlotta Franchi[1], Alessandro Nobili[1], Daniela Mari[2], Mauro Tettamanti[1], Codjo D. Djade[1], Luca Pasina[1], Francesco Salerno[3], Salvatore Corrao[4], Alessandra Marengoni[5], Alfonso Iorio[6], Maura Marcucci[6], Pier Mannuccio Mannucci[7] on behalf of REPOSI* Investigators

- **19% of patients were re-admitted** at least once within 3 month after discharge.
- **AEs during hospital stay, previous hospital admission, vascular and liver diseases** were significantly associated with likelihood of readmission

	Model 5	
Re-hospitalization	**OR (95% CI)**	***P-value***
Sex (Female)	1.27 (0.87 – 1.88)	*0.20*
Age (>= 85)	1.01 (0.62 – 1.60)	*0.97*
CIRS severity index	-	-
Adverse clinical events during hospitalization	1.74 (1.19 – 2-56)	*0.0045*
Previous hospital admission (6 months before current admission)	1.92 (1.31 – 2.82)	*0.0009*
cardiovascular diseases (level of impairment ≥3)	1.48 (1.00 – 2.17)	*0.0481*
Liver diseases (level of impairment ≥3)	2.32 (1.42 – 3.77)	*0.0010*

Model 5: Adjusted for sex, age, adverse clinical events during hospitalization, previous hospital admission and CIRS severity index, vascular and hepatic illnesses.

Prevalence and appropriateness of drug prescriptions for peptic ulcer and gastro-esophageal reflux disease in a cohort of hospitalized elderly

L. Pasina [a,*], A. Nobili [a], M. Tettamanti [a], F. Salerno [b], S. Corrao [c], A. Marengoni [d], A. Iorio [e], M. Marcucci [e], P.M. Mannucci [f] and on behalf of REPOSI Investigators [1]

European Journal of Internal Medicine 22 (2011) 205–210

- Among 1155 eligible patients**, 40.3%** were treated with drugs for GERD or PU at hospital **admission** and **56.0% at discharge**.
- **65.2%** of patients receiving a drug for PU or GERD at **admission** and **64.1%** at **discharge** were **inappropriately treated.**
- **Polypharmacy** was **associated** with a **greater use of these drugs**, even after adjustment for age, sex and number of diagnoses at **admission** (OR=1.25;95%CI: 1.18-1.34), or **discharge** (OR=1.11;95%CI: 1.05-1.18).

POLITERAPIA

Rischi associati alla politerapia

- ↑ **rischio** di reazioni avverse (**ADR**) e **interazioni** tra farmaci
- Uso di farmaci **inappropriati**
- Non somministrazione di farmaci necessari (“**treatment risk paradox**”)
- **Errori** nella corretta somministrazione dei farmaci (**dose**, **durata**)
- **Riduzione della compliance**
- **Declino** funzionale (**disabilità**) e cognitivo
- ↑ **rischio** di **sindromi geriatriche** (delirium, cadute, incontinenza, disturbi alimentari, ecc.)
- ↑ **rischio** di **istituzionalizzazione** e di **mortalità**
- ↑ **costi assistenziali**

"Your green pills are all gone. Do you wanna take a blue and a yellow?"

Polypharmacy and Prescribing Quality in Older People

Michael A. Steinman, MD,[†‡] C. Seth Landefeld, MD,[*†‡] Gary E. Rosenthal, MD,[§‖] Daniel Berthenthal, MPH,[†] Saunak Sen, PhD,[†] and Peter J. Kaboli, MD, MS[§‖]*

Con più aumenta il numero di farmaci prescritti, **maggiore è la probabilità** di assumere sia **farmaci inappropriati** che di **non assumere** farmaci raccomandati (**treatment risk paradox**).

Steinman MA, et al. JAGS 2006;54:1516-23

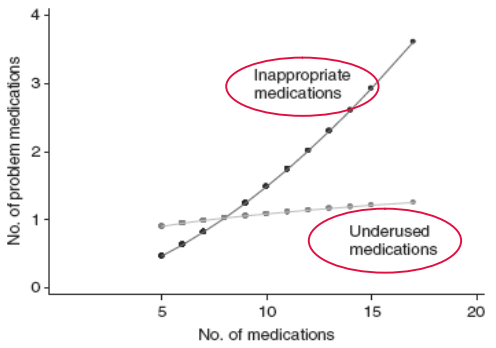


Figure 1. Number of medications and frequency of problem medication use. Lines show frequency of inappropriate medication use and underused medications according to log-linear models.

Inappropriate prescribing for the elderly—a modern epidemic?

Gunhild Nyborg · Jørund Straand · Mette Brekke

Eur J Clin Pharmacol (2012) 68:1085–1094

Conclusions About one-third of the elderly Norwegian population is exposed to potentially inappropriate medications, and elderly females are at particular risk.

High Prevalence of Poor Quality Drug Prescribing in Older Individuals: A Nationwide Report From the Italian Medicines Agency (AIFA)

Graziano Onder,[1] Stefano Bonassi,[2] Angela M. Abbatecola,[3] Pietro Folino-Gallo,[4] Francesco Lapi,[5] Niccolò Marchionni,[6] Luca Pani,[4] Sergio Pecorelli,[4] Daniele Sancarlo,[7] Angelo Scuteri,[8] Gianluca Trifirò,[9] Cristiana Vitale,[2] Stefano Maria Zuccaro,[10] Roberto Bernabei,[1] and Massimo Fini[2]; on behalf of the Geriatrics Working Group of the Italian Medicines Agency (AIFA)

Table 2. Prevalence of Quality Indicators in the Italian Elderly Population

Quality Indicator	All Age Groups (≥65 y), *n* = 12,301,537 (%)	65–74 y, *n* = 6,154,421 (%)	75–84 y, *n* = 4,474,887 (%)	≥85 y, *n* = 1,672,229 (%)
1. Polypharmacy				
5–9 drugs	6,024,383 (49.0)	2,681,639 (43.6)	2,462,378 (55.0)	880,366 (52.6)
≥10 drugs	1,389,591 (11.3)	529,506 (8.6)	629,043 (14.1)	231,042 (13.8)
2. Low adherence to antidepressant drug treatment*	201,290 (63.9)	83,110 (62.6)	82,623 (63.0)	35,557 (69.6)
3. Low adherence to antihypertensive drug treatment*	179,975 (46.4)	84,983 (43.2)	65,450 (47.2)	29,542 (56.1)
4. Low adherence to hypoglycemic drug treatment*	92,017 (63.0)	44,227 (63.0)	35,497 (64.7)	12,293 (70.1)
5. Low adherence to antiosteoporotic drug treatment*	56,621 (52.4)	24,424 (48.7)	24,351 (53.4)	7,846 (64.0)
6. Use of anti-Parkinson and antipsychotic drugs	25,949 (0.2)	10,200 (0.2)	10,625 (0.2)	5,124 (0.3)
7. Underutilization of statins in diabetic patients (as % of the whole elderly population)	918,662 (7.5)	418,257 (6.8)	366,813 (8.2)	133,592 (8.0)
As % of the elderly population on hypoglycemic drugs†	53.4	48.3	54.4	73.1
8. Concomitant use of drugs increasing the risk of bleeding				
Warfarin + traditional NSAIDs/COX-2 inhibitors	178,458 (1.5)	64,939 (1.1)	90,580 (2.0)	22,939 (1.4)
Warfarin + aspirin/antiplatelets	100,236 (0.8)	38,953 (0.6)	49,736 (1.1)	11,547 (0.7)
Warfarin + NSAIDs/COX-2 inhibitors + aspirin/antiplatelets	22,174 (0.2)	8,574 (0.1)	11,135 (0.2)	2,465 (0.1)
9. Concomitant use of drugs increasing the risk of renal failure and/or hyperkalemia (ACE inhibitors/ARB + aldosterone antagonists + NSAIDs/COX-2 inhibitors)	85,412 (0.7)	28,860 (0.5)	40,665 (0.9)	15,887 (1.0)
10. Concomitant use of ≥2 QT prolonging drugs‡	36,359 (0.3)	13,580 (0.2)	15,903 (0.4)	6,876 (0.4)
11. Use of antihypertensive drugs with unfavorable risk–benefit profile (doxazosin, clonidine, or methyldopa as monotherapy or any use of short-acting calcium antagonists; as % of the whole elderly population)	196,690 (1.6)	88,069 (1.4)	78,826 (1.8)	29,795 (1.8)
As % of the elderly population on antihypertensive drugs¶	2.5	2.3	2.5	2.8
12. Use of high dosage of digoxin (>0.125 mg/d)	47,314 (0.4)	16,323 (0.3)	22,488 (0.5)	8,503 (1.3)
13. Use of oral hypoglycemic agents associated with high risk of hypoglycemia (chlorpropamide or glibenclamide; as % of the whole elderly population)	87,755 (0.7)	35,786 (0.6)	37,626 (0.8)	14,343 (0.9)
As % of the elderly population on hypoglycemic drugs†	5.1	4.1	5.6	7.8

Notes: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; COX-2 inhibitors = cyclooxygenase-2 inhibitors; NSAIDs = nonsteroidal anti-inflammatory drugs.
*Prevalence has been calculated for newly treated participants only (Indicator 2: *n* = 315,015; Indicator 3: *n* = 388,079; Indicator 4: *n* = 146,094; Indicator 5: *n* = 108,037). Low adherence is defined as proportion of days covered < 40%.
†*n* = 1,721,767.
‡List of drugs that are well known to carry a risk of Torsades de Pointes, as reported in Arizona Cert list (available at http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm, accessed January 2012).
¶*n* = 7,999,099.

J Gerontol A Biol Sci Med Sci doi:10.1093/gerona/glt118

Non-adherence (compliance)

- Strongest predictor is **number of medications** (**complexity**)
  - Rates estimated at **25-50%**
  - **Intentional about 75%** of the time
    - Changes in regimen made by patients to increase convenience, reduce adverse effects, or decrease refill expense

The Implications of Therapeutic Complexity on Adherence to Cardiovascular Medications

Niteesh K. Choudhry, MD, PhD; Michael A. Fischer, MD, MS; Jerry Avorn, MD; Joshua N. Liberman, PhD; Sebastian Schneeweiss, MD, ScD; Juliana Pakes, MEd; Troyen A. Brennan, MD, JD, MPH; William H. Shrank, MD, MSHS

Background: Patients with chronic disease often take many medications multiple times per day. Such regimen complexity is associated with medication nonadherence. Other factors, including the number of pharmacy visits patients make to pick up their prescriptions, may also undermine adherence. Our objective was to estimate the extent of prescribing and filling complexity in patients prescribed a cardiovascular medication and to evaluate its association with adherence.

Methods: The study population comprised individuals prescribed a statin (n=1 827 395) or an angiotensin-converting enzyme inhibitor or renin angiotensin receptor blocker (ACEI/ARB) (n=1 480 304) between June 1, 2006, and May 30, 2007. We estimated complexity by measuring the number of medications, prescribers, pharmacies, pharmacy visits, and refill consolidation (a measure of the number of visits per fill) during the 3 months from the first prescription. The number of daily doses was also measured in ACEI/ARB users. After this period, adherence was evaluated over the subsequent year. The relationship between complexity and adherence was assessed with multivariable linear regression.

Results: The statin cohort had a mean age of 63 years and were 49% male. On average, during the 3-month complexity assessment period, statin users filled 11.4 prescriptions for 6.3 different medications, had prescriptions written by 2 prescribers, and made 5.0 visits to the pharmacy. Results for ACEI/ARB users were similar. Greater prescribing and filling complexity was associated with lower levels of adherence. In adjusted models, patients with the least refill consolidation had adherence rates that were 8% lower over the subsequent year than patients with the greatest refill consolidation.

Conclusion: Medication use and prescription filling for patients with cardiovascular disease is complex, and strategies to reduce this complexity may help improve medication adherence.

Arch Intern Med. 2011;171(9):814-822. Published online January 10, 2011. doi:10.1001/archinternmed.2010.495

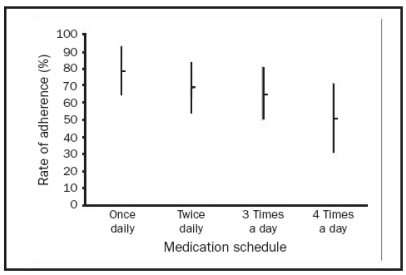
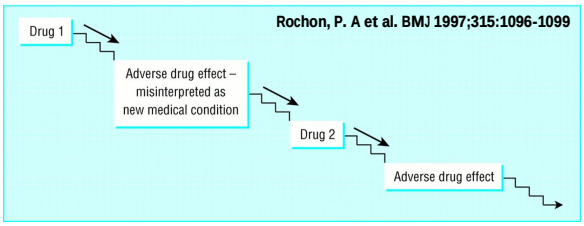


FIGURE 3. Adherence to medication according to frequency of doses. Vertical lines represent 1 SD on either side of the mean rate of adherence (horizontal bars).
From *N Engl J Med*,[3] with permission from the Massachusetts Medical Society. All rights reserved.

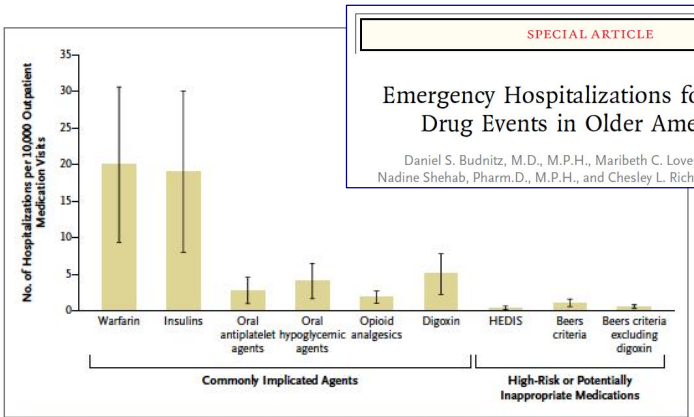
"Cascata prescrittiva (prescribing cascade)"

Donna di 82 anni affetta da demenza che sviluppa una sindrome dolorosa acuta:

Analgesico oppioide
Constipazione
Lassativo
Diarrea
Squilibrio idro-elettrolitico
Delirium
Olanzapina
Diabete
????



REAZIONI AVVERSE AI FARMACI



SPECIAL ARTICLE

Emergency Hospitalizations for Adverse Drug Events in Older Americans

Daniel S. Budnitz, M.D., M.P.H., Maribeth C. Lovegrove, M.P.H., Nadine Shehab, Pharm.D., M.P.H., and Chesley L. Richards, M.D., M.P.H.

Figure 1. Estimated Rates of Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, 2007–2009.
Estimates were based on hospitalization data from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project for 2007 through 2009, and data for outpatient visits during which medications were ordered or continued are from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey for 2007 and 2008. High-risk medications are those designated as such in the elderly by the 2011 Healthcare Effectiveness Data and Information Set (HEDIS).[12] Potentially inappropriate medications are those identified by the updated 2002 Beers criteria for potentially inappropriate medication use in older adults.[13] All high-risk or potentially inappropriate medications were included in the analysis, regardless of the dose, frequency of use, formulation (e.g., short-acting), or duration of use. I bars denote 95% confidence intervals. For oral antiplatelet agents, the coefficient of variation was greater than 30%.

N Engl J Med 2011;365:2002-12

Table 2 Patient Characteristics Predictive of Higher Risk of Adverse Drug Reactions[26,27]

No. of drugs*
≥8 drugs = high risk
5-7 drugs = intermediate risk
Previous ADR
≥4 medical comorbidities
Liver disease
Heart failure
Renal disease
Receiving high-risk drugs
Anticoagulants
Insulin or oral hypoglycemic drugs
Psychotropic medications
Sedatives/hypnotics
Cardiovascular drugs (especially digoxin, nitrates, and vasodilators)
Nonsteroidal anti-inflammatory drugs
Cognitive impairment
Living alone
History of nonadherence
Known psychologic disorders or substance abuse

ADR=adverse drug reaction.

*Although several definitions of polypharmacy appear in the literature, we argue that a number > 5 is associated with significant increase in ADR risk and is the number most commonly used in published literature.[12,13]

Am J Med 2012;125:529-37

Drug–drug interactions in a cohort of hospitalized elderly patients†

Luca Pasina[1]*, Codjo D. Djade[1], Alessandro Nobili[1], Mauro Tettamanti[1], Carlotta Franchi[1], Francesco Salerno[2], Salvatore Corrao[3], Alessandra Marengoni[4], Alfonso Iorio[5], Maura Marcucci[5] and Pier Mannuccio Mannucci[6]

Among 2712 patients aged 65 years or older, 1642 (60.5%) were exposed at hospital admission to at least one potential DDI and 512 (18.9%) to at least one potentially severe DDI.

Among 2314 patients discharged, 1598 (69.1%) were exposed to at least one potential DDI and 1561 (24.2%) to at least one potentially severe DDI.

Multivariate analysis found a significant association with an increased risk of mortality at 3 months in patients exposed to at least two potentially severe DDIs (Odds ratio 2.62; 95% confidence interval, 1.00–6.68; p = 0.05).

Adverse clinical events were potentially related to severe DDIs in two patients who died in the hospital, in five readmitted, and one who died at 3 months after discharge.

Table 5. Adverse events reported at follow-up and potentially severe drug–drug interactions after hospital discharge

Drug combination	Adverse events reported at follow-up	Time from discharge
Digoxin + furosemide Ramipril + spironolactone	Readmission for cardiac arrhythmias	2 months
Simvastatin + amlodipine	Readmission for myopathy	1 month
Clopidogrel + esomeprazole	Readmission for TIA	2 months
Clopidogrel + lansoprazole	Readmission for TIA	19 days

TIA = transient ischemic attack.

Pharmacoepidemiology and Drug Safety, (2013) DOI: 10.1002/pds

Prevention of Inappropriate Prescribing in Hospitalized Older Patients Using a Computerized Prescription Support System (INTERcheck®)

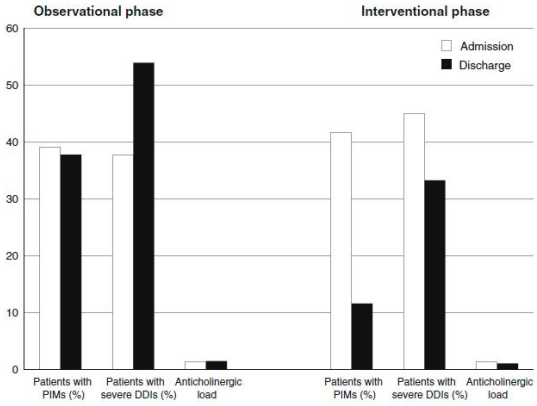
Simona Ghibelli · Alessandra Marengoni · Codjo D. Djade · Alessandro Nobili · Mauro Tettamanti · Carlotta Franchi · Silvio Caccia · Flavio Giovarruscio · Andrea Remuzzi · Luca Pasina

Drugs Aging
DOI 10.1007/s40266-013-0109-5

In the observational phase, the number of patients exposed to at least one PIM remained unchanged on both admission and discharge.

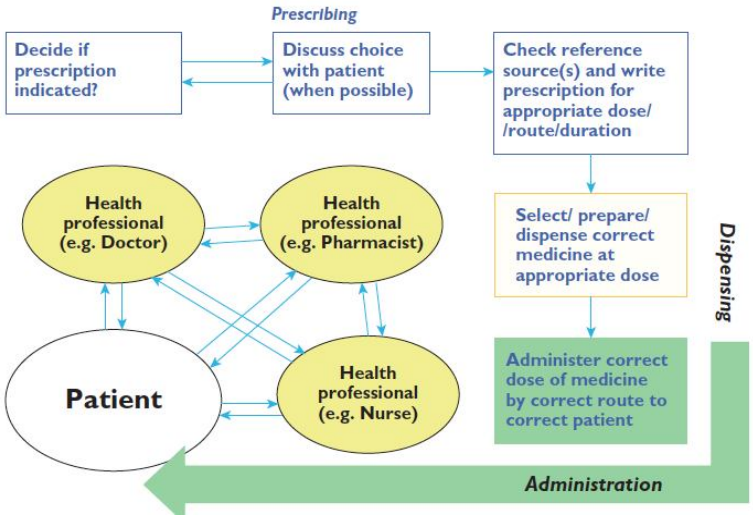
In the intervention phase, 25 patients (41.7 %) were exposed to at least one PIM at admission and 7 (11.6 %) at discharge (p<0.001).

The number of patients exposed to at least one potentially severe DDI decreased from 27 (45.0 %) to 20 (33.3 %), while the number of new-onset potentially severe DDIs decreased from 37 (59.0 %) to 9 (33.0 %) [p<0.001].



PROMUOVERE UNA NUOVA PRATICA PRESCRITTIVA

The prescribing process

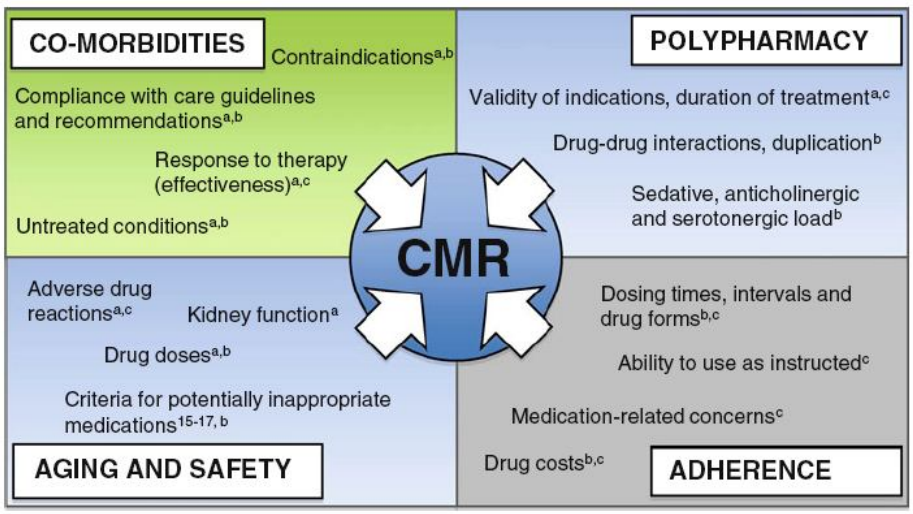


Optimal prescribing is dependent upon **close communication and collaborative** working between highly trained health professionals.

BICP 2012; 74: 676-684

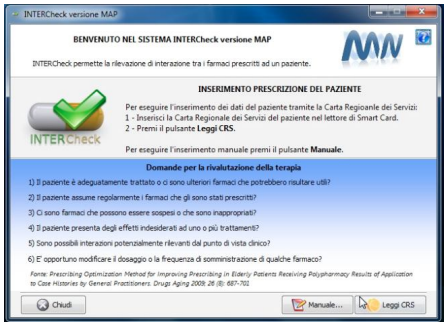
Comprehensive medication review

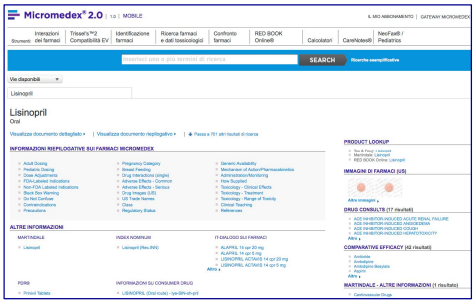
Development of a collaborative procedure:
key areas of geraiatric pharmacotherapy



Int J Clin Pharm (2012) 34:510–514

Gli strumenti





Electronic Health Record

Criteri "espliciti" per valutare l'uso inappropriato di farmaci nell'anziano

Table I. Basic characteristics of the seven sets of explicit criteria of potentially inappropriate medications evaluated

Characteristics	Beers	McLeod	Rancourt	Laroche	STOPP	Winit-Watjana	NORGEP
Year	2003	1997	2004	2007	2008	2008	2009
Country	US	Canada	Canada	France	Ireland	Thailand	Norway
Authors	Fick et al.[13]	McLeod et al.[21]	Rancourt et al.[25]	Laroche et al.[24]	Gallagher et al.[25]	Winit-Watjana et al.[15]	Rognstad et al.[26]
Method	Delphi	Delphi	Delphi	Delphi	Delphi	Delphi	Delphi
Experts (n)	12	32	4	15	18	17	47
Delphi rounds	2	2	2	2	2	3	3
Applicable age group (y)	≥65	≥65	≥65	≥75	≥65	NA	≥70
Statements (n)	68	38	111	34	65	77	36
Drug-disease interactions (n)	20	11	0	5	39	32	0
Drug-drug interactions (n)	1	11	37	2	5	12	15
Prescription duplications (n)	0	0	10	2	2	0	1
Suggestions for alternative drugs provided	No	Yes	No	Yes	No	No	No
Prevalence (%)*							
community	18.3–41.9	10.4	NA	NA	21.4	NA	NA
hospital	14–44.4	12.5	NA	NA	35.0	NA	NA
long-term care	18–34.9	14.9	54.7	NA	NA	NA	NA

a Prevalence range given for Beers criteria data.

NA= not available; **NORGEP** =Norwegian General Practice criteria; **STOPP** =Screening Tool of Older Person's potentially inappropriate Prescriptions criteria.

Drugs Aging 2010; 27 (12): 947-957

NEW MODELS FOR DRUG PRESCIBING

Discontinuing Medications: A Novel Approach for Revising the Prescribing Stage of the Medication-Use Process

Kevin T. Bain, PharmD,[*†] Holly M. Holmes, MD,[‡§] Mark H. Beers, MD,[†‖] Vittorio Maio, PharmD, MS, MSPH,[#] Steven M. Handler, MD, MS,[**] and Stephen G. Pauker, MD[††]*

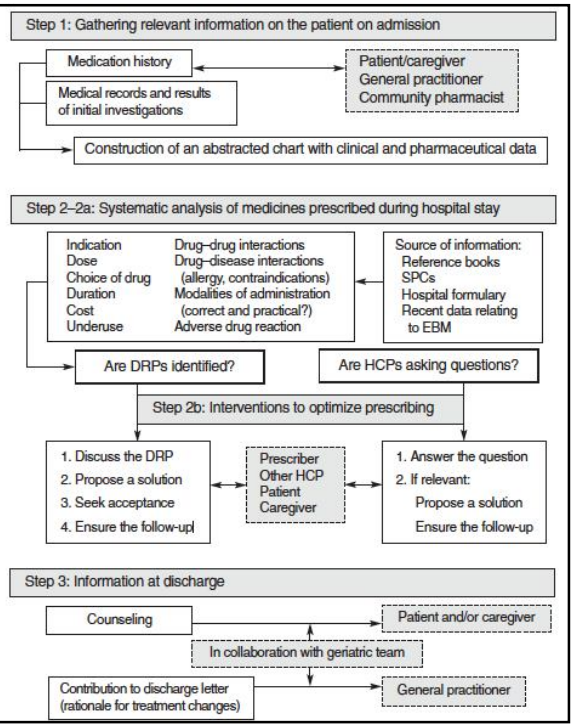
Bain KT, et al. JAGS 2008; 561946-52.

Indications that may warrant discontinuing medication:

- reduced benefit
- Inappropriate
- clinical improvement and stabilization
- increased risk (ADR, DDI)
- worsening medical condition
- no longer needed

Physicians and patients should rigorously reconsider which drugs are really need (**PRIORITIZATION**) and which could be stopped (**DISCONTINUATION**).

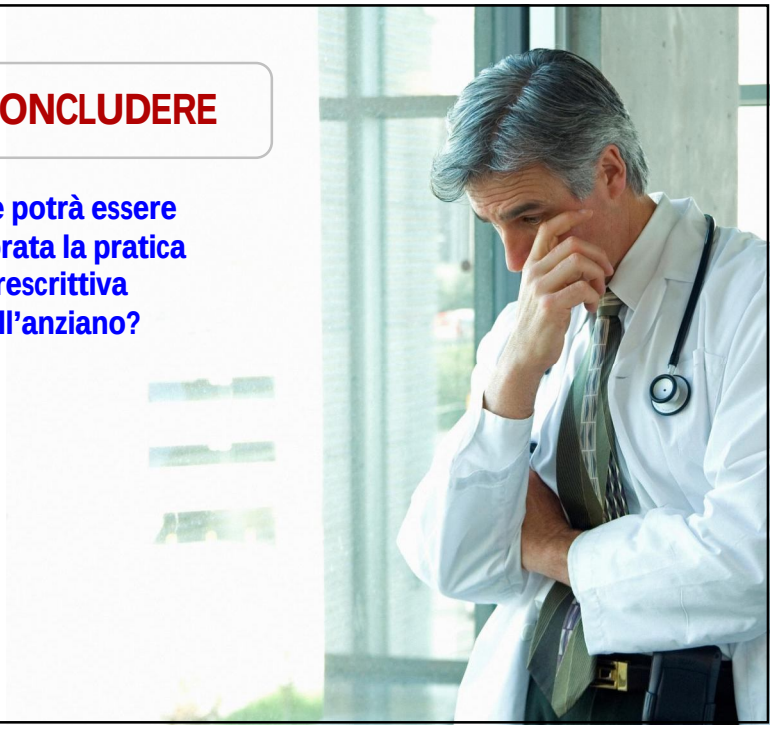
Implementation of Ward-Based Clinical Pharmacy Services in Belgium—Description of the Impact on a Geriatric Unit



Ann Pharmacother 2006;40:720-8.

PER CONCLUDERE

Come potrà essere migliorata la pratica prescrittiva nell'anziano?



Approaches to improve prescribing in elderly patients

	Description	Advantages	Disadvantages
Educational approaches	Can be passive (eg, didactic courses, dissemination of printed material), or more interactive (eg, academic detailing) Academic detailing: repeated face-to-face delivery of educational messages to individual prescribers, by doctors or pharmacists Audit and feedback can be added to enhance the effect	Directly addresses the absence of training in geriatric pharmacotherapy Can promote changes in prescribing behaviours Personalised, interactive, and multidisciplinary approaches most likely to be effective	Usually restricted to specific drugs or diseases Passive approaches likely to be ineffective Effect not sustained without continued intervention Low participation rate; barriers to implementation of interactive and multidisciplinary meetings
CPOE and CDSS	Support with regard to drug interactions, dosage, choice of drug, and monitoring Effect of CPOE based on the use of prescription data only, whereas CDSS uses prescription and clinical data to provide support	Potentially powerful tools to prevent adverse drug events Support at the time of prescribing All categories of inappropriate prescribing can be addressed, if prescription data are linked to clinical data	Challenging to implement Existing systems are not geriatric-specific High volume of alerts; therapeutic flags usually overridden by physicians; risk of unimportant warnings. Some prescribers are reluctant to use
Clinical pharmacists	Provide pharmaceutical care and drug regimen review	Specialist clinical pharmacists have expertise in geriatric pharmacology and pharmacotherapy Drug regimen review can potentially improve all categories of inappropriate prescribing	Successful interventions require that pharmacists work in close liaison with the prescriber, and have access to the full clinical record of the patient
Geriatric medicine services	Usually an interdisciplinary team composed of geriatricians, nurses, and other specialised health-care professionals (sometimes pharmacists) delivers medical care that includes optimisation of the drug regimen Comprehensive geriatric assessment is the usual process of care	Can potentially address most causes of inappropriate prescribing Every team member brings specific competences with regard to drug use Service is tailored to meet the needs of elderly people, and criteria to enter the programme are related to frailty and functional decline	Barriers to implementing multidisciplinary team meetings in the ambulatory and nursing home settings (challenge to organise and coordinate a multidisciplinary group, financial barriers)
Multidisciplinary approaches	Usually a group of health-care professionals undertake drug regimen review of individual patients	Can address distinct causes of inappropriate prescribing Every team member brings specific competences with regard to medicines use	Health-care professionals may not be involved in patient care and communication of recommendations to the prescriber
Multifaceted approaches	Interventions that incorporate two or more distinct strategies (eg, academic detailing and CDSS)	Can address distinct causes of inappropriate prescribing More likely to work than single interventions	Complex and costly to implement

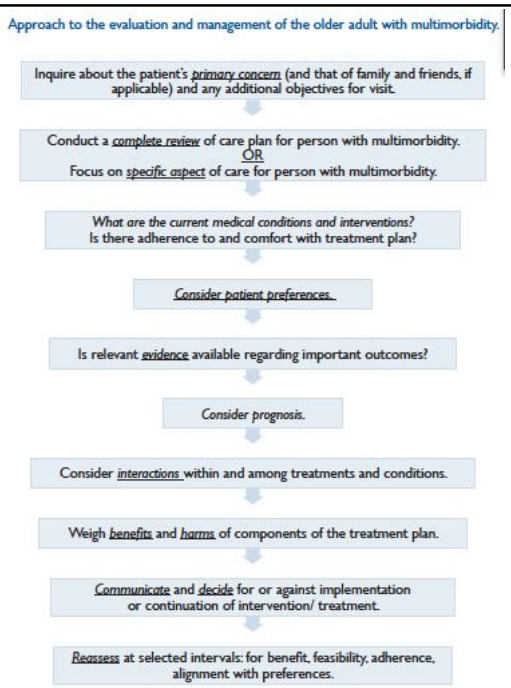
CDSS=computerised decision support system. CPOE=computerised physician order entry.

Table 3: **Advantages and disadvantages of approaches to improve prescribing in elderly patients**

Lancet 2007; 370: 173–84

Guiding Principles for the Care of Older Adults with Multimorbidity Pocket Card

FROM THE AMERICAN GERIATRICS SOCIETY



http://www.americangeriatrics.org/health_care_professionals/clinical_practice/multimorbidity

Interventions to improve the appropriate use of polypharmacy for older people (Review)

Patterson SM, Hughes C, Kerse N, Cardwell CR, Bradley MC

THE COCHRANE COLLABORATION®

Patterson SM, Hughes C, Kerse N, Cardwell CR, Bradley MC. Interventions to improve the appropriate use of polypharmacy for older people.

Cochrane Database of Systematic Reviews 2012, Issue 5. Art. No.: CD008165. DOI 10.1002/14651858.CD008165.pub2.

- Le **attuali evidenze** sono **piuttosto deboli**, e **non è chiaro** se gli interventi per migliorare l'appropriatezza prescrittiva e la gestione della politerapia determinino anche un miglioramento significativo su **ri-ospedalizzazioni** e su **eventi avversi da farmaci**.
- Vi è invece una **buona evidenza** che questi interventi abbiano un impatto significativo:
  - sulla **riduzione** della prescrizione di **farmaci inappropriati** e dei **problemi farmaco-corelati**,
  - sul **miglioramento** della **pratica prescrittiva**, sulla **promozione** della salute in generale e sulla **formazione** degli operatori coinvolti.
- Emerge inoltre che questi interventi sono **più efficaci** soprattutto quando vi è un **approccio multidisciplinare e integrato** per per la gestione dei pazienti con politerapia.
- Infine, l'impiego di **supporti decisionali computerizzati** (CDS) è risultato **utile** per migliorare l'appropriatezza prescrittiva

Cochrane Database of Systematic Reviews 2012, Issue 5. Art. No.: CD008165. DOI 10.1002/14651858.CD008165.pub2.

BMJ open

BMJ Open 2013;**3**: e001563.
doi:10.1136/bmjopen-2012-001563

Health economic evaluation of the Lund Integrated Medicines Management Model (LIMM) in elderly patients admitted to hospital

Ola Ghatnekar,[1] Åsa Bondesson,[2] Ulf Persson,[1] Tommy Eriksson[3]

Table 2 Base case results of the LIMM process versus standard care (costs in Euro)

		LIMM		Standard care		Difference	
		Mean	SE	Mean	SE	Mean	SE
Drug review cost	Admission	34	14	46	24	−12	28
	Discharge	5	2	0	0	5	2
	Subtotal	39	14	46	24	−7	28
Primary care nurse/physician administration cost	Admission	0	0	0	0	0	0
	Discharge	10	4	33	10	−23	11
	Subtotal	10	4	33	10	−23	11
OP visit and hospital stay cost	Admission	226	200	488	396	−262	278
	Discharge	15	21	63	63	−48	58
	Subtotal	241	209	551	440	−310	308
Grand total cost	Admission	260	200	534	397	−273	280
	Discharge	30	21	96	64	−66	59
	Total	290	210	630	441	−340	310
QALY loss	Admission	0.003	0.005	0.007	0.011	−0.004	0.007
	Discharge	0.000	0.000	0.002	0.002	−0.001	0.001
	Total	0.004	0.005	0.009	0.011	−0.005	0.007
Incremental cost-utility ratio	Admission	Dominant					
	Discharge	Dominant					
	Total	Dominant					

LIMM, Lund Integrated Medicines Management; OP, outpatient; QALY, quality-adjusted life-year.
Dominant, cost saving and greater utility with the LIMM model.

In total, the integrated process could be expected to generate **savings of € 340**, in spite of an **intervention cost of € 39**, and gained utility of 0.005.

Multiple diseases and polypharmacy in the elderly: challenges for the internist of the third millennium

Alessandro Nobili[1], Silvio Garattini[1], Pier Mannuccio Mannucci[2]

Journal of Comorbidity 2011;1:28–44

The clinicians of the Third Millennium must become more cognizant and proficient in the methods meant to:

- ✓ emphasize and practice a combination of problem-based and patient-oriented medicine
- ✓ consider the usefulness of tools of geriatric multidimensional evaluation
- ✓ identify realistic therapeutic goals reflecting age-related risk, standard of care, available guidelines, and patient's health expectations (quality of life)
- ✓ avoid potentially inappropriate prescriptions and drug interactions
- ✓ implement electronic prescribing tools and computerized clinical decision support systems
- ✓ promote and practice multidisciplinary and team care
- ✓ improve communication with primary care
- ✓ educate and involve the patient and caregiver in therapeutic choices

Un appuntamento da non perdere

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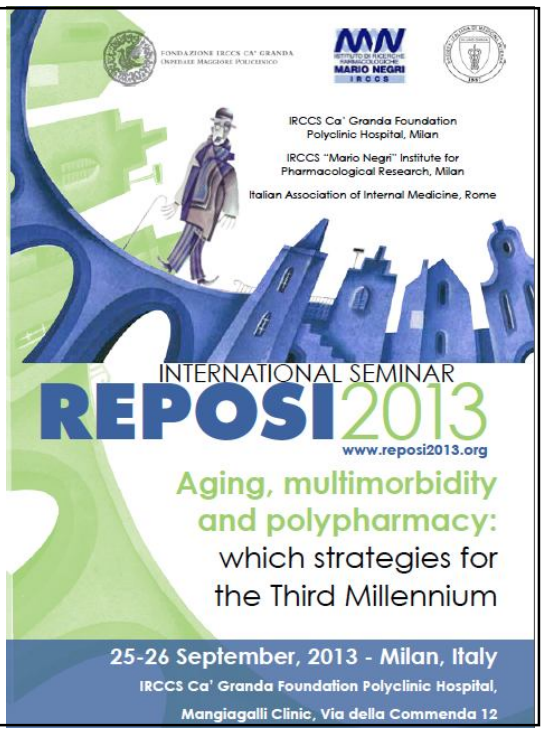

... e per finire

Insanity: doing the same thing over and over again and expecting different results.

Albert Einstein

Grazie per l'attenzione .