



**LA POLIFARMACOTERAPIA:
STATO DELL'ARTE E PROPOSTE 2019**

FEDERICO PEA

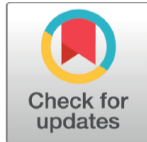
DIPARTIMENTO DI AREA MEDICA, UNIVERSITA' DI UDINE

ISTITUTO DI FARMACOLOGIA CLINICA, AZIENDA SANITARIA UNIVERSITARIA INTEGRATA, UDINE

Udine, 13 Dicembre 2018



VIEWS AND REVIEWS



PROVOCATIONS

Mass medicalisation is an iatrogenic catastrophe

Profligate prescribing has brought a hidden epidemic of side effects and no benefit to most individuals, says **James Le Fanu**

James Le Fanu *retired GP and journalist*



POLYTHERAPY AND THE RISK OF POTENTIALLY INAPPROPRIATE PRESCRIPTIONS AMONG ELDERLY AND VERY ELDERLY PATIENTS IN THREE DIFFERENT SETTINGS OF THE FVG REGION, ITALY

Cojutti PG, Arnoldo L, Cattani G, Brusaferrò S, Pea F
Pharmacoepidemiol Drug Safety 2016 Sep;25(9):1070-8.

PATIENTS' CHARACTERISTICS

	Hospital (n = 528)	GPs (n = 527)	LTCFs (n = 527)	p
<i>Demographics</i>				
Sex (male/female), n (%)	267/261 (50.6/49.4)*	225/303 (42.7/57.5)*°	156/372 (29.6/70.6)†°	<0.001
Age (years), median (IQR)	81 (75–87)*†	76 (71–82)*°	85 (79–89)†°	<0.001
Elderly, n (%)	209 (39.6)*†	329 (62.4)*°	121 (22.9)†°	<0.001
Very elderly, n (%)	319 (60.4)*†	198 (37.6)*°	406 (77.1)†°	<0.001
Number of per patient underlying diseases, median (IQR)	3 (2–4)*	4 (2–5)*°	3 (2–4)°	<0.001
<i>Drug prescription pattern</i>				
Number of patients with polypharmacy, n (%)	389 (73.7)*	304 (57.7)*°	370 (70.2)°	<0.001
Number of patients with hyperpolypharmacy, n (%)	80 (15.2)*	51 (9.7)*°	82 (15.6)°	0.008
Number of drugs per patient, median (IQR)	6 (4–8)*	5 (3–7)*°	6 (4–8)°	<0.001
<i>PIP pattern</i>				
Total number of PIPs, n (% of total prescriptions)	307 (9.1)†	292 (10.2)°	553 (16.6)†°	<0.001
Number of patients with:				
1 PIP, n (%)	159 (30.1)	126 (23.9)	159 (30.2)	0.035
≥2 PIPs, n (%)	60 (11.4)†	69 (13.1)°	155 (29.4)†°	<0.001

GP, general practitioner; IQR, interquartile range; LTCFs, long-term care facilities; PIPs, potentially inappropriate prescriptions. Polypharmacy and hyperpolypharmacy were defined as 5–9 and ≥10 drug co-prescription, respectively. *P*-value was obtained by means of the Kruskal–Wallis test. Asterisks, open circles, and crosses refer to statistically significant differences between groups ($p < 0.05$) after post-hoc Bonferroni correction.



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FACTORS ASSOCIATED AT MULTIVARIATE ANALYSIS WITH POTENTIALLY INAPPROPRIATE PRESCRIPTION (PIP)

Variables	1 PIP		≥2 PIPs	
	OR (95%CI)	<i>p</i>	OR (95%CI)	<i>p</i>
<i>Age (years)</i>				
65–79	1	—	1	—
>79	1.416 (1.105–1.813)	0.006	1.372 (1.025–1.837)	0.033
<i>Sex</i>				
Male	1	—	1	—
Female	1.071 (0.835–1.376)	0.588	1.629 (1.202–2.207)	0.002
<i>Drug prescriptions</i>				
Normal	1	—	1	—
Polypharmacy	3.019 (2.267–4.020)	<0.001	2.322 (1.657–3.253)	<0.001
Hyperpolypharmacy	4.964 (3.283–7.506)	<0.001	6.744 (4.318–10.534)	<0.001
<i>Underlying diseases</i>				
CKD	1.207 (0.832–1.752)	0.322	1.130 (0.732–1.746)	0.581
	1.153 (0.849–1.567)	0.361	1.445 (1.029–2.027)	0.033

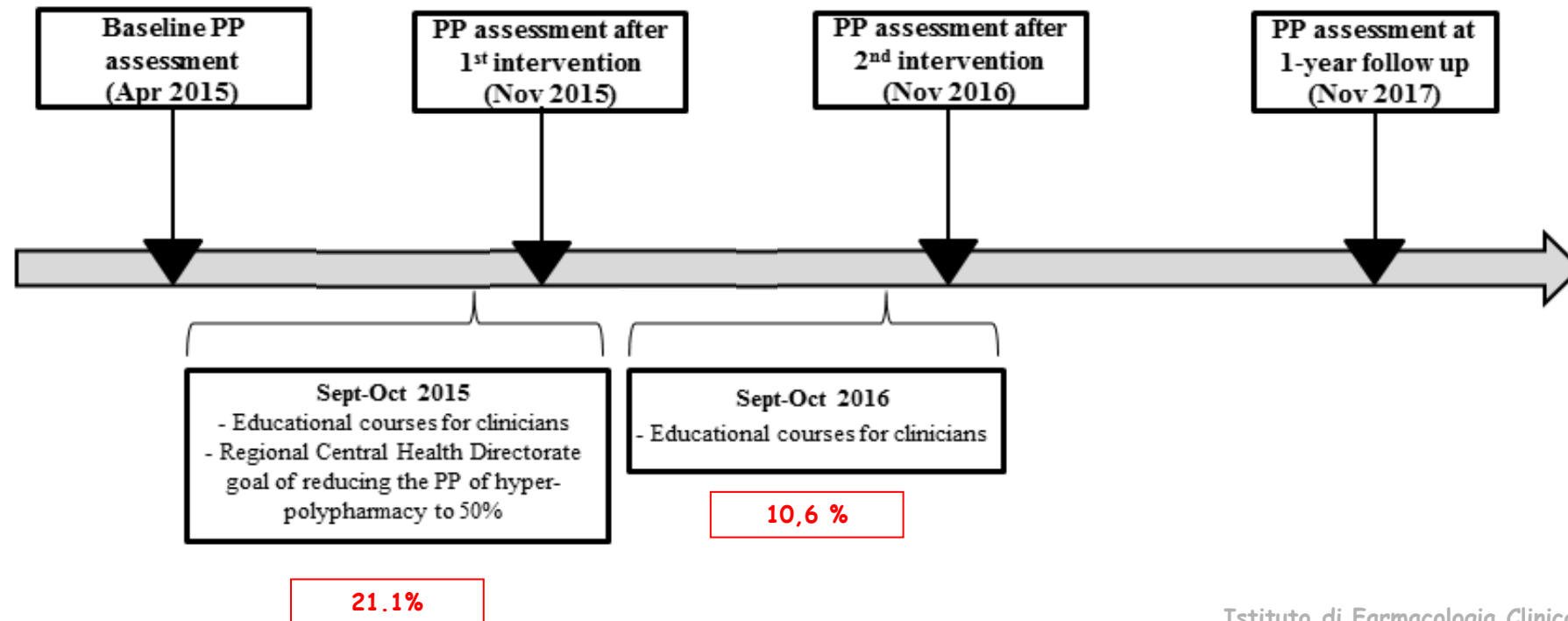
CKD, chronic kidney disease (CLCr < 60 ml/min/1.73 m²); hyperpolypharmacy, ≥10 drugs; normal prescription, 1–4 drugs; polypharmacy, 5–9 drugs; underlying diseases, ≥2 diseases. Other variables tested at the univariate analyses and resulting nonsignificant were dementia and cognitive impairment, heart failure, chronic seizures or epilepsy, Parkinson's disease, and history of gastric or duodenal ulcers.



PROSPECTIVE STUDY AIMS

To assess the role of an educational project in reducing the prevalence of hyperpolypharmacy and of potentially inappropriate prescriptions (PIPs) among hospitalized elderly patients at time of hospital discharge

PROSPECTIVE STUDY FLOW CHART



**PATIENT CHARACTERISTICS AND DISTRIBUTION OF POLYPHARMACY, HYPER-POLYPHARMACY
AND POTENTIALLY INAPPROPRIATE PRESCRIPTIONS (PIPS)**

	Baseline PP assessment (n=1201)	PP assessment after 1 st intervention (n=1221)	PP assessment after 2 nd intervention (n=1196)	PP assessment at 1-year follow up (n=1317)	<i>p</i>
Age (years), median (IQR)	82 (75-87)	81 (75-87)	81 (75-87)	82 (76-88)	0.281
elderly, <i>n</i> (%)	447 (37.2)	473 (38.7)	469 (39.2)	466 (35.4)	0.221
very elderly, <i>n</i> (%)	754 (62.8)	748 (61.3)	727 (60.8)	851 (64.6)	0.221
Gender (males), <i>n</i> (%)	547 (45.5)	570 (46.7)	586 (48.9)	637 (48.4)	0.305
Number of patients with polypharmacy, <i>n</i> (%)	753 (62.7)	746 (61.1)	712 (59.9)	783 (59.4)	0.304
Number of patients with hyper-polypharmacy, <i>n</i> (%)	142 (11.8)*	121 (9.9)* ^o †	154 (12.8) ^o	182 (13.8)†	0.019
Total number of PIPs, <i>n</i> (% of total prescriptions)	711 (9.4)	617 (8.4)	611 (8.3)	745 (5.7)	0.056
Number of patients with ≥ 1 PIP, <i>n</i> (%)	549 (45.7)* ^x °	496 (40.6)*†	478 (40.0) ^x §	602 (45.7)†§	0.002

PIP, potentially inappropriate prescription; PP. point-prevalence



**PROGETTO REGIONALE PER L'APPROPRIATEZZA PRESCRITTIVA
DEGLI INIBITORI DI POMPA PROTONICA NELL'AMBITO
DELL'ATTIVITÀ PROGRAMMATICA "POLIFARMACOTERAPIA" DELLA
RETE SANITARIA REGIONALE "RETE CURE SICURE - FVG"**



POLY THERAPY AND THE RISK OF POTENTIALLY INAPPROPRIATE PRESCRIPTIONS AMONG ELDERLY AND VERY ELDERLY PATIENTS IN THREE DIFFERENT SETTINGS OF THE FVG REGION, ITALY

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DISTRIBUTION (%) OF THE 10 DRUGS MOST FREQUENTLY PRESCRIBED IN THE DIFFERENT SETTINGS ACCORDING TO THE ATC CLASSIFICATION

Drug	Hospital (n = 528)	GPs (n = 527)	LTCF (n = 527)	p
A02BC (proton pump inhibitors)	352 (66.6)*	193 (36.6)*°	363 (68.9)°	<0.001
B01AC (PLT aggregation inhibitors excl. heparin)	297 (56.3)	249 (47.2)	265 (50.3)	0.408
C03CA (diuretics, sulfonamides)	230 (43.6)*	115 (27.8)*°	180 (34.2)°	<0.001
C07AB (beta-blocker selective)	209 (39.6)†	158 (29.9)	144 (27.3)†	0.003
C09AA (ACE inhibitors)	194 (36.7)†	143 (27.1)	138 (26.2)†	0.010
C10AA (statins)	146 (27.7)*†	206 (39.1)*°	85 (16.1)†°	<0.001
B01AA (vitamin K antagonists)	104 (19.7)†	69 (13.1)°	34 (6.5)†°	<0.001
C08CA (dihydropyridine derivatives)	85 (16.1)*	106 (20.1)*°	76 (14.4)°	0.002
C01DA (organic nitrates)	83 (15.7)	61 (11.6)	64 (12.1)	0.315
N05BA (benzodiazepines)	75 (14.2)*†	117 (22.2)*	150 (28.5)†	<0.001





deprescribing.org

Reducing medications safely
to meet life's changes

Moins de médicaments, sécuritairement –
pour mieux répondre aux défis de la vie



Barbara Farrell

Pharmacist, Researcher

Dr. Barbara Farrell is passionate about deprescribing – especially for the frail elderly. As a pharmacist working in the Bruyère Geriatric Day Hospital, she sees many older people often taking more than 20 medications a day. Working closely with physicians, an interprofessional team and the patients and their families, she is able to help reduce or stop medications safely. More frequently than not, this helps patients feel better, be less confused, fatigued and dizzy. These experiences prompted Dr. Farrell to pursue research in the field of deprescribing and models that improve medication-related care for older people.

Dr. Farrell is currently a scientist with the Bruyère Research Institute and the CT Lamont Primary Health Care Research Centre, an Assistant Professor with the Department of Family Medicine, University of Ottawa, and an Adjunct Assistant Professor with the School of Pharmacy, University of Waterloo. She is also a member of the Ontario Pharmacy Research Collaboration.

In 2011, Dr. Farrell was named the Canadian Pharmacist Association's "Pharmacist of the Year" for her work in pharmacist education, patient-centred care and research.



Cara Tannenbaum

Geriatrician, Researcher

Dr. Cara Tannenbaum is a leader in cutting-edge geriatric research both nationally and internationally. As a Professor in the Faculties of Medicine and Pharmacy at the Université de Montréal, she became the inaugural Chair of the Michel Saucier Endowed Fund in Geriatric Pharmacology, Health and Aging of the in 2008, and won the CIHR Betty Haven's Knowledge Transfer Prize in Aging in 2013 for her work on the EMPOWER study: "Eliminating Medications through Patient Ownership of End Results". Her EMPOWER brochure for reducing benzodiazepines has since been translated into 10 languages worldwide. As the principal investigator on a CIHR Partnership for Health System Improvement Grant, she founded and co-chairs the [Canadian Deprescribing Network](#), and continues to conduct deprescribing trials involving patients, pharmacists and primary care practitioners across Canada.

In 2015 Dr. Tannenbaum received a Y Woman of Distinction Award for Health, and was appointed Scientific Director of the CIHR [Institute of Gender and Health](#). She is dedicated to her clinical practice as a geriatrician, women's health specialist and Director of the Geriatric Incontinence Clinic at the Institut universitaire de gériatrie de Montréal, which fuels her vision for her patient-oriented research program.



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BRUYÈRE
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Dr. Marie-Thérèse Lussier

Dr. Tejal Patel

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Dr. Justin Turner

Dr. Dan Zou

Dr. Richard Birtwhistle

Dr. Vakaramoko Diaby

Philippe Martin

Dr. Kevin Pottie

Denis Roy

Lynda Weaver

Inibitore di Pompa Protonica	Dose standard (trattamento) (una volta al dì)*	Basso dosaggio (mantenimento) (una volta al dì)
Omeprazolo	20 mg ^a	10 mg ^a
Esomeprazolo	20 ^a o 40 ^b mg	20 mg
Lansoprazolo	30 mg ^a	15 mg ^a
Pantoprazolo	40 mg	20 mg
Rabeprazolo	20 mg	10 mg

Legenda

- a) Malattia da reflusso non-erosiva
- b) Esofagite da reflusso

= Può essere assunto insieme al cibo

* La dose standard di PPI può essere presa due volte al dì solo nel trattamento dell'ulcera peptica causata da *Helicobacter pylori*. L'uso del PPI dovrebbe, in genere, terminare una volta conclusa la terapia eradicante, a meno della presenza di fattori di rischio che ne suggeriscano il continuamento (consultare le linee guida per maggiori dettagli)

GERD = malattia da reflusso gastroesofageo
 FANS = anti-infiammatori non steroidei
 Anti-recettori H2 = Antagonisti dei recettori H2
 GRADE = Grading of Recommendations, Assessment, Development and Evaluations)

Coinvolgimento dei pazienti e "caregivers"
 È più semplice coinvolgere pazienti e/o caregivers se li si mette in condizione di capire il 'razionale' legato alla deprescrizione (rischi associati all'uso continuativo di PPI: la terapia a lungo termine può non essere necessaria) e le modalità del processo di deprescrizione

Effetti collaterali da PPI

- Quando l'indicazione d'uso corrente non è chiara, i rischi di effetti collaterali possono superare i benefici
- I PPI sono associati a un maggior rischio di fratture, di infezioni da *Clostridium difficile* e di diarrea, di polmoniti acquisite in comunità, di deficienza di vitamina B12 e ipomagnesia
- Effetti collaterali più comuni includono cefalea, nausea, diarrea e rash

Riduzione del dosaggio

- Non c'è nessuna evidenza che un tipo di approccio di riduzione del dosaggio sia migliore di un altro
- Due validi approcci ugualmente raccomandati sono la riduzione del dosaggio di PPI (per esempio, da due volte al dì a una volta al dì, o il dimezzamento della dose, o la assunzione a giorni alterni), oppure la interruzione del PPI e il suo uso al bisogno
- Si consiglia di scegliere ciò che è più opportuno e accettabile per il paziente

Definizione di uso al bisogno

- Il PPI va utilizzato giornalmente per un periodo sufficiente alla risoluzione dei sintomi individuali del paziente relativi al reflusso. Una volta risolti i sintomi, il farmaco va discontinuato. Nel caso i sintomi nel soggetto dovessero comparire, il farmaco va utilizzato di nuovo, quotidianamente, fino al risolvimento dei sintomi

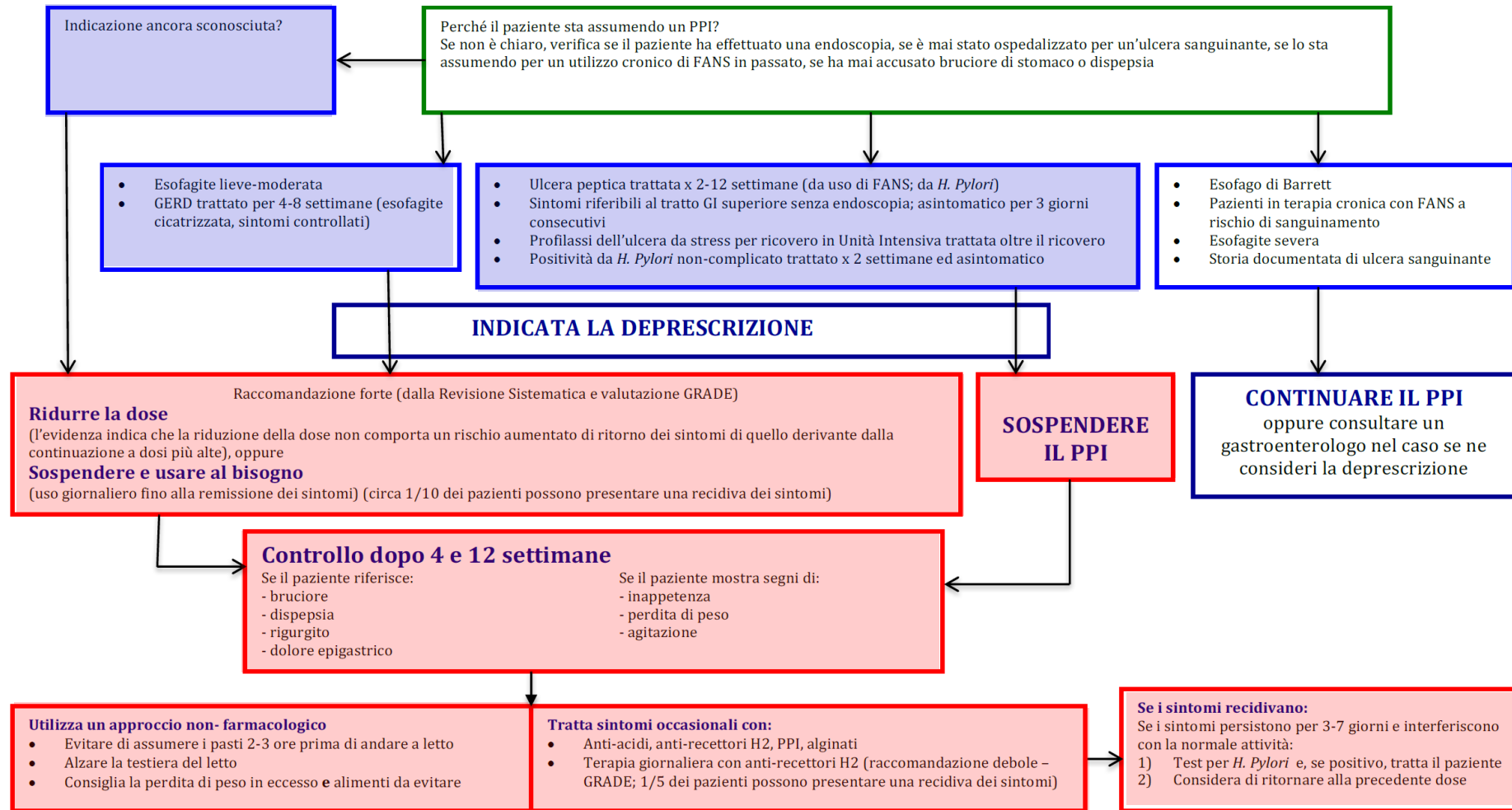
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Farrell B, Pottie K, Thompson W, Boghossian T, Pizzola L, Rashid J, et al. Deprescribing proton pump inhibitors. Evidence-based clinical practice guideline. Can Fam Physician 2017;63:354-64 (Eng), e253-65 (Fr).

La traduzione Italiana dell'Algoritmo sulla Deprescrizione dei PPI è stata autorizzata dagli autori e completata usando il processo riportato al seguente: <http://www.open-pharmacy-research.ca/evidence-based-ppi-deprescribing-algorithm>

Traduzione a cura di: Vittorio Maio, PharmD, MS, MSPH (Thomas Jefferson University, USA); Stefano Del Canale, MD, PhD, e Marco Lombardi, MD (Azienda U.S.L. di Parma, Italia)





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- **Revisione multidisciplinare degli ambiti di inappropriatezza di prescrizione dei PPI in base all'evidenza scientifica più recente e contestualizzazione nella realtà regionale**
- **Creazione e applicazione di una strategia di de-prescrizione relativamente agli ambiti di inappropriatezza d'uso identificati**
- **Condivisione del percorso con i risk-manager aziendali al fine di consentire un'applicazione diffusa nelle realtà cliniche regionali**



- **Identificazione degli ambiti di appropriatezza d'uso dei PPI:**

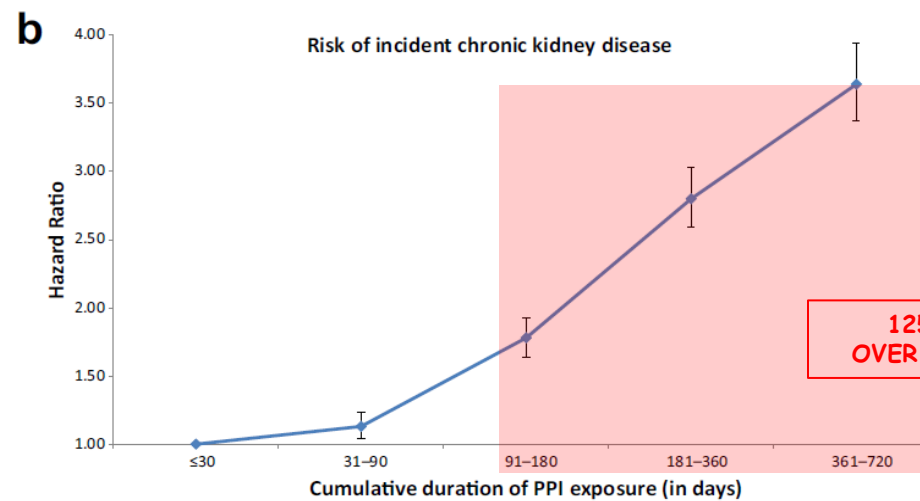
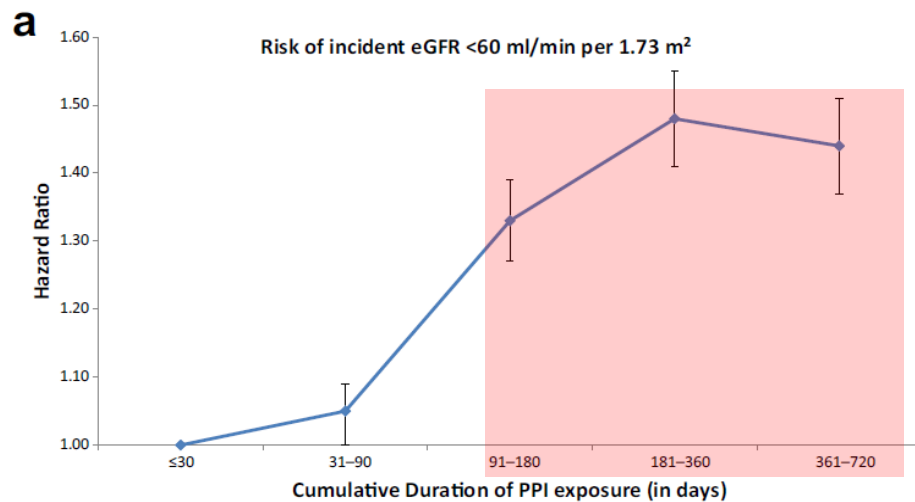
1. Malattia da reflusso gastro-esofageo (GERD): PPI per < 8 settimane
2. Esofagite erosiva (gradi A-D): PPI per < 12 settimane
3. Esofagite eosinofila: PPI per < 12 settimane
4. Eradicazione dell'infezione da *Helicobacter pylori*: PPI per < 2 settimane
5. Sindrome di Zollinger-Ellison: PPI long-term
6. Profilassi dell'ulcera da stress: PPI solo durante il ricovero in Terapia Intensiva
7. Dispepsia:
 - senza sintomi di allarme in soggetti <45 anni: PPI < 4 settimane
 - funzionale: PPI < 8 settimane
8. Prevenzione della gastropatia da FANS: PPI per tutta la durata del co-trattamento
9. Uso corticosteroidi: PPI non indicati
10. Uso anticoagulanti: PPI non indicati
11. Uso antiaggreganti piastrinici: PPI per tutta la durata del co-trattamento
12. Sanguinamento da malattia ulcerosa peptica: PPI indicati
13. Pazienti neoplastici: PPI non indicati
14. Pazienti cirrotici: PPI non indicati
15. Pazienti con malattie pancreatiche: PPI non indicati se pancreatite acuta; indicati se steatorrea o in pazienti refrattari alla terapia con pancrealipasi



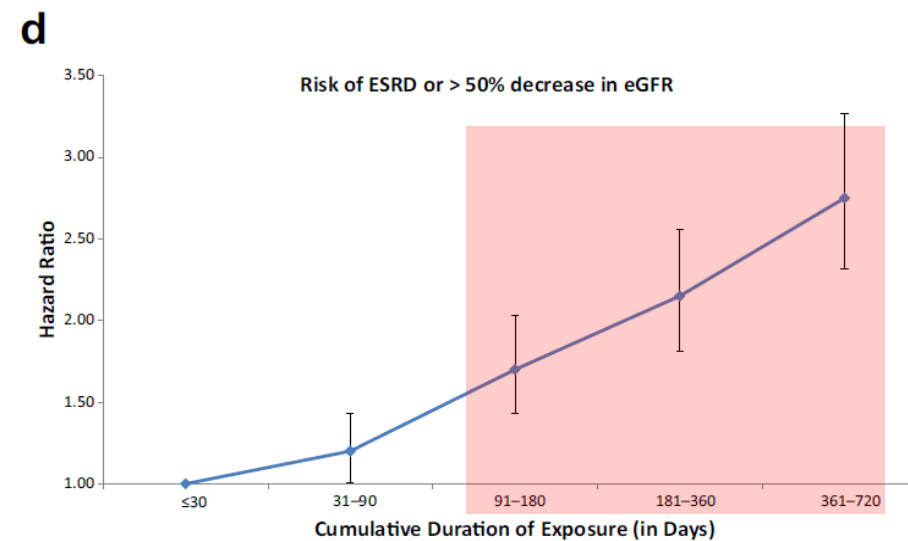
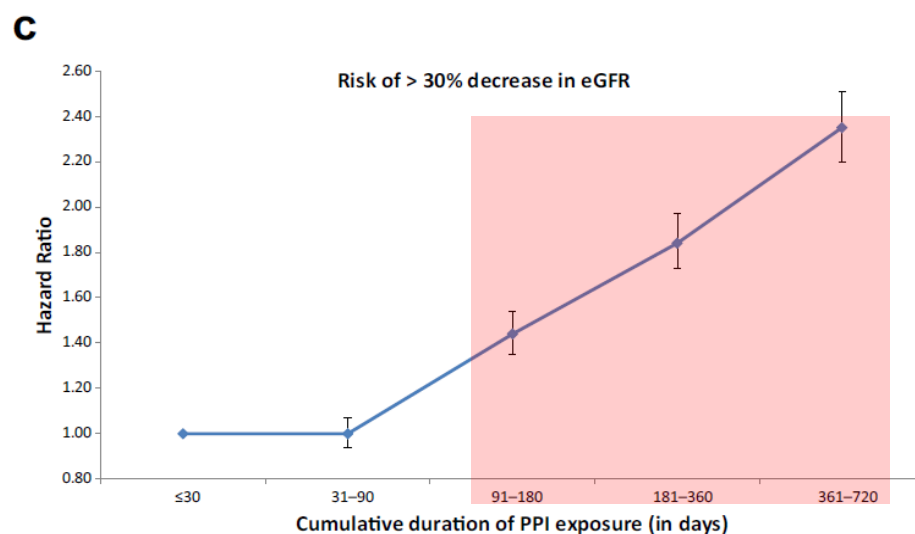
LONG-TERM KIDNEY OUTCOMES AMONG USERS OF PROTON PUMP INHIBITORS WITHOUT INTERVENING ACUTE KIDNEY INJURY

Xie Y et al *Kidney Int* 2017 Jun; 91(6): 1482-1494

CUMULATIVE DURATION OF PROTON PUMP INHIBITOR (PPI) EXPOSURE AND THE RISK OF CHRONIC RENAL OUTCOMES



125,596 PPI CONSUMERS
OVER 5 YEARS OF FOLLOW-UP



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- **Creazione di un gruppo multidisciplinare al fine di condividere una strategia di deprescribing**
 - risk manager, medico di direzione sanitaria, gastroenterologo, internista, medico di medicina generale, farmacologo, farmacista
- **Condivisione del programma con referenti regionali per renderlo applicabile su vasta scala**
- **Produzione di materiale informativo cartaceo (depliants, leaflets e poster) e/o audiovisivo da divulgare a operatori sanitari e/o cittadini sull'importanza dell'appropriatezza d'uso dei PPI e sugli eventi avversi che si possono verificare a lungo termine**
- **Eventuali corsi ECM**



- **Condivisione** con i risk-manager aziendali in occasione delle **riunioni mensili del Rischio Clinico** per la definitiva **approvazione e implementazione** nelle rispettive realtà cliniche
- **Durata del progetto**
 - **Pluriennale**
- **Indicatore di performance**
 - **Riduzione annuale 5% prescrizioni PPI su database**



Overcoming Inertia to Improve Medication Use and Deprescribing

Michael A. Steinman, MD; C. Seth Landefeld, MD

JAMA November 13, 2018 Volume 320, Number 18 1867

- **Inertia is a powerful force**
- **Stopping or starting is difficult in health care as well as in other sciences.**
- **Ineffective or potentially harmful treatments are often not stopped, even years after they have been started, and effective treatments are too often not started at all**
- **Even if a clinician recognizes a medication as potentially inappropriate and a candidate for discontinuation, both the clinician and the patient may be concerned that “the devil they know is better than the devil they don't know,” and that stopping a medication may worsen symptoms or biomarkers or may be perceived as giving up**
- **Clinicians also may be unsure about how to best taper different medications or how to recognize and manage adverse drug withdrawal events**
- **Thus, use of unnecessary and potentially harmful medications is common among older adults**

