«CORSO SIFO UNDER 40. AGGIORNAMENTO PROFESSIONALE PER IL FARMACISTA»

IN MEMORIA DI STEFANO FEDERICI

Milano, 21 settembre - 23 novembre 2016

Informazione indipendente sui farmaci: le banche dati

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Fonti dell'informazione medica

1. Articoli originali
2. Revisioni
3. Testi di medicina
4. Riviste divulgative
5. Parere degli Esperti
6. Informatori scientifici
7. Banche dati
8. Internet
9. Servizi di informazione

Shaughnessy AF et al, 1994

Fonti primarie

<u>Riviste scientifiche</u>

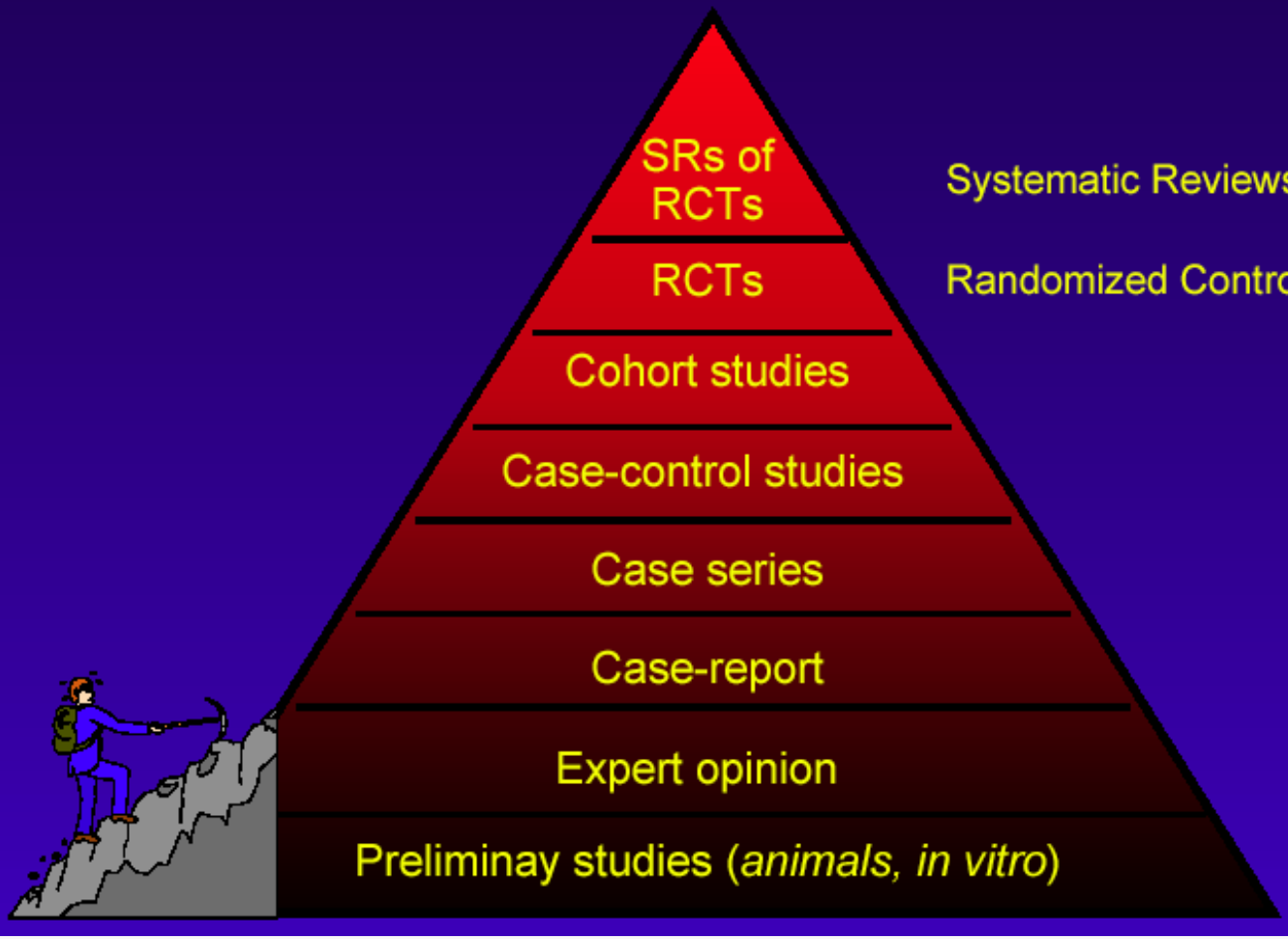
- New England Journal of Medicine
- JAMA
- The Lancet
- BMJ… ecc

<u>Banche dati</u>

- Medline
- Embase

Shaughnessy AF et al, 1994

Hierarchy of Evidence



Influences on GPs' decision to prescribe new drugs: the importance of who says what

Factors influencing new drug update:

- pharmaceutical representative	39%
- patient request	22%
- professional collegues	15%
- local and national guidelines	15%

The pharmaceutical industry was the most frequently used information source and there was an evident association between the evidence distilled from representatives and prescribing

Prosser, Family Practice 2003

Original Investigation

Pharmaceutical Industry–Sponsored Meals and Physician Prescribing Patterns for Medicare Beneficiaries

Colette DeJong, BA; Thomas Aguilar, MS; Chien-Wen Tseng, MD, MPH; Grace A. Lin, MD, MAS; W. John Boscardin, PhD; R. Adams Dudley, MD, MBA

Key Points

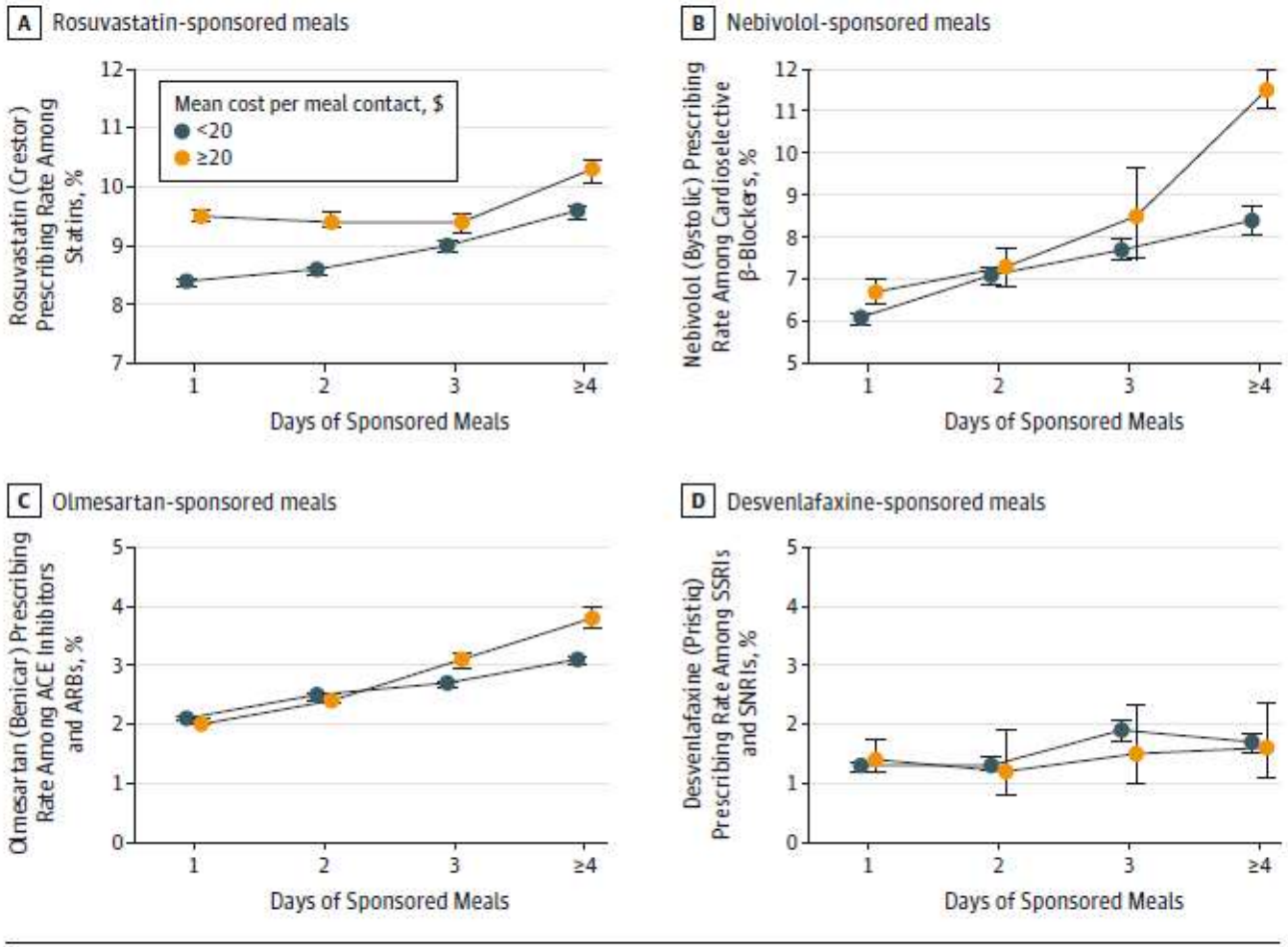
Question Is the receipt of pharmaceutical industry-sponsored meals by physicians associated with their prescribing the promoted brand-name drug at higher rates to Medicare beneficiaries?

Findings In this cross-sectional study of 279 669 physicians, physicians who received a single meal promoting the drug of interest, with a mean value of less than $20, had significantly higher rates of prescribing rosuvastatin as compared with other statins; nebivolol as compared with other β-blockers; olmesartan as compared with other angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers; and desvenlafaxine as compared with other selective serotonin and serotonin-norepinephrine reuptake inhibitors.

Meaning Receipt of industry-sponsored meals was associated with an increased rate of prescribing the promoted brand-name medication to Medicare patients.

DeJong, JAMA Int Med 2016

Figure 2. Predicted Probabilities for Prescribing the Target Drug as a Percentage of All Prescriptions in the Class, According to the Number and Cost of Sponsored Meals Received by Each Physician



The figure shows predicted probabilities for prescribing the target drug over alternatives within the treatment class, based on the cost and number of meals received promoting the target drug. Predicted probabilities are calculated for physicians with the highest-frequency values of all characteristics in Table 1 (male sex, internal medicine specialty, Southern region, urban location, group size ≥51, ≥20 years since medical school graduation, and mean values for prescribing volume, income in zip code, and percentage of low-income subsidy and Medicare Advantage Part D patients). A, Statins. B, Cardioselective β-blockers. C, Angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers (ACE inhibitors and ARBs). D, Selective serotonin and serotonin-norepinephrine reuptake inhibitors (SSRIs and SNRIs). Error bars indicate 95% confidence intervals.

DeJong, JAMA Int Med 2016

Industry-sponsored meals have been associated with learning **inaccurate information about the sponsor's and competitor's drug** and with increased cost of prescribing

Ziegler, JAMA 1995

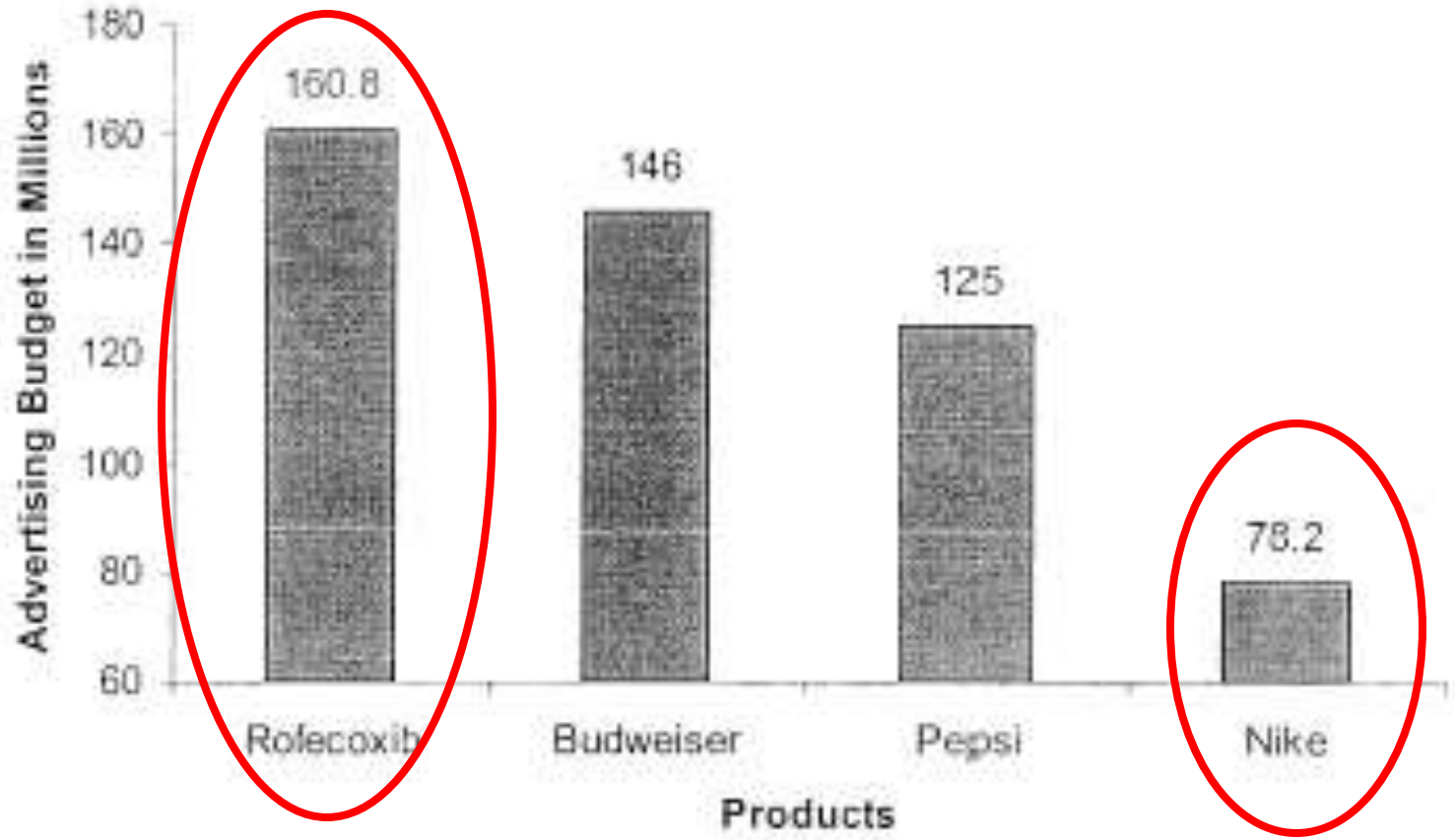
Pharmaceutical advertising versus research spending: Are profits more important than patients?

Debabrata Mukherjee, MD,[a] and Eric J. Topol, MD[b] *Ann Arbor, Mich, and Cleveland, Ohio*

Table I. 2000 Direct-to-consumer spending with drugs ranked in terms of year 2000 spending (adapted from NIH[15])

Rank	Name	Type of drug	DTC Spending in 2000 ($millions)
1	Vioxx	Antiarthritic	$160.8
2	Prilosec	Antiulcerant	$107.5
3	Claritin	Oral Antihistamine	$ 99.7
4	Paxil	Antidepressant	$ 91.8
5	Zocor	Cholesterol Reducer	$ 91.2
6	Viagra	Sex Function Disorder	$ 89.5
7	Celebrex	Antiarthritic	$ 78.3
8	Flonase	Respiratory Steroids (Inhaled)	$ 73.5
9	Allegra	Oral Antihistamine	$ 67.0
10	Meridia	Antiobesity	$ 65.0

Am Heart J 2003;146:563–4.



Direct-to-consumer spending on rofecoxib (Vioxx) contrasted with several consumer products (adapted from Reference 15).

Am Heart J 2003;146:563–4.

Il **18 febbraio 2005** vengono rese note le conclusioni dell'Advisory Panel su rofecoxib, celecoxib e valdecoxib. Il parere espresso dalla maggioranza del Panel **è favorevole al mantenimento in commercio di celecoxib e valdecoxib e alla reintroduzione sul mercato del rofecoxib**, come indicato nella tabella sottostante:

Permanenza/riammissione in commercio		
Farmaco	**voti a favore**	**voti contro**
rofecoxib	17	**15**
celecoxib	31	**1**
valdecoxib*	17	**13**

* 2 astenuti

Il **25 febbraio 2005** il New York Times pubblica in merito ai risultati dell'Advisory Panel un articolo dal titolo molto significativo: ***"10 voters on Panel backing pain pills had industry ties".*** Secondo l'autore dell'articolo, **10 esperti del Panel** avrebbero avuto in tempi recenti **"legami" con l'industria farmaceutica**. Quindi, se si dovessero togliere i voti di questi 10 esperti, i risultati dei rimanenti 22 esperti sarebbero i seguenti:

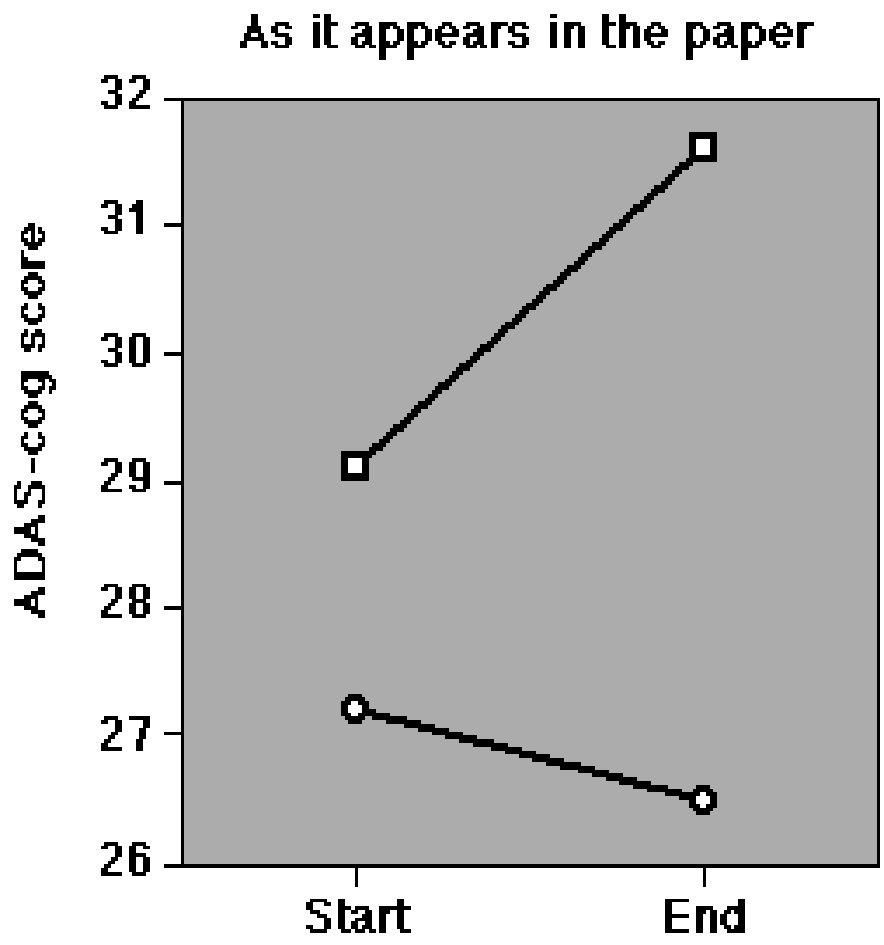
Permanenza/riammissione in commercio		
Farmaco	**voti a favore**	**voti contro**
rofecoxib	8	**14**
celecoxib	21	**1**
valdecoxib*	8	**12**

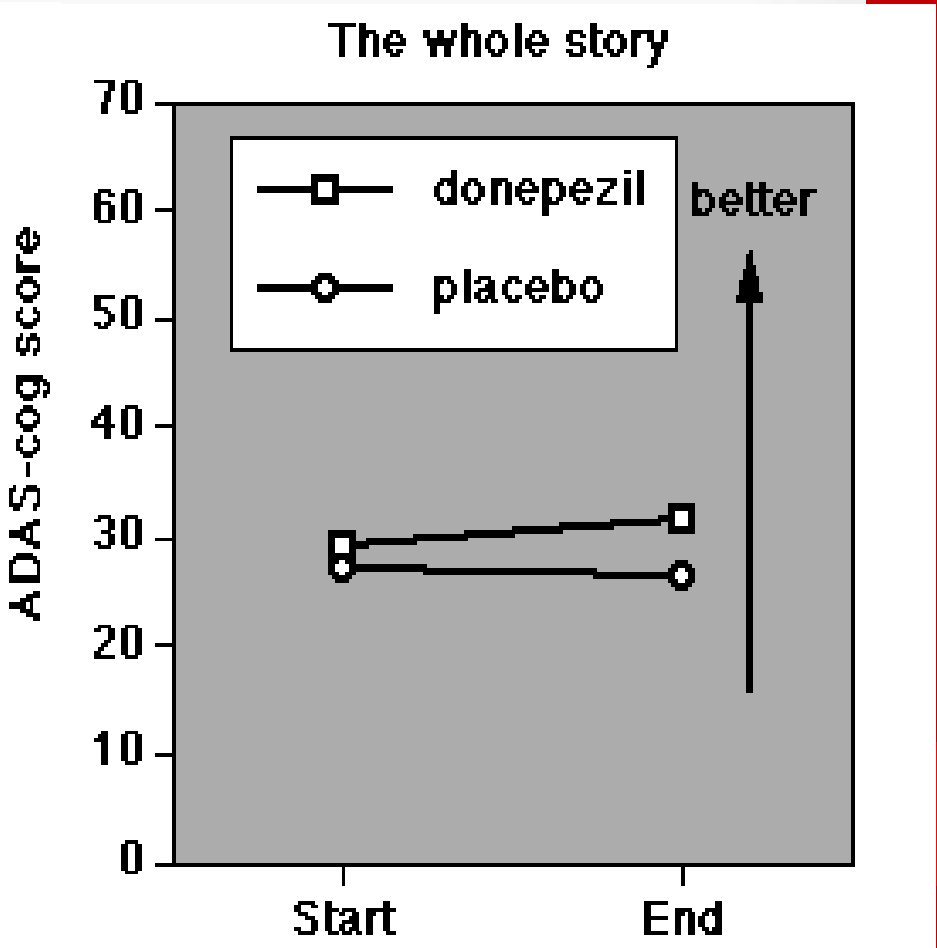
* 2 astenuti

Difficoltà pratiche dalle fonti primarie

Sbilanciamento verso i risultati positivi

Effect of 14 weeks donepezil treatment in mild or moderately severe Alzheimer disease





SL Rogers,. Dementia 1996

Rosiglitazone, marketing, and medical science

Attempts to play down the potential cardiac risks of a popular diabetes drug raise questions about the need for fundamental changes in drug regulation, writes **Ray Moynihan**

Casually following the fortunes of the blockbuster diabetes drug rosiglitazone (Avandia), you can't help but imagine a Hollywood thriller. There is the scene where a leading scientist secretly records a meeting with drug company executives, a high powered congressional investigation, and a bitter legal battle waiting in the wings. Yet when you look more closely, the facts are even stranger than fiction. An expensive new drug shown to raise the risk of heart events, ranging from 30 percent to 43 percent!"[1] Yet on the following day, the company was developing "key messages" to counteract Nissen and Wolski's findings. By the time the meta-analysis was published less than two weeks later, complete with the authors' acknowledgment of its limitations,[2] GSK announced it was based on incomplete evidence and that the company strongly disagreed with its conclusions. In their report, released this February, the congressional investigators concluded that corporate

JUSTIN SULLIVAN/GETTY

bmj.com archive
Recently published research on rosiglitazone:

- Association between industry affiliation and position on cardiovascular risk with rosiglitazone: cross sectional systematic review, by Amy T Wang *et al* *BMJ* 2010;340:c1344
- Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database, by Ioanna Tzoulaki *et al.* *BMJ* 2009;339:b4731

EVOLUTION OF ROSIGLITAZONE STORY

1999
MAY: Drug approved by FDA with label precautions for use in patients with heart failure

2000
JULY: Approved in Europe, with warnings on heart failure

2001
FEBRUARY: FDA approved new warnings on potential for heart failure

2005
SEPTEMBER: Internal GSK meta-analysis finds 29% non-significant increased risk of ischaemic cardiovascular events

2006
APRIL: FDA approves new warnings on risks of cardiovascular events

MAY: Internal GSK meta-analysis finds 31% increase in ischaemic events

2007
MAY: *New England Journal of Medicine* publishes meta-analysis reporting 43% increase risk of myocardial infarction[2]

JULY: FDA advisory committee finds increased cardiac ischaemic risk but votes to keep drug on market

OCTOBER: European Medicines Evaluation Agency asserts positive benefit-risk profile, recommends new warnings for patients with ischaemic heart disease

NOVEMBER: FDA approves new boxed warnings that drug may increase myocardial ischaemic events, including myocardial infarction, though evidence "inconclusive"

DECEMBER: UK Medicine and Healthcare Products Regulatory Agency warns drug might be associated with small increased risk of cardiac ischaemia

2008
Updated internal GSK analysis finds no risk of myocardial infarction or other major cardiovascular events

2009
MARCH: *International Journal of Cardiology* meta-analysis finds no risk of myocardial infarction

2010
FEBRUARY: US Senate finance committee releases report that includes internal FDA safety report calling for drug to be withdrawn

FEBRUARY: GSK responds with 30 page document

July: FDA advisory committee meeting scheduled

Insider criticises FDA's decision not to withdraw rosiglitazone

Deborah Cohen BMJ

The decision of the US Food and Drug Administration to place more restrictions on GlaxoSmithKline's diabetes drug rosiglitazone (Avandia) rather than withdraw it has drawn criticism from senior officials within the agency.

In simultaneous statements last week both the FDA and the European Medicines Agency (EMA) suggested that the drug was associated with important safety concerns and that data pointed to a raised risk of cardiovascular events, such as heart attack and stroke, in patients taking rosiglitazone.

Unlike the EMA—which said that the "benefits of rosiglitazone no longer outweigh its risks" and recommended its suspension from the market in Europe—the FDA has recommended a package of measures to try to determine the safety of the drug and further restrict its use.

The US drug regulator does not have the legal means to suspend a drug, although it did not rule out removing the drug from the market at a later date. In Europe suspension means that rosiglitazone's manufacturer, GlaxoSmithKline (GSK), has scope to "provide convincing data" to identify a group of patients in whom the drug's benefits outweigh the risks.

The FDA will implement a risk evaluation and mitigation strategy. This will mean that rosiglitazone will be available to new patients only if they are unable to achieve glucose control with other drugs and are unable to take Takeda's pioglitazone (Actos), the only other drug in this class. Current users of rosiglitazone who are benefiting from the drug will be able to continue using it if they choose to do so.

REUTERS

Dr David Graham: "The FDA decision was . . . not in the best interests of patient safety and public health"

Doctors will have to attest to and document their patients' eligibility; and patients will have to review statements describing the cardiovascular safety concerns associated with this drug and acknowledge that they understand the risks.

David Graham, associate director for science and medicine at the FDA's Office of Surveillance and Epidemiology, was critical of the FDA's response. "The FDA decision was disappointing, was not in the best interests of patient safety and public health, was not evidence based, and was inherently self contradictory," he told the *BMJ*.

"By calling for a REMS [risk evaluation and mitigation strategy], with restricted distribution, FDA is implicitly stating that the health benefits of Avandia exceed its risks for patients who will receive Avandia under the REMS system. This is a demonstrably false assumption, because there are no subgroups of patients with diabetes for whom the cardiovascular and mortality risks of Avandia are not increased compared with Actos. There are also no studies that show unique meaningful health benefits with Avandia. So how could anyone conclude that the benefits exceed the risks?"

Cite this as: *BMJ* 2010;341:c5333

Meta-analysis confirms raised risk of bladder cancer from pioglitazone

Barbara Kermode-Scott

Edmonton

A new meta-analysis[1] seems to confirm findings from a nested, case-control study published in the *BMJ* in May[2] that thiazolidinediones are associated with an increased risk of bladder cancer in people with type 2 diabetes.

Both analyses also found that in the studies that looked at individual drugs in this class pioglitazone, but not rosiglitazone, was associated with an increased risk of bladder cancer.

In the *BMJ* study, Azoulay and colleagues from McGill University in Montreal looked at a cohort that included 115 727 new users of oral hypoglycaemic agents, of whom 470 were given a diagnosis of bladder cancer during follow-up (89.4 cases per 100 000 person years). They concluded that the risk rose with duration of use and cumulative dosage. Risk was highest among those using pioglitazone for more than 24 months (rate ratio 1.99 (95% confidence interval 1.14 to 3.45)) and among those receiving cumulative dosages greater than 28 000 mg (rate ratio 2.54 (1.05 to 6.14)).

In the latest study, researchers at the University of Alberta in Edmonton conducted a systematic review and meta-analysis of randomised controlled trials and observational studies involving over 2.6 million patients. A pooled estimate from three cohort studies involving more than 1.7 million people showed that use of pioglitazone was associated with an increased risk of bladder cancer. The researchers did not find an association with rosiglitazone.

"Of the 1787 studies identified, we selected four RCTs [randomised controlled trials], five cohort studies and one case-control study," wrote the authors. "The total number of patients was 2 657 365, of whom 3643 had newly diagnosed bladder cancer, for an overall incidence of 53.1 per 100 000 person-years. The one RCT that reported on pioglitazone use found no significant association with bladder cancer (risk ratio (RR) 2.36, 95% confidence interval (CI) 0.91-6.13). The cohort studies of thiazolidinediones (pooled RR 1.15, 95% CI 1.04-1.26; I^2=0%) and of pioglitazone specifically (pooled RR 1.22, 95% CI 1.07-1.39; I^2=0%) showed significant associations with bladder cancer. No significant association with bladder cancer was observed in the two RCTs that evaluated rosiglitazone use (pooled RR 0.87, 95% CI 0.34-2.23; I^2=0%)."

The findings of Azoulay and colleagues are entirely consistent with the previous studies summarised by the Edmonton researchers in *CMAJ*, said their principal investigator, Jeffrey Johnson, who holds the Canada Research chair in diabetes health outcomes.

He said, "We have re-run the meta-analysis for bladder cancer risk with pioglitazone use, including this new study, and found the pooled risk estimate went from 1.22 to 1.26. In addition, the new study corroborated the dose-risk gradient reported in some of the previous studies (the more pioglitazone used, the greater the risk of bladder cancer)."

"We are pretty confident that people with type 2 diabetes exposed to pioglitazone have an increased risk of bladder cancer, but this risk is quite small and largely confined to men. Given that pioglitazone has some benefits and a number of risks, the challenge for busy clinicians is to balance the totality of available evidence and fully inform their patients as treatment decisions are agreed upon."

1 Colmers IN, Bowker, SL, Majumdar SR, Johnson JA. Use of thiazolidinediones and the risk of bladder cancer among people with type 2 diabetes: a meta-analysis. *CMAJ* 2012. doi:10.1503/cmaj.112102.

2 Azoulay L, Yin H, Filion KB, Assayag J, Majdan A, Pollak MN, Suissa S. The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. *BMJ* 2012;344:e3645.

Cite this as: *BMJ* 2012;345:e4541

Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence

Joanna Le Noury,[1] John M Nardo,[2] David Healy,[1] Jon Jureidini,[3] Melissa Raven,[3] Catalin Tufanaru,[4] Elia Abi-Jaoude[5]

WHAT IS ALREADY KNOWN ON THIS TOPIC

There is a lack of access to data from most clinical randomised controlled trials, making it difficult to detect biased reporting

In the absence of access to primary data, misleading conclusions in publications of those trials can seem definitive

SmithKline Beecham's Study 329, an influential trial that reported that paroxetine was safe and effective for adolescents, is one such study

WHAT THIS STUDY ADDS

On the basis of access to the original data from Study 329, we report a reanalysis that concludes that paroxetine was ineffective and unsafe in this study

Access to primary data makes clear the many ways in which data can be analysed and represented, showing the importance of access to data and the value of reanalysis of trials

There are important implications for clinical practice, research, regulation of trials, licensing of drugs, and the sociology and philosophy of science

Our reanalysis required development of methods that could be adapted for future reanalyses of randomised controlled trials

RESEARCH CONDUCT

No correction, no retraction, no apology, no comment: paroxetine trial reanalysis raises questions about institutional responsibility

As a new data analysis adds weight to calls for retraction of a paper on paroxetine in adolescents, **Peter Doshi** examines the resistance to action of a professional society, its journal, and an Ivy League university

Peter Doshi *associate editor, The BMJ*

Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials

WHAT IS ALREADY KNOWN ON THIS TOPIC

Reboxetine has been approved for the treatment of major depression in many European countries, but the application for approval was rejected in the United States

Doubts have been raised about the efficacy of reboxetine

Research into antidepressants is particularly affected by publication bias

WHAT THIS STUDY ADDS

Overall, reboxetine is not effective for the treatment of major depressive disorder

We found a higher rate of patients affected by adverse events than with placebo and higher withdrawal rates owing to adverse events than with placebo and fluoxetine

This meta-analysis provides a striking example of publication bias, in which the previously favourable risk-benefit profile of reboxetine shown in published trials is reversed by the addition of unpublished data

Post-approval regulatory decisions (for example, reimbursement decisions based on the findings of health technology assessment reports) might be affected by publication bias

Our findings underline the need for mandatory publication of clinical trial results

Eyding, BMJ 2010

Farmaci equivalenti

Bioequivalence and Other Unresolved Issues in Generic Drug Substitution

Clinical concerns of bioequivalence

- Cardiovascular drugs (cardiac glycosides, antiarrhythmic drugs)
- Anticonvulsant drugs (phenitoin, carbamazepine)
- Psycotropic drugs (neuroleptics)
- Anticoagulant drugs
- Levothyroxine
- Oral contraceptives
- Proton pump inhibitors

Conclusion: I recommend that health care providers continue to exercise caution in the consideration of generic drug substitution under certain circumstances. (*Clin Ther.* 2003;25:2875–2890)

Meredith, Clin Ther 2003

Annals of Internal Medicine | EDITORIAL

Generic Statins: Effectiveness, Affordability, and Patient Adherence

Ann Intern Med. 2014;161:447-448

Educational campaigns focusing on these domains are effective in influencing generic medication use (*Med Care. 2009;47:319-25*).

Patient education is key to the wider use of generic medications.

A randomized, controlled trial found that an educational intervention involving the dissemination of verbal and written information on advantages and disadvantages of generic and brand-name drugs resulted in 98.9% of patients who received the intervention agreeing to receive a generic formulation (*Health Policy. 2003;65:269-75*).

Un problema di (in-)formazione e comunicazione!

a. Farmaci cardiovascolari

Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease: A Systematic Review and Meta-analysis

Aaron S. Kesselheim; Alexander S. Misono; Joy L. Lee; et al.

JAMA. 2008;300(21):2514-2526 (doi:10.1001/jama.2008.758)

Class	Trials showing clinical equivalence
Beta blockers	7/7
Diuretics	10/11
Calcium-channel blockers	5/7
Antiplatelet agents	3/3
Statins	2/2
ACE inhibitors	1/1
Alpha blockers	1/1
Class 1 antiarrhythmic agents	1/1
Warfarin	5/5

ORIGINAL RESEARCH | Annals of Internal Medicine

Comparative Effectiveness of Generic and Brand-Name Statins on Patient Outcomes

A Cohort Study

Joshua J. Gagne, PharmD, ScD; Niteesh K. Choudhry, MD, PhD; Aaron S. Kesselheim, MD, JD, MPH; Jennifer M. Polinski, ScD, MPH; David Hutchins, MBA, MHSA; Olga S. Matlin, PhD; Troyen A. Brennan, MD; Jerry Avorn, MD; and William H. Shrank, MD, MSHS

A total of 90,111 pts aged ≥ 65 years who initiated a statin during the study was included: 83,731 (93%) a generic drug and 6,380 (7%) a brand-name statin.

Table 2. Hazard Ratios for Outcomes Among Generic Versus Brand-Name Statin Recipients

Outcome	Hazard Ratio (95% CI)	
	Unmatched (Crude)	Propensity Score–Matched
Composite end point	0.94 (0.88–1.00)	0.92 (0.86–0.99)
Hospitalization for an acute coronary syndrome	0.92 (0.86–0.98)	0.92 (0.85–0.99)
Hospitalization for stroke	1.04 (0.85–1.26)	0.96 (0.78–1.18)
Death from any cause	1.14 (0.85–1.54)	0.95 (0.69–1.30)

Conclusion: Compared with those initiating brand-name statins, patients initiating generic statins were more likely to adhere and had a lower rate of a composite clinical outcome.

Ann Intern Med 2014, 161:400-407

b. Farmaci antiepilettici e antipsicotici

Are there potential problems with generic substitution of antiepileptic drugs? A review of issues

Seizure (2006) 15, 165—176

Table 6 Case reports of problems following replacement of the innovator brand (Tegretol) with generic carbamazepine

References	Type of study	Findings
[41]	Case report of 16-year old boy	Boy with partial epilepsy caused by cerebral hemiatrophy stable on Tegretol experienced convulsions when switched to the generic
[14]	Case report of three patients	Loss of seizure control following generic substitution of Tegretol, with restoration of control when Tegretol reinstituted
[42]	Case report of woman	Seizure activity increased following generic substitution of Tegretol, with fall in serum carbamazepine level. Control regained when Tegretol reinstituted
[43]	Case report of two patients	Breakthrough seizures occurred within 3—7 days of generic substitution of Tegretol
[39]	Case report of two patients	Breakthrough seizures associated with drop in serum levels of carbamazepine following switch from Tegretol to generic
[33]	Case reports of two 6-year-old children	Increases in carbamazepine C_{max} of 22% and 41% after mandatory generic substitution, resulting in toxicity that reversed when Tegretol reinstituted. One child required hospitalisation

Antiepilettici

Mancano evidenze concrete circa un aumento delle reazioni avverse o una riduzione dell'efficacia. Evidenze per lo più da singoli casi.

Approccio razionale e di estrema cautela soprattutto verso i pazienti che non hanno convulsioni prevede che la prescrizione degli equivalenti sia riservato:

1. pazienti con nuova diagnosi di epilessia

2. pazienti con crisi non controllate

No sostituibilità nei pazienti che ben controllati con farmaco brand

Gidal, Epilepsia, 2008

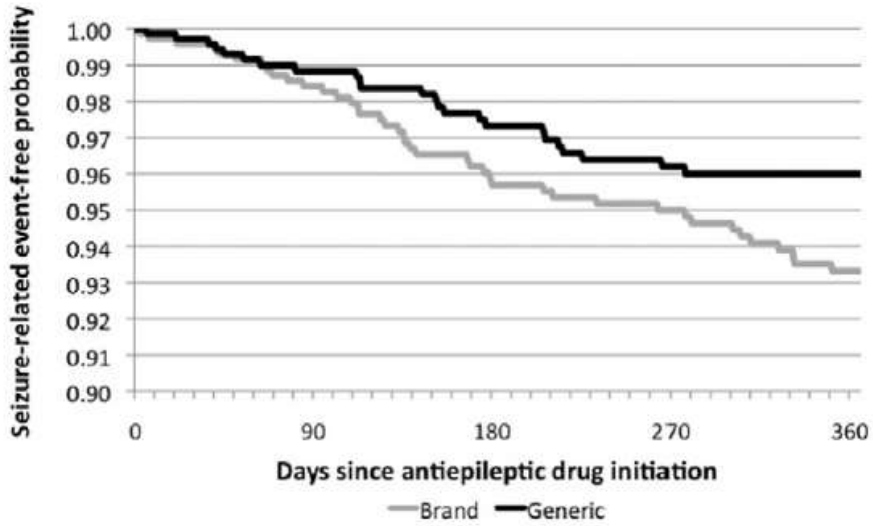
Comparative effectiveness of generic versus brand-name antiepileptic medications

Joshua J. Gagne [a,*], Aaron S. Kesselheim [a], Niteesh K. Choudhry [a], Jennifer M. Polinski [b], David Hutchins [b], Olga S. Matlin [b], Troyen A. Brennan [b], Jerry Avorn [a], William H. Shrank [b]

[a] Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[b] CVS Health, Woonsocket, RI, USA

Results: We identified 19,760 AED initiators who met study eligibility criteria; 18,306 (93%) initiated a generic AED. In the matched cohort, we observed 47 seizure-related hospitalizations and ER visits among brand-name initiators and 31 events among generic initiators, corresponding to a hazard ratio of 0.53 (95% confidence interval, 0.30 to 0.96). Similar results were observed for the secondary clinical endpoint and across sensitivity analyses. Mean time to first treatment gap was 124.2 days (standard deviation [sd], 125.8) for brand-name initiators and 137.9 (sd, 148.6) for generic initiators.

Significance: Patients who initiated generic AEDs had fewer adverse seizure-related clinical outcomes and longer continuous treatment periods before experiencing a gap than those who initiated brand-name versions.



clonazepam, gabapentin, oxcarbazepine, phenytoin, zonisamide

Gagne, Epilepsy & Behavior 2015

Converting Patients from Brand-Name Clozapine to Generic Clozapine

Terrie A Sajbel, Gary W Carter, and Roy B Wiley

Obiettivo: valutare ADR (agrabulocitosi), aumento delle dosi e perdita di efficacia a seguito del passaggio da brand a equivalente

Studio retrospettivo, 17 pazienti affetti da schizofrenia; periodo di osservazione 1 anno

Nessuna differenza nelle ADR (in particolare nelle reazini ematologiche); nessun soggetto ha sospeso l'equivalente per perdita di efficacia; nessun aumento del dosaggio.

Sajbel, Ann Pharmacother 2001

Abilify

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
PSUSA/234/201507	Periodic Safety Update EU Single assessment - ARIPIPRAZOLE	25/02/2016	21/04/2016	SmPC and PL	Please refer to Abilify - PSUSA/00000234/201507 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
X/0001	Addition of a new orodispersible form. Annex I_2.(d) Change or addition of a new pharmaceutical form	16/03/2005	20/06/2005	SmPC, Labelling and PL	The overall benefit/risk assessment for the orodispersible tablet was considered positive with an established bioequivalence between the tablet and orodispersible formulations. The orodispersible tablets may be used as an alternative to Abilify tablets for patients who have difficulty in swallowing tablets.
X/0004	Addition of a new oral solution form. X-3-iv_Change or addition of a new pharmaceutical form	27/07/2005	28/10/2005	SmPC, Annex II, Labelling and PL	The overall benefit/risk assessment for the oral solution was considered positive with an established bioequivalence between the tablet and oral solution formulation. The oral solution may be used as an alternative to Abilify tablets for patients who have difficulty in swallowing tablets.

http://www.ema.europa.eu/

Biosimilari

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

Review

The use of biosimilars in immune-mediated disease: A joint Italian Society of Rheumatology (SIR), Italian Society of Dermatology (SIDeMaST), and Italian Group of Inflammatory Bowel Disease (IG-IBD) position paper

Gionata Fiorino [a,*], Giampiero Girolomoni [b], Giovanni Lapadula [c], Ambrogio Orlando [d], Silvio Danese [a], Ignazio Olivieri [e,**], on behalf of SIR, SIDeMaST, and IG-IBD

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[c] Interdisciplinary Department of Medicine, University of Bari, Bari, Italy
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[e] Rheumatology Deparment of Lucania, San Carlo Hospital of Potenza and Madonna delle Grazie Hospital of Matera, Italy

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Available online 19 March 2014

ABSTRACT

Biological agents are widely used in rheumatology, dermatology and inflammatory bowel disease. Evidence about their efficacy and safety has been strengthened for all those therapeutic indications over the last decade. Biosimilar agents are monoclonal antibodies similar to previously approved biologics. In the European Union, they have been approved for all the indications in the management of immune-mediated inflammatory diseases (IMIDs), although data only in rheumatoid arthritis and ankylosing spondylitis are currently available. Direct evidence on efficacy, safety, and immunogenicity of biosimilars is mandatory in psoriasis, psoriatic arthritis, and inflammatory bowel disease, as well as in children. Based on the current evidence in the literature, we present the joint official position of the Italian Societies of Rheumatology, Dermatology and Inflammatory Bowel Disease on the use of biosimilars in IMIDs.

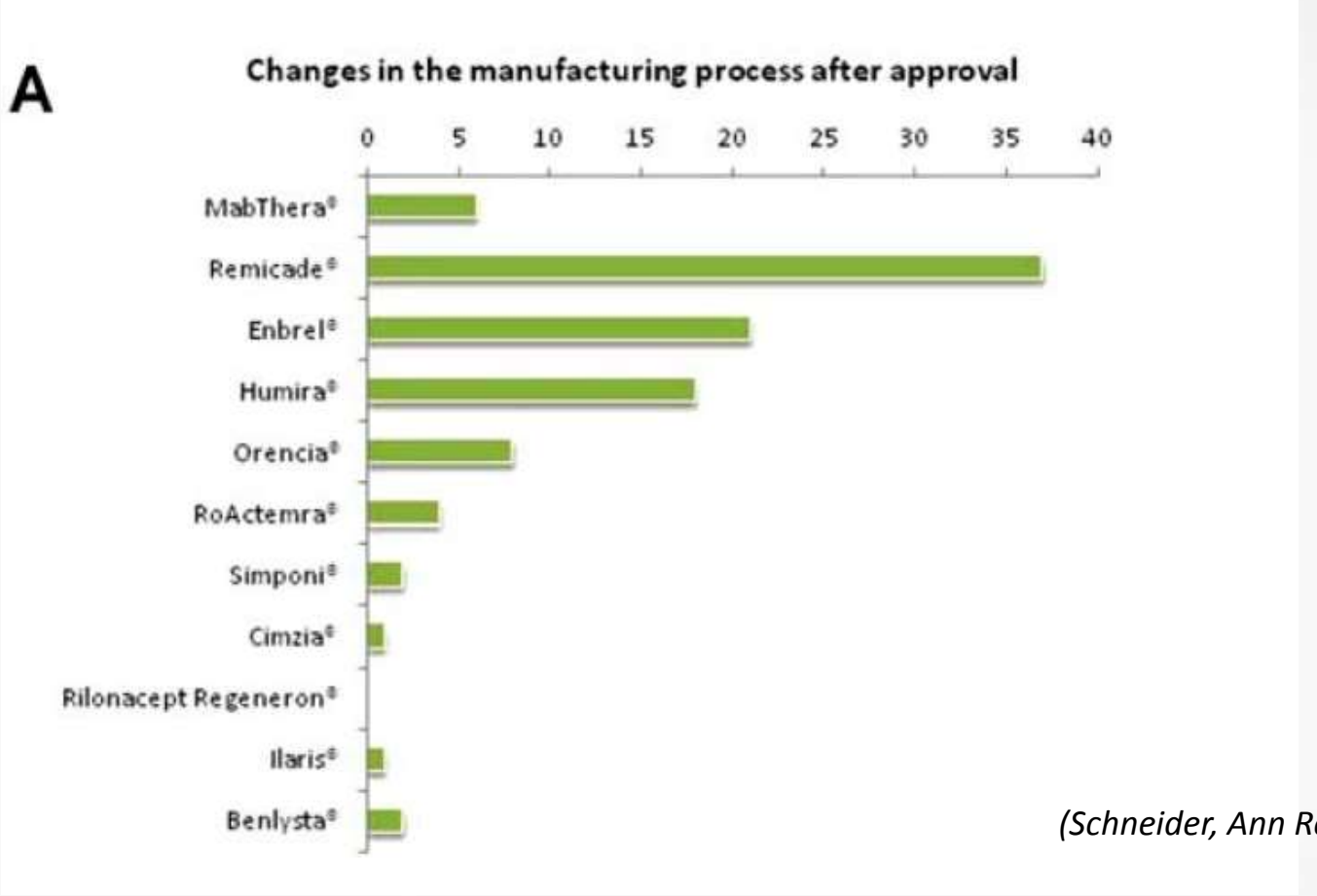
Take-home messages

- Biosimilar agents are monoclonal antibodies similar to previously approved biologics.
- Biosimilarity for monoclonal antibodies has been investigated only in rheumatoid arthritis and ankylosing spondylitis.
- EMA approved the use of biosimilars for all indications, including psoriasis and inflammatory bowel disease.
- Biosimilars still need to be tested for efficacy and safety by well-designed trials with an adequate sample size calculation, especially for psoriasis and inflammatory bowel diseases.
- Caution is recommended for extrapolation of data across indication, interchangeability and traceability.
- Post-marketing surveillance for safety and immunogenicity is strongly required.

Biosimilari: simili ma non identici…
…vale anche per gli originator?

Nella maggior parte dei casi non sono richiesti dati clinici aggiuntivi ai produttori a fronte delle evidenze fornite degli esercizi di comparabilità

(Weise, Blood 2014)



(Schneider, Ann Reum Dis 2013)

Analisi sistematica dei cambiamenti autorizzati da EMA per mAbs originator (documentati su 29 EPAR tra 1998 e settembre 2014): **404 cambiamenti produttivi di cui 22 ad alto rischio, 286 medio rischio, 96 basso rischio**

(Zrubka, Ann Reum Dis 2015)

Remicade (Infliximab)

Remicade

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
II/0149	Change in the manufacturing process of the finished product B.II.b.3.c - Change in the manufacturing process of the finished product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability	17/02/2011	01/03/2011		

(http://www.ema.europa.eu/)

Esempio di estrapolazione delle indicazioni nella comune pratica clinica

Trastuzumab (Herceptin)

I primi 30 principi attivi rappresentano il 47,6% della spesa e comprendono in prevalenza principi attivi che rientrano nella categoria degli antineoplastici. I primi tre principi attivi a maggiore spesa nei primi nove mesi del 2014, utilizzati in ambito ospedaliero, rimangono il trastuzumab (136,5 milioni di euro), il rituximab (105,1 milioni di euro) e il bevacizumab (97,7 milioni di euro)(Tabella 24).

Tabella 24. Primi 30 principi attivi in ordine decrescente di spesa regionale per medicinali erogati nell'ambito dell'assistenza farmaceutica ospedaliera ed ambulatoriale

	Principio attivo	ATC I	Classe	Spesa	Inc%	Cum%
1	Trastuzumab	L	H	136.536.825	6,8%	6,8%
2	Rituximab	L	H	105.084.830	5,2%	12,0%
3	Bevacizumab	L	H	97.734.466	4,8%	16,8%
4	Bortezomib	L	H	48.562.492	2,4%	19,2%
5	Ranibizumab	S	C/H	41.720.470	2,1%	21,3%

Carcinoma mammario metastatico

Herceptin è indicato per il trattamento di pazienti adulti con carcinoma mammario metastatico (MBC) HER2 positivo

Carcinoma mammario in fase iniziale

Herceptin è indicato nel trattamento di pazienti adulti con carcinoma mammario in fase iniziale (EBC) HER2 positivo

(Codifa 2015)

Trastuzumab (Herceptin): sottocute (2012)

Esercizio di comparabilità (analitica e clinica) richiesto per valutare efficacia e sicurezza della formulazione sc (**con maggior rischio immunogenicità**) e contenente ialuronidasi umana ricombinante (rHuPH20) per aumentare assorbimento dei farmaco.

Efficacia, sicurezza e immunogenicità: Studio randomizzato in aperto in pazienti con **carcinoma mammario NON metastatico**. 596 pazienti: 299 trastuzumab IV vs 297 trastuzumab SC. (Enpoint principale *surrogato*: pCR, *pathological complete response**).

Analisi a 20 mesi ritenute soddisfacenti per l'immissione in commercio nonostante la richiesta di **dati aggiuntivi a supporto di efficacia e sicurezza a 60 mesi**

Estrapolazione indicazione nei pazienti con **carcinoma mammario metastatico**

(EMA/CHMP/751770/2012/corr1)

* assenza di cellule neoplastiche invasive nel tessuto residuo dopo chirurgia e chemioterapia adiuvante

Darbepoetina (Aranesp)

Trattamento dell'anemia sintomatica associata all'insufficienza renale cronica (IRC) in adulti e in pazienti pediatrici

Trattamento dell'anemia sintomatica in pazienti adulti affetti da neoplasie non mieloidi che ricevono chemioterapia.

(Codifa 2015)

Esercizio di comparabilità (analitica e clinica) richiesto nel 2008 per valutare effetti del passaggio ad un più efficiente processo di produzione (darbepoetina alfa RB -> darbepoetina alfa HT)

(EMEA/H/C/332/X/0042)

Efficacia: Studio di mantenimento (28 settimane) in pazienti anemici con **IRC in emodialisi**. 446 pazienti in trattamento stabile con darbepoetina alfa RB randomizzati ai due trattamenti (222 vs 224). (Enpoint principale: variazioni conc. emoglobina)

Sicurezza: studio in aperto a braccio singolo (53 settimane) su 1.127 pazienti con anemia e IRC dializzati (567) e non in dialisi (560).

Immunogenicità: Nessun dato conclusivo da studio di efficacia (RCT vs darbepoetina RB, **maggior parte dei pazienti trattati per ev**). Dati disponibili solo per studio a braccio singolo (no dati di switch) presentati in maniera separata per soggetti trattati con formulazioni ev e sc.

Estrapolazione indicazione nei pazienti con anemia e affetti da neoplasie non mieloidi che ricevono chemioterapia

Risk Management Plan

(EMEA/H/C/332/X/0042)

Table 1. Summary of All Proposed Pharmacovigilance and Risk Minimization Measures

	Risk Assessment and Minimization Activities			
Safety Concern	Routine Risk Minimization and Communication	Post-marketing Safety Surveillance	Safety Monitoring in Ongoing and Future Clinical Studies	Studies Targeting Specific Concerns
Important Identified Risks				
Immunogenicity	X	X	X	
Thromboembolic and cardiovascular events	X	X	X	
Tumour progression and/or survival	X	X	X	X[a]
Important Potential Risks				
Lack or loss of response	X	X	X	
Product quality complaints associated with adverse events	X	X	X	
Important Missing (or Limited) Information				
Pregnant women	X	X		
Lactating women	X	X		
Paediatric patients	X	X	X	X
Geriatric patients	X	X	X	
Non-white patients	X	X	X	
Patients with hepatic, cardiac, or pulmonary impairment	X	X	X	
Patients with other indications	X	X	X	X[a]
Milestone of Risk Assessment and Minimization Activity	Update of prescribing information and IB	PSUR	CSRs; IB; periodic reports to regulatory agencies	CSRs; IB; DMB recommendations; periodic reports to regulatory agencies

[a] Included in separate RMP for tumour progression and survival in the oncology setting; not specific to darbepoetin alfa HT . CSR = clinical study report; DMB = data monitoring board; IB = Investigator Brochure; PSUR = Periodic Safety Update Report

(EMEA/H/C/332/X/0042)

Early release, published at www.cmaj.ca on October 13, 2015. Subject to revision.

Canada's approach to biosimilars questioned

Health Canada's regulatory approach to a new category of cost-saving drugs known as biosimilars has been halting and overly restrictive, according to generic drug-industry insiders at the recent International Generic and Biosimilar Medicines Association conference. So far, Health Canada — which in 2012 became one of seven World Health Organization (WHO) collaborating centres for biosimilar regulation — has approved four biosimilar drugs; 19 are approved and widely used in Europe. (Health Canada refers to biosimilars as subsequent entry biologics.)

Biosimilars are near-exact copies of biologic drugs, but are produced through slightly different manufacturing processes that allow companies to bypass patent protections. Biologic drugs, which are derived from biological processes, are expensive to develop; treatment for a single patient ranges from $25 000 to $100 000 annually. But biosimilars sold in Europe are 10%–35% less expensive.

Those cost savings could be crucial as sales of biologic drugs in Europe are expected to swell from US$13 billion in 2014 to US$23 billion by 2019. In the United States, biologic drugs already account for about US$82 billion, or 22% of annual drug spending, according to IMS Health. The Cana-

aponares/iStock

Inflectra, a biosimilar that costs 25% less than the biologic drug, is widely used in Europe for inflammatory bowel disease. Health Canada prohibits this use.

in encouraging clinicians and patients to use biosimilars instead of biologics.

Though Europe is using biosimilars to cut the cost of biologics, both the US Food and Drug Administration (FDA) and Health Canada are still developing policies in the face of resistance and lawsuits from brand-name drug makers, said Jeff Watson, president of global generics at Toronto-based Apotex, which has

Biosimilars "are new drugs that are not declared to be pharmaceutically or therapeutically equivalent with their reference products, and this should inform decisions regarding interchangeability and substitutability," says the guidance statement. "The authority to declare two products automatically substitutable by a pharmacist does not rest with the federal government."

Annals of Internal Medicine

REVIEW

Bioequivalence of Biosimilar Tumor Necrosis Factor-α Inhibitors Compared With Their Reference Biologics

A Systematic Review

Francine Chingcuanco, MHS; Jodi B. Segal, MD, MPH; Seoyoung C. Kim, MD, ScD, MSCE; and G. Caleb Alexander, MD

Background: Biosimilars are of growing clinical, regulatory, and commercial importance.

Purpose: To summarize evidence about the bioequivalence between biosimilar and reference tumor necrosis factor-α (TNF-α) inhibitors.

Data Sources: PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and LILACS from inception through 13 April 2016 and ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, EU Clinical Trials Register, U.S. Food and Drug Administration, and European Medicines Agency from inception through 30 April 2016.

Study Selection: Published English-language studies of any size or design that compared the pharmacokinetics, clinical efficacy, adverse events, or immunogenicity of a biosimilar TNF-α inhibitor with a reference biologic in humans.

Data Extraction: Two reviewers independently screened titles and abstracts, extracted data from selected studies, and assessed study quality.

Data Synthesis: Of 19 eligible studies, 8 were phase 1 randomized trials, 5 were phase 3 randomized trials, and 6 were observational studies. Most phase 1 trials ($n = 7$) involved healthy volunteers, phase 3 trials involved patients with rheumatoid arthritis, and observational studies involved those with rheumatoid arthritis or inflammatory bowel disease. All phase 1 trials showed that pharmacokinetic parameters of the biosimilar and respective biologic were within the prespecified equivalence margin of 80% to 125%. Phase 3 trials suggested similar clinical responses and adverse events. Adverse events were usually of mild to moderate severity. Two cross-sectional observational studies showed cross-reactivity between products, whereas 4 cohort studies of patients switched from reference to biosimilar products suggested similar efficacy and safety outcomes.

Limitation: Possible publication bias, small sample sizes of many studies, and lack of published studies for several biosimilars.

Conclusion: Preliminary evidence supports the biosimilarity and interchangeability of biosimilar and reference TNF-α inhibitors.

Primary Funding Source: Johns Hopkins Center of Excellence in Regulatory Science and Innovation. (PROSPERO: CRD42015025262)

Ann Intern Med. doi:10.7326/M16-0428 **www.annals.org**

For author affiliations, see end of text.

This article was published at www.annals.org on 2 August 2016.

Are biosimilars interchangeable?

Finnish Medicines Agency Fimea has presented its position towards interchangeability of biosimilars licensed in the European Union. The position is a recommendation to the local health care system.

It has been argued that a switch from an original biological medicinal product (reference product) to its biosimilar copy is risky. The recommendation of Fimea concludes that

- switches between biological products are common and usually not problematic, e.g. in the context of hospital tendering processes,
- for time being, there is no evidence for adverse effects due to the switch from a reference product to a biosimilar,
- the theoretical basis of such adverse effects is weak,
- risk of adverse effects can be expected to be similar to the risk associated with changes in the manufacturing process of any biological product, and
- automatic substitution at the pharmacy level is not within the scope of this recommendation.

http://www.fimea.fi/web/en/-/are-biosimilars-interchangeable-

Banca dati appropriatezza prescrittiva (INTERCheck)

Fervid Trimble, age 86, enjoying her apartment in a senior's residence she'd chosen for herself

Moynihan, BMJ 2011

A visible difference in Fervid during & after over-medication

Moynihan, BMJ 2011

Epidemiologia delle reazioni avverse da farmaco

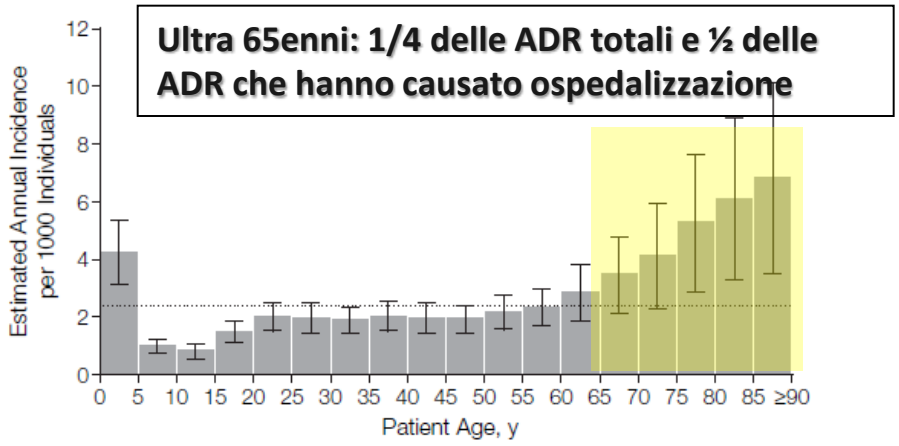
Rappresentano la 4° - 6° causa di morte negli Stati Uniti. Numero di morti/anno ≈ 106.000

Biennio 2004-2005 negli USA 700mila pazienti/anno si sono recati al pronto soccorso a causa di una ADR e circa 1/6 sono stati ricoverati.

Rischio è superiore negli anziani:

- 2 volte per le visite al PS
- 7 volte per ricovero

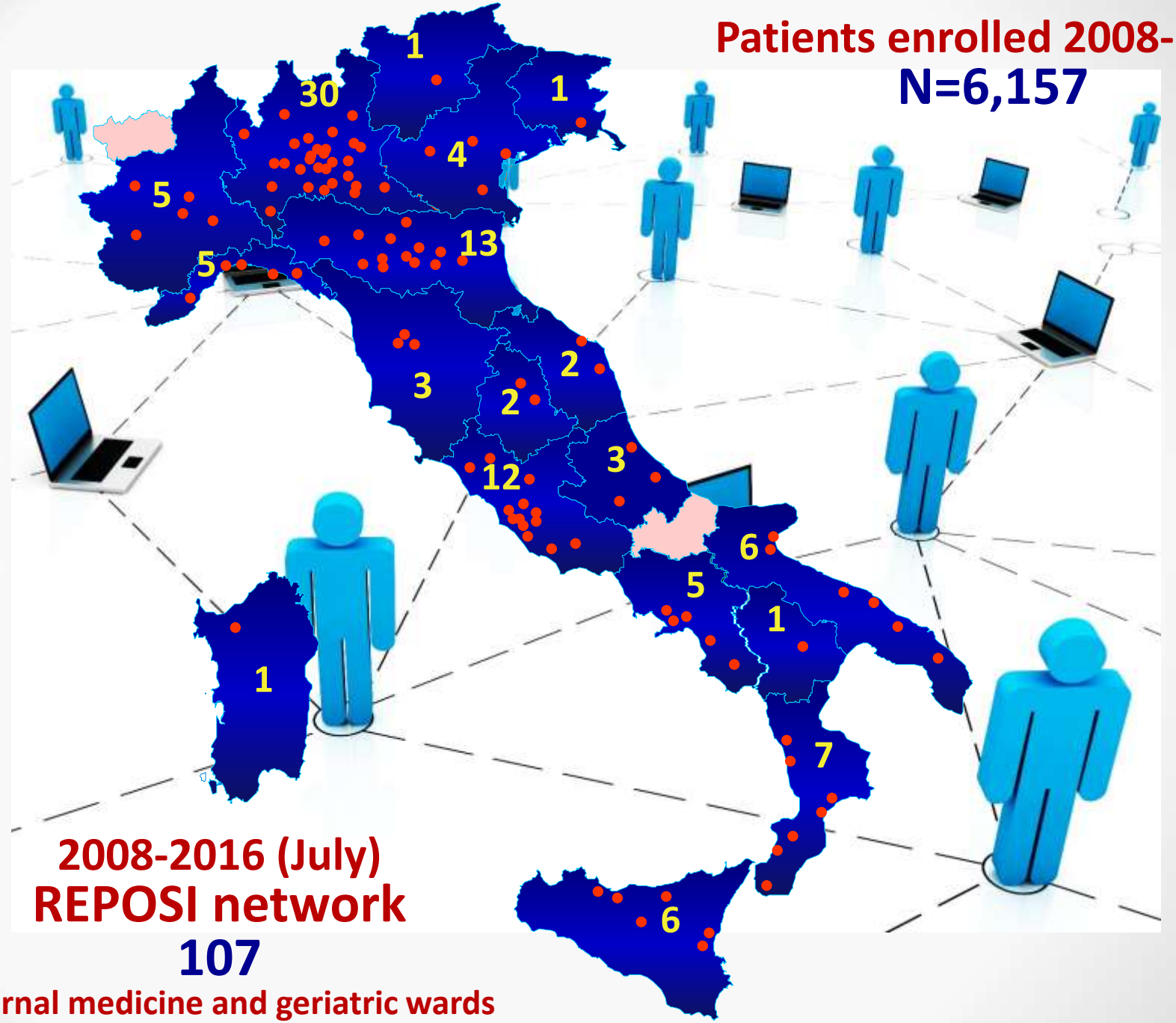
Figure. Estimated Annual Incidence of Adverse Drug Events Treated in US Emergency Departments



The estimated annual population rate of adverse drug events (dotted line) is 2.4 per 1000 (95% confidence interval, 1.7-3.0). Error bars represent 95% confidence intervals. Data are from the 2004-2005 National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project.

Budnitz, JAMA 2006

1. Farmaci non appropriati
   - assenza di indicazione
   - potenzialmente inappropriati nel'anziano


Patients enrolled 2008-2
N=6,157
1
30
1
4
5
13
5
3
2
2
12
3
6
5
1
1
7
6
2008-2016 (July)
REPOSI network
107
internal medicine and geriatric wards

Overprescribing proton pump inhibitors

Is expensive and not evidence based

1. Frequente uso inappropriato: 25%-80% pazienti in trattamento con PPI senza un'indicazione appropriata

2. Frequente uso in condizioni che non richiedono una gastroprotezione (es. profilassi sanguinamenti in soggetti a basso rischio; profilassi in corso di trattamento con bifosfonati)

3. Rapporto Osmed 2014: seconda classe di farmaci per consumo e spesa. Inappropriati in quasi il 50% dei casi

REPOSI

- ***Inibitori della pompa protonica:*** *prescritti 40% soggetti ricoverati e 56% dimessi. Uso inappropriato in oltre 60% dei casi.*
- *Prescrizione inappropriata associata al crescente numero di farmaci.*

Pasina, Eur J Intern Med 2011

Comparison of Published Explicit Criteria for Potentially Inappropriate Medications in Older Adults

Chirn-Bin Chang[1,2] and *Ding-Cheng Chan*[2]

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.[23]	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 (%)[a]							
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.

Organ System, Therapeutic Category, Drugs	Rationale	
Non-cyclooxygenase-selective NSAIDs, oral: Aspirin >325 mg/d Diclofenac Diflunisal Etodolac Fenoprofen Ibuprofen Ketoprofen Meclofenamate Mefenamic acid Meloxicam Nabumetone Naproxen Oxaprozin Piroxicam Sulindac Tolmetin	Increased risk of gastrointestinal bleeding or peptic ulcer disease in high-risk groups, including those aged >75 or taking oral or parenteral corticosteroids, anticoagulants, or antiplatelet agents; use of proton-pump inhibitor or misoprostol reduces but does not eliminate risk. Upper gastrointestinal ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3–6 months and in ~2–4% of patients treated for 1 year; these trends continue with longer duration of use	Avoid chro alternative can take g pump inhi
Indomethacin	Indomethacin is more likely than other NSAIDs to have adverse CNS effects. Of all the NSAIDs, indomethacin has the most adverse effects.	Avoid
Ketorolac, includes parenteral	Increased risk of gastrointestinal bleeding, peptic ulcer disease, and acute kidney injury in older adults	
Pentazocine	Opioid analgesic that causes CNS adverse	Avoid

2. Farmaci ad alto rischio di effetti indesiderati gravi

Farmaci a maggior rischio di ospedalizzazione

Table 4. National Estimates of Medications Commonly Implicated in Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, 2007–2009.*

Medication	Annual National Estimate of Hospitalizations (N=99,628)		Proportion of Emergency Department Visits Resulting in Hospitalization
	no.	*% (95% CI)*	%
Most commonly implicated medications†			
Warfarin	33,171	33.3 (28.0–38.5)	46.2
Insulins	13,854	13.9 (9.8–18.0)	40.6
Oral antiplatelet agents	13,263‡	13.3 (7.5–19.1)	41.5
Oral hypoglycemic agents	10,656	10.7 (8.1–13.3)	51.8
Opioid analgesics	4,778	4.8 (3.5–6.1)	32.4
Antibiotics	4,205	4.2 (2.9–5.5)	18.3
Digoxin	3,465	3.5 (1.9–5.0)	80.5
Antineoplastic agents	3,329‡	3.3 (0.9–5.8)‡	51.5
Antiadrenergic agents	2,899	2.9 (2.1–3.7)	35.7
Renin–angiotensin inhibitors	2,870	2.9 (1.7–4.1)	32.6
Sedative or hypnotic agents	2,469	2.5 (1.6–3.3)	35.2
Anticonvulsants	1,653	1.7 (0.9–2.4)	40.0
Diuretics	1,071‡	1.1 (0.4–1.8)‡	42.4
High-risk or potentially inappropriate medications§			
HEDIS high-risk medications	1,207	1.2 (0.7–1.7)	20.7
Beers-criteria potentially inappropriate medications	6,607	6.6 (4.4–8.9)	42.0
Beers-criteria potentially inappropriate medications, excluding digoxin	3,170	3.2 (2.3–4.1)	27.6

≈ 70% ospedalizzazioni per ADR

Budnitz, NEJM 2011

3. Interazioni tra farmaci

Drug-disease and drug-drug interactions: systematic examination of recommendations in 12 UK national clinical guidelines

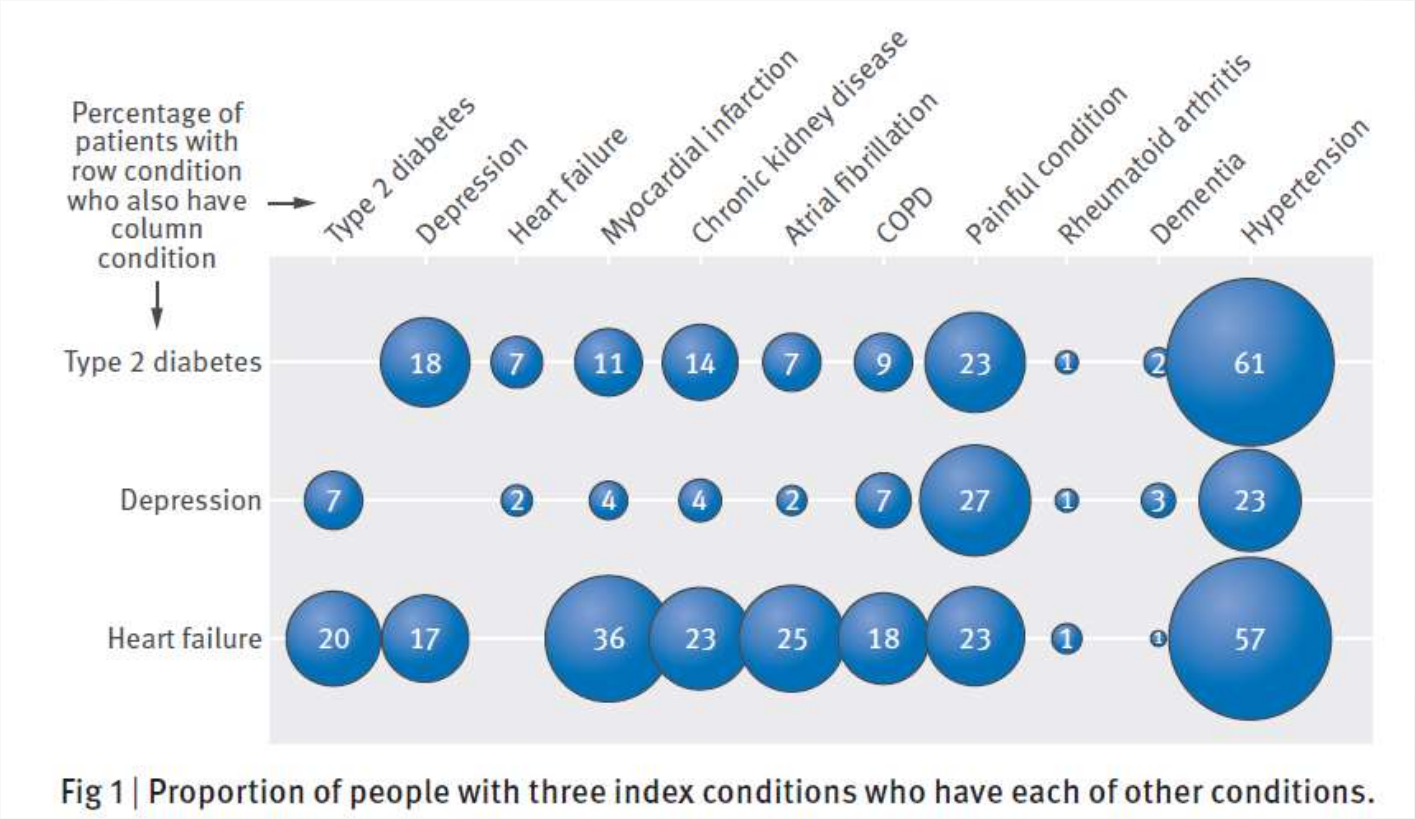


Fig 1 | Proportion of people with three index conditions who have each of other conditions.

Poche DDIs segnalate nelle linee guida (es. nessuna in quelle dello scompenso). Circa 20% DDIs gravi associate a farmaci di prima linea. Escluse le terapie acute (antibiotici, FANS)

Dumbreck, BMJ 2015

Drug-Drug Interactions Among Elderly Patients Hospitalized for Drug Toxicity

JAMA. 2003;289:1652-1658

Obiettivo:

Valutare se il ricovero di pazienti anziani (>65 anni) per tossicità da farmaci fosse associato **all'assunzione nella settimana precedente di farmaci a rischio di interazioni**

Caso controllo condotto in Canada tra gennaio 1994 e dicembre 2000

3 possibili interazioni:

a. Gliburide: rischio **ipoglicemia** in associazione a farmaci inibitori CYP 2C9 (Cotrimossazolo)
b. Digossina: **tossicità** indotta da farmaci inibitori della PgP (Claritromicina)
c. Ace inibitori: **iperpotassiemmia** con diuretici risparmiatori K

Table 3. Association Between Hospital Admission for Hypoglycemia and Use of Co-trimoxazole in Patients Receiving Glyburide

	No. (%) Exposed			
	Cases (n = 909)	Controls (n = 43 766)	Univariate Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
	Hospitalization Within 1 Week of Exposure to Second Drug			
Co-trimoxazole	35 (3.9)	189 (0.4)	8.5 (5.8-12.4)	6.6 (4.5-9.7)
Amoxicillin†	10 (1.1)	246 (0.6)	1.8 (1.0-3.5)	1.5 (0.8-2.9)

Gliburide + Cotrimossazolo aumenta di **7 volte** il rischio di ospedalizzazione per **ipoglicemia**

Table 4. Association Between Hospital Admission for Digoxin Toxicity and Use of Clarithromycin in Patients Receiving Digoxin

	No. (%) Exposed			
	Cases (n = 1051)	Controls (n = 51 896)	Univariate Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)
	Hospitalization Within 1 Week of Exposure to Second Drug			
Clarithromycin	27 (2.6)	101 (0.2)	13.6 (8.8-20.8)	11.7 (7.5-18.2)
Cefuroxime†	3 (0.3)	68 (0.1)	2.0 (0.6-6.4)	1.3 (0.4-4.1)

Digossina+ Claritromicina aumenta di **12 volte** il rischio di ospedalizzazione per **tossicità da digossina**

Table 5. Association Between Hospital Admission for Hyperkalemia and Use of Potassium-Sparing Diuretics* in Patients Receiving Angiotensin-Converting Enzyme Inhibitors

	No. (%) Exposed			
	Cases (n = 523)	Controls (n = 25 807)	Univariate Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)†
	Hospitalization Within 1 Week of Exposure to Second Drug			
K^+-sparing diuretics	43 (8.2)	87 (0.3)	27.2 (18.6-39.9)	20.3 (13.4-30.7)
Indapamide‡	3 (0.6)	117 (0.4)	1.3 (0.4-4.0)	2.6 (0.8-8.5)

ACE-I + Diuretico risparmiatore di K aumenta di **20 volte** il rischio di ospedalizzazione per **iperpotassiemia**

Risultati dello studio evidenziano che molte ospedalizzazioni sono avvenute dopo la somministrazione di farmaci di cui era già NOTO il rischio di interazione. **Evitabili con più stretto monitoraggio o con farmaci alternativi**

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

Ospedalizzazione è associata ad un aumento dei pazienti esposti al rischio di interazioni totali (61-> 69%) e potenzialmente gravi (19 -> 24%)

Table 2. Prevalence of the first 10 potentially severe drug–drug interactions (DDIs) at hospital admission and discharge among patients with at least one potentially severe DDI

Drug combination	Potential adverse events	Patients (*n* (%))	
		At admission (512)	At discharge (561)
Digoxin + furosemide	Increased risk of digoxin toxicity	149 (29.1)	147 (26.2)
Potassium-sparing diuretics + ACEi	Increased risk of hyperkalemia	78 (15.2)	74 (13.2)
Aspirin (low dose) + clopidogrel or ticlopidine	Increased risk of bleeding	51 (10.0)	43 (7.7)
Statin* + calcium antagonist†	Increased risk of myopathy including rhabdomyolysis	44 (8.6)	40 (7.1)
Amiodarone + beta-blocker	Hypotension, bradycardia, or cardiac arrest	35 (6.8)	33 (5.9)
Digoxin + spironolactone	Increased risk of digoxin toxicity	27 (5.3)	34 (6.1)
Clopidogrel + proton pump inhibitor‡	Reduction in clinical efficacy of clopidogrel and increased risk for thrombosis	27 (5.3)	40 (7.1)
Allopurinol + enalapril	Hypersensitivity reactions (Stevens–Johnson syndrome and skin eruptions)	23 (4.5)	26 (4.6)
Simvastatin + amiodarone	Increased risk of myopathy including rhabdomyolysis	12 (2.3)	9 (1.6)
Digoxin + hydrochlorothiazide	Increased risk of digoxin toxicity	11 (2.1)	6 (1.1)
Potassium + potassium-sparing diuretics	Increased risk hyperkalemia	6 (1.2)	16 (2.9)

ACEi = angiotensin-converting enzymes inhibitors.
*Statin: simvastatin and atorvastatin.
†Calcium antagonist: amlodipine, verapamil, or diltiazem.
‡Excluding pantoprazole.

n=2.712
Age = 79
Drugs = 5.0

Pasina, Pharmacoepidemiology and Drug Safety 2013

4. Numero di farmaci

- scarsa aderenza
- poca conoscenza indicazioni

Aderenza negli RCT

"I farmaci non funzionano nei pazienti che non li assumono" (Everett Koop)

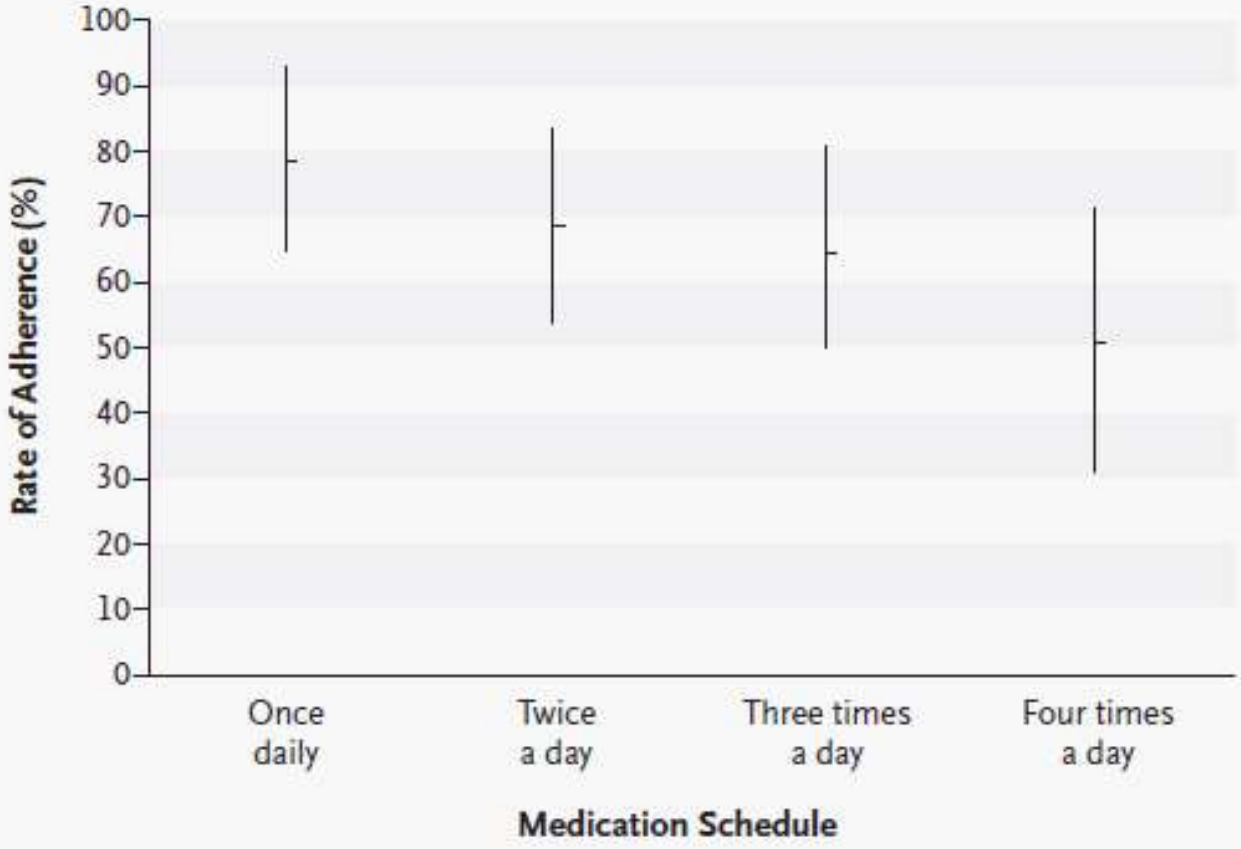


Figure 1. Adherence to Medication According to Frequency of Doses.
Vertical lines represent 1 SD on either side of the mean rate of adherence (horizontal bars). Data are from Claxton et al.[7]

Osterberg, NEJM 2005

Aderenza in contesto reale

Medication Non-Adherence Among Elderly Patients Newly Discharged and Receiving Polypharmacy

Table 2 Medication adherence and knowledge of indication for drugs

Variable	First follow-up [*n* (%)]		Second follow-up [*n* (%)]	
	Patients	Drugs	Patients	Drugs
Medication adherence				
Regular adherence	40 (45)	708 (88)	24 (30)	562 (78)
Medication non-adherence[a]	49 (55)	96 (12)	55 (70)	157 (22)
Drug withdrawn	26 (29)	51 (6)	40 (50)	97 (13)
Change of dosage	20 (22)	21 (3)	27 (34)	34 (5)
Replaced with another drug	16 (18)	16 (2)	15 (19)	16 (2)
Non-adherence not classified[b]	8 (9)	8 (0)	10	10 (1)
Total	89	804	79	719
Indication for drugs[c]				
Understood	25 (28)	479 (69)	20 (25)	413 (76)
Wrong	28 (31)	32 (5)	21 (27)	27 (5)
Not known	50 (56)	161 (23)	33 (42)	88 (16)
Not reported	n/a	19 (3)	n/a	14 (3)
Total	89	691	79	542

n/a not applicable

[a] Patients were considered non-adherent in the case of non-adherence to at least one drug, and each patient could give more than one reason for non-adherence

[b] Patients did not remember or could not explain the reason for non-adherence

[c] Excluding drugs withdrawn or replaced. All patients reported the indication for at least one drug

Pasina, Drugs Aging 2014

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

INTERCheck WEB

DONA ORA

Drugs Aging. 2013;30(10):821-8

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UTENTI ATTIVI: 608

CONTATTI

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STRUMENTO PER LA VALUTAZIONE DELL'APPROPRIATEZZA PRESCRITTIVA.

INTERCheck è stato realizzato con l'obiettivo di migliorare l'appropriatezza prescrittiva nel paziente anziano attraverso un approccio di valutazione delle terapie che tiene in considerazione diversi aspetti della farmacologia geriatrica:

a. Interazioni tra farmaci (database delle interazioni realizzato ed aggiornato dall'IRCCS - Istituto di Ricerche Farmacologiche Mario Negri).
b. Farmaci potenzialmente inappropriati nell'anziano secondo differenti criteri delle letteratura scientifica (Beers; START/STOPP).
c. Valutazione del carico anticolinergico (Anticholinergic Cognitive Burden scale).
d. Modalità di sospensione dei farmaci che necessitano riduzione graduale delle dosi.
e. Dosaggio dei farmaci in soggetti con alterata funzionalità renale.
f. GerontoNet ADR Risk Score, per l'identificazione dei pazienti a maggior rischio di effetti indesiderati da farmaco.

ISCRIZIONE AL SERVIZIO.

INTERCheck WEB è fornito gratuitamente dall'IRCCS - Istituto di Ricerche Farmacologiche Mario Negri a tutti i medici e farmacisti che ne richiedono l'utilizzo. Per procedere all'iscrizione è necessario inviare una mail a intercheckweb@marionegri.it indicando il proprio nominativo, la professione svolta e il centro di appartenenza.

Eventuali donazioni saranno impiegate per sostenere la ricerca dell'Istituto, consentendo inoltre di mantenere aggiornato e attivo il sistema.

SOSTIENI LA RICERCA

L'Istituto Mario Negri studia le cause e le possibili terapie delle malattie e da 50 anni lavora per la difesa della salute e della vita umana.

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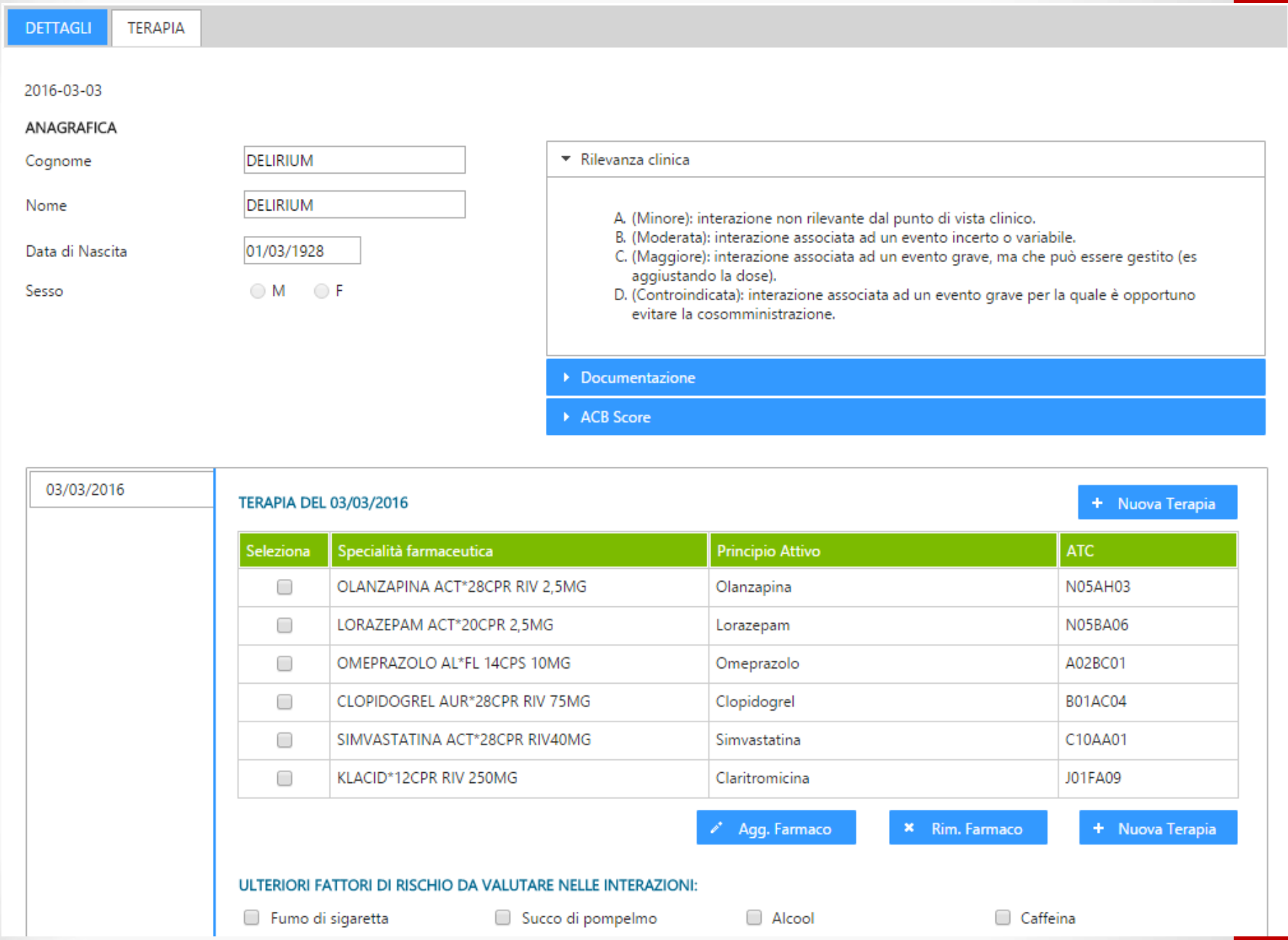
SCARICA LA APP


DETTAGLI
TERAPIA
2016-03-03
ANAGRAFICA
Cognome
DELIRIUM
Nome
DELIRIUM
Data di Nascita
01/03/1928
Sesso
M
F
Rilevanza clinica
A. (Minore): interazione non rilevante dal punto di vista clinico.
B. (Moderata): interazione associata ad un evento incerto o variabile.
C. (Maggiore): interazione associata ad un evento grave, ma che può essere gestito (es aggiustando la dose).
D. (Controindicata): interazione associata ad un evento grave per la quale è opportuno evitare la cosomministrazione.
Documentazione
ACB Score
03/03/2016
TERAPIA DEL 03/03/2016
Nuova Terapia
Seleziona
Specialità farmaceutica
Principio Attivo
ATC
OLANZAPINA ACT*28CPR RIV 2,5MG
Olanzapina
N05AH03
LORAZEPAM ACT*20CPR 2,5MG
Lorazepam
N05BA06
OMEPRAZOLO AL*FL 14CPS 10MG
Omeprazolo
A02BC01
CLOPIDOGREL AUR*28CPR RIV 75MG
Clopidogrel
B01AC04
SIMVASTATINA ACT*28CPR RIV40MG
Simvastatina
C10AA01
KLACID*12CPR RIV 250MG
Claritromicina
J01FA09
Agg. Farmaco
Rim. Farmaco
Nuova Terapia
ULTERIORI FATTORI DI RISCHIO DA VALUTARE NELLE INTERAZIONI:
Fumo di sigaretta
Succo di pompelmo
Alcool
Caffeina

Raccomandazione criteri Beers - STOPP

Interazioni | Criteri BEERS | Criteri START | Criteri STOPP | Criteri AIFA | Modalità di Sospensione | Indicazione sul dosaggio | ACB Score

NOTE DI APPROPRIATEZZA SECONDO I CRITERI DI BEERS

Principio Attivo	Razionale Inappropriatezza	Raccomandazione	Stampa
Digossina	• Fibrillazione atriale: non dovrebbe essere usata come farmaco di prima linea, perché esistono alternative più efficaci e può essere associata ad un incremento di mortalità. • Scompenso cardiaco: i benefici sul rischio di ospedalizzazione sono discutibili e potrebbe essere associata ad un incremento della mortalità negli anziani. L'aumento delle dosi non comporta benefici aggiuntivi e potrebbe aumentare il rischio di tossicità. • La riduzione della clearance renale nell'anziano può portare ad un aumento del rischio di effetti tossici; potrebbe essere necessario un ulteriore diminuzione della dose in pazienti con insufficienza renale cronica (stadio 4 o 5).	L'uso dovrebbe essere evitato come terapia di prima linea per la fibrillazione atriale e per lo scompenso cardiaco. Se usata per la fibrillazione atriale o per lo scompenso cardiaco, evitare dosaggi > 0.125 mg/d.	☑
Glibenclamide Metformina	Ha il rischio più alto di grave e prolungata ipoglicemia nell'anziano.	L'uso dovrebbe essere evitato.	☑
Lorazepam	Gli anziani hanno un'aumentata sensibilità alle benzodiazepine e il metabolismo di quelle a lunga durata d'azione è un più lento. In generale negli anziani tutte le benzodiazepine aumentano il rischio di compromissione delle capacità cognitive, delirium, cadute, fratture e incidenti stradali. Quelle a lunga emivita (come ad esempio diazepam, flurazepam, flunitrazepam o, clonazepam) possono essere appropriate nelle seguenti condizioni: convulsioni,	L'uso dovrebbe essere evitato.	☑

Interazioni

Interazioni | Criteri BEERS | Criteri START | Criteri STOPP | Criteri AIFA | Modalità di Sospensione | Indicazione sul dosaggio | ACB Score

ATTENZIONE: LE INTERAZIONI SONO STATE FILTRATE: LIVELLO MINORE **A**

OLANZAPINA

Principio Interagente	Rilevanza clinica (Documentazione)	Possibili effetti	Meccanismo	Comportamento clinico	Ulteriori Problematiche	Stampa
Claritromicina	D (2)	Aumento del rischio di cardiotossicità (prolungamento dell'intervallo QT, torsione di punta, arresto cardiaco).	Effetto additivo sul prolungamento dell'intervallo QT.	La cosomministrazione dovrebbe essere evitata; in caso contrario può essere opportuno effettuare controlli periodici dell'elettrocardiogramma (soprattutto prima e durante le prime fasi di trattamento).	Considerare la presenza di ulteriori fattori di rischio per il prolungamento dell'intervallo QT cardiaco, quali: età avanzata, elevati dosaggi di farmaco, sesso femminile, scompensi elettrolitici (bassi livelli ematici K, Ca, Mg), presenza di patologie cardiache (ipertrofia cardiaca, insufficienza cardiaca, cardiomiopatie, bradicardia, fibrillazione atriale) e sindrome congenita del QT lungo.	☑

SIMVASTATINA

Principio Interagente	Rilevanza clinica (Documentazione)	Possibili effetti	Meccanismo	Comportamento clinico	Ulteriori Problematiche	Stampa
Claritromicina	C (4)	Aumento dell'esposizione alla statina e del rischio di miopatia o rabdomiolisi (dolore, debolezza, rigidità muscolare).	Inibizione del metabolismo della statina (mediato dal citocromo P450 3A4 con il contributo di 2C8) causata da claritromicina (potente inibitore di 3A4).	Monitorare l'insorgenza di sintomi muscolari e i livelli di creatinchinasi; sospendere immediatamente la statina all'apparire dei primi sintomi muscolari; può essere opportuno sospendere momentaneamente la statina durante il periodo di cosomministrazione.		☑

Modalità di sospensione

Interazioni | Criteri BEERS | Criteri START | Criteri STOPP | Criteri AIFA | Modalità di Sospensione | Indicazione sul dosaggio | ACB Score

Principio Attivo	Classe	Indicazioni per la sospensione	Possibili sintomi da sospensione
Lorazepam	Benzodiazepine	La dose deve essere diminuita gradualmente, riducendola ad esempio di 1/8 ogni due settimane. La sospensione nei pazienti che assumono il farmaco da lungo tempo deve avvenire molto lentamente (nell'arco ad esempio di 6 mesi). Se insorgono sintomi da sospensione mantenere la dose corrente fino a quando i sintomi scompaiono e poi continuare a diminuire il dosaggio, procedendo ad un ritmo più lento. Metodo di sospensione alternativo. 1. Passare all'assunzione di una dose giornaliera equivalente di diazepam, preferibilmente assunto di notte. 2. Ridurre la dose di diazepam ogni due o tre settimane di 2 o 2.5 mg. 3. Continuare a ridurre la dose, se necessario di piccole quantità. E' preferibile ridurla molto lentamente. 4. Il periodo di sospensione può variare da circa quattro settimane a più di un anno.	L'interruzione improvvisa può causare ansia, cambiamenti di umore, insonnia, palpitazioni, tremore, mal di testa, disturbi gastrointestinali, rigidità e spasmi muscolari.
Omeprazolo	Inibitori della pompa protonica	Dimezzare la dose nell'arco di 4-8 settimane (considerare l'assunzione a giorni alterni se non è possibile dividere le compresse) poi interrompere l'assunzione. Considerare il passaggio agli anti-H_2 se è richiesta una più graduale diminuzione del farmaco.	L'interruzione improvvisa può causare ipersecrezione acida da rebound, che può causare dispepsia. Valutare la possibilità di un antiacido per gestire la dispepsia.

Carico anticolinergico

Interazioni | Criteri BEERS | Criteri START | Criteri STOPP | Criteri AIFA | Modalità di Sospensione | Indicazione sul dosaggio | ACB Score

ACB Score (Anticholinergic Cognitive Burden): **6**

ATTENZIONE: I farmaci con effetti anticolinergici possono indurre nel soggetto anziano effetti indesiderati a carico del sistema nervoso centrale (deficit cognitivo, confusione mentale, stato confusionale acuto e demenza). Un punteggio totale all'ACB Score uguale superiore a 5 è associato ad rischio clinicamente rilevante di manifestare deficit cognitivo farmaco indotto e riduzione dell'autonomia funzionale.

Principio Attivo	ACB Score
Quetiapina	3
Aloperidolo	1
Digossina	1
Ranitidina	1

Fonte: Boustani M et al. Impact of anticholinergics on the aging brain: a review and practical application. Aging Health 2008;4(3):311-320

Modalità di sospensione

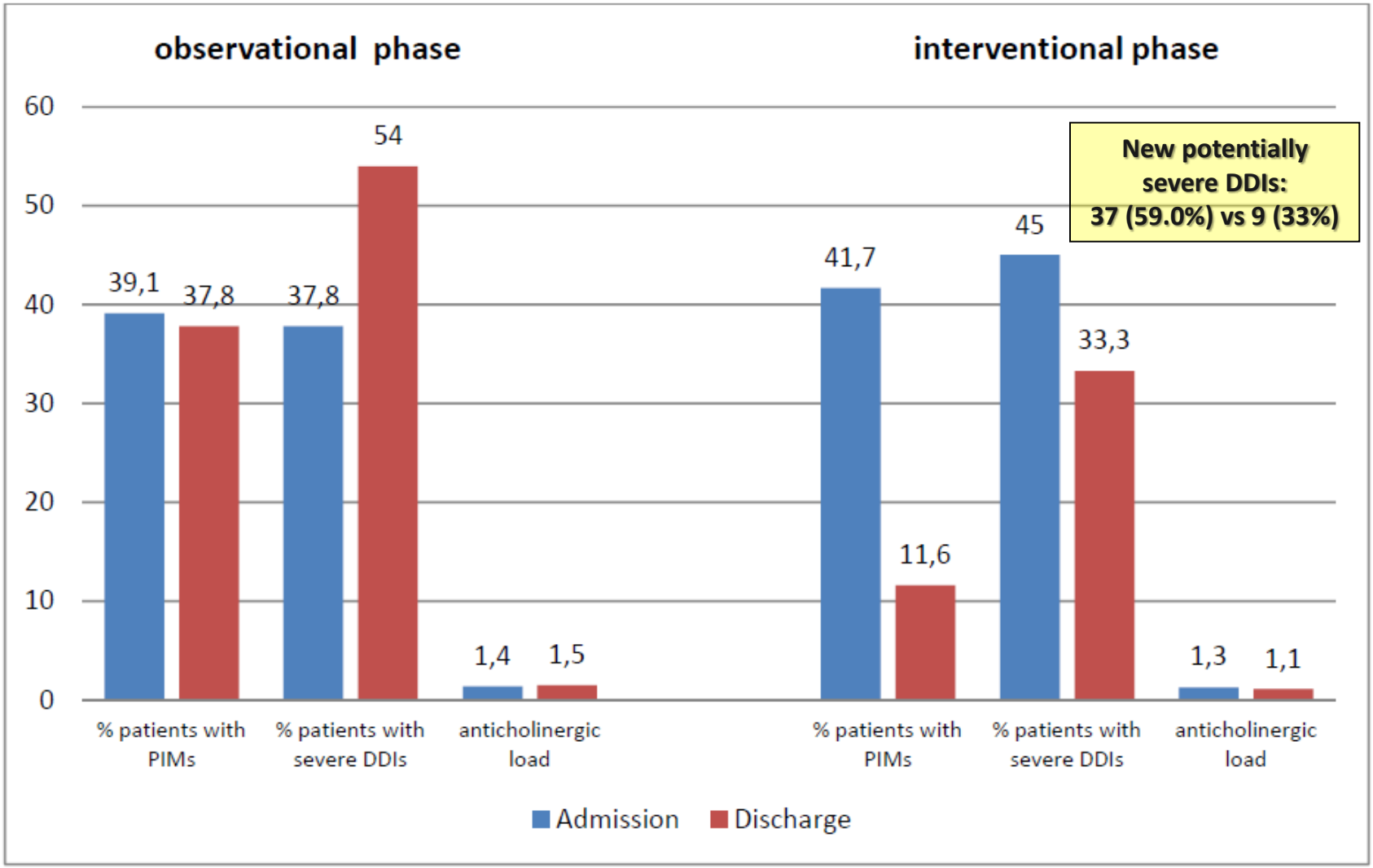
Interazioni | Criteri BEERS | Criteri START | Criteri STOPP | Criteri AIFA | Modalità di Sospensione | Indicazione sul dosaggio | ACB Score

INDICAZIONE SULL'USO DEGLI ANTIPERTENSIVI			
Classe		**Indicazioni per la sospensione**	**Possibili sintomi da sospensione**
Antipertensivi		La maggior parte dei farmaci antipertensivi dovrebbe essere sospesa gradualmente, riducendo la dose a intervalli approssimativamente mensili e poi ad intervalli di 3-6 mesi.	Un'ampia gamma di sintomi che dipendono dal farmaco specifico e della condizione da trattare. Possono includere edema alle caviglie, aumento di peso, aumento della pressione arteriosa, peggioramento dell'insufficienza cardiaca o angina, infarto del miocardio.
Principio Attivo	**Classe**	**Indicazioni per la sospensione**	**Possibili sintomi da sospensione**
Enalapril	ACE-inibitori	Considerare una graduale riduzione della dose.	Possibile esacerbazione di malattie sottostanti.
Spironolattone Idroclorotiazide	Tiazidi	Considerare inizialmente la somministrazione della medesima dose a giorni alterni e poi 2 volte alla settimana.	Possibile esacerbazione di malattie sottostanti.
Principio Attivo	**Classe**	**Indicazioni per la sospensione**	**Possibili sintomi da sospensione**
Lorazepam	Benzodiazepine	La dose deve essere diminuita gradualmente, riducendola ad esempio di 1/8 ogni due settimane. La sospensione nei pazienti che assumono il farmaco da lungo tempo deve avvenire molto lentamente (nell'arco ad esempio di 6 mesi). Se insorgono sintomi da sospensione mantenere la dose corrente fino a quando i sintomi scompaiono e poi continuare a diminuire il dosaggio, procedendo ad un ritmo più lento. Metodo di sospensione alternativo. 1. Passare all'assunzione di una dose giornaliera equivalente di diazepam, preferibilmente assunto di notte. 2. Ridurre la dose di diazepam ogni due o tre settimane di 2 o 2.5 mg. 3. Continuare a ridurre la dose, se necessario di piccole quantità. E' preferibile ridurla molto lentamente. 4. Il periodo di sospensione può variare da circa quattro settimane a più di un anno.	L'interruzione improvvisa può causare ansia, cambiamenti di umore, insonnia, palpitazioni, tremore, mal di testa, disturbi gastrointestinali, rigidità e spasmi muscolari.
Ranitidina	Antagonisti dei recettori H_2	Dimezzare la dose nell'arco di 4-8 settimane poi interrompere l'assunzione.	L'interruzione improvvisa può causare ipersecrezione acida da rebound, che può causare dispepsia. Valutare la possibilità di un antiacido per gestire la dispepsia.

Fonte: A practical guide to stopping medicine in older people. BPJ,27:11-22

Valutazione appropriatezza in Reparto Geriatria

Figure 1. Main results of observational and interventional phases of the study



Ghibelli, Drugs Aging 2013

Ottimizzazione terapia psicotropa (RSA - Brescia)

Studio multicentrico: 14 MMG

9 mesi: Settembre 2013 - Maggio 2014

Interventi formativi + INTERCheck

Pasina, Drugs Aging 2015

Ottimizzazione terapia psicotropa n RSA - Brescia

	First visit	Last visit	*p* value
Age, years (mean ± SD)	84.9 ± 7.7		
Women	193 (77.2)		
No. of drugs (mean ± SD)	7.0 ± 2.9	5.9 ± 2.6	<0.0001
Patients receiving:			
Psychotropic drugs	215 (79.0)	190 (69.9)	<0.0001
Potentially inappropriate psychotropic drugs	203 (74.6)	141 (51.8)	<0.0001
Potentially inappropriate antipsychotics	78 (28.7)	64 (23.5)	0.008
Potentially inappropriate benzodiazepines	88 (32.4)	72 (26.5)	0.002
SSRIs	66 (24.3)	44 (16.2)	0.0002
Duplicates			
Antipsychotics	20 (7.4)	6 (2.2)	0.0005
Benzodiazepines	10 (3.7)	4 (1.5)	0.01
Antidepressants (SSRI)	14 (5.2)	8 (2.9)	0.03

Data are expressed as *n* (%) unless otherwise specified

SD standard deviation, *SSRI* selective serotonin reuptake inhibitors

Pasina, Drugs Aging 2015

Grazie per l’attenzione..

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