EPID 765

Pharmacoepidemiology

Potentially Inappropriate Prescribing
(off-label drug use)

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Potentially Inappropriate Prescribing

- Beers criteria for potentially inappropriate medication (PIM) use in the elderly (Archives 1991, 1997, JAGS 2012)
  - Drugs
  - Dose
  - Drugs in combination with medical conditions
- START/STOP criteria (Int J Pharmacol Ther 2008)
  - Note: added notion of under-prescribing
  - Potential medication omissions (PMO)
- Both PIM and PMO are potentially inappropriate prescribing (PIP)!

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Potentially Inappropriate Prescribing

- Data:
  - GPs
  - Hospitals
  - Nursing homes (MDS)
  - Population based (Part D)
- "Potentially" allows for leeway (individual)
- Still relevant at population level, even if not inappropriate for each individual
- Quality of care measure

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What is Inappropriate?

- Contraindications (& START: indications)
- Pharmacokinetic/pharmacodynamic interactions
- Main kinetic parameter: kidney function
  - Cave: Age related decline not detected by serum Cr!
- Important for drugs mainly cleared by kidney
  (Dettli LC. Drug dosage in patients with renal disease. Clin Pharmacol Ther 1974;16:274-80)
- Estimate kidney function from serum creatinine
  - Cockroft-Gault: [140 - age(yr)] x weight(kg) / [72 x SCr(mg/dL)] x 0.85 (if female)
  - MDRD: 186.3 x $(SCr)^{-1.154}$ x $(age(yr))^{-0.203}$ x 1.212 (if black) x 0.742 (if female)

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PIP in Medicare

- Medicare enrollees ≥65 years of age.
- Point prevalence of PIM defined by STOPP
- Within each calendar month
- Generalized estimating equations (GEE) to account for the dependence of multiple monthly observations of a single person
- One record per enrollee each month.
- Conditions and diagnoses identified using ICD9 codes, Medicare Part A&B previous 12 months.
- Drugs and combinations identified using ATC
- Daily dose calculated strength & days supply

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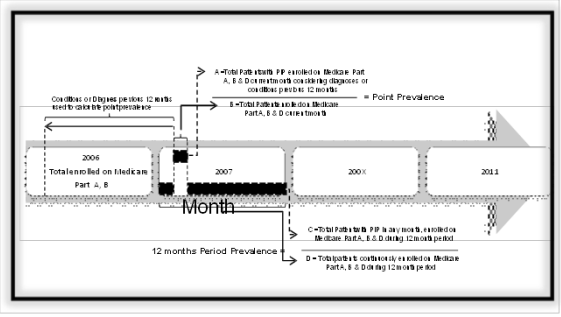
PIP in Medicare



Jirón M, Pate V, Hanson LC, Lund JL, Jonsson Funk M, Stürmer T. Trends in Prevalence and Determinants of Potentially Inappropriate Prescribing in the US 2007 – 2012. Journal of the American Geriatric Society 2016;64(4):788-97.

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PIP in Medicare: PIM

Table 2. Overall PIM prevalence and 95% Confidence Intervals (CI) among US older population between 2007 to 2011

Prevalence of PIM	2007 % (95% CI)	2008 % (95% CI)	2009 % (95% CI)	2010 % (95% CI)	2011 % (95% CI)
Point Prevalence	19.2 (18.8-19.7)	19.2 (18.7-19.6)	18.9 (18.5-19.4)	19.2 (18.8-19.7)	18.7 (18.2-19.1)

Table 3. Distribution of PIM by STOPP Grouping

System or condition	%	Group of Drugs or Drugs implicated
Drugs that adversely affect falls	20.7	BZD, neuroleptics, first generation antihistamines, vasodilators, long term opiates
Musculoskeletal system	19.3	NSAIDs, warfarin, long term corticosteroids, colchicine
Cardiovascular system	18.8	Digoxin dose >0.125 mg/d, loop diuretics, thiazide diuretic, betablockers, diltiazem, verapamil, calcium channel blockers, aspirin, warfarin, dipyridamole, clopidogrel
Urogenital	16.4	Antimuscarinic drugs, alpha blockers
CNS	12.7	TCA, long term long acting BZD, long term neuroleptics, long term hypnotics, phenothiazines, anticholinergics, SSRIs, prolonged use of first-generation antihistamines
Other	12.1	Diphenoxylate, loperamide, codeine, prochlorperazine, PPI, anticholinergic antispasmodic drugs. Thephylline, systemic corticosteroids, ipratropium. Glibenclamide, chlorpropamide, beta blockers, estrogens.

BZD: benzodiazepine; NSAIDs Non steroidal anti-inflammatories drugs; CNS: central nervous system, TCA: tricyclic antidepressants SSRI: selective serotonin reuptake inhibitors; PPI: proton pump inhibitor

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PIP in Medicare: PIM

Table 4. Factors associated with PIM

Condition	Level	OR crude (95% CI)**	OR adjusted (95% CI)***
Age Group (years)	65-69	reference	
	70-74	1.01 (0.96-1.07)	0.96 (0.91-1.02)
	75-79	1.19 (1.12-1.28)	1.04 (0.97-1.10)
	80-84	1.44 (1.35-1.54)	1.13 (1.06-1.21)
	85+	1.58 (1.48-1.68)	1.08 (1.02-1.16)
Any Outpatient Office Visit *	No	reference	
	Yes	0.99 (0.87-1.12)	1.13 (1.03-1.24)
Any Emergency Visit *	No	reference	
	Yes	2.79 (2.70-2.88)	1.53 (1.48-1.59)
Any Hospitalization *	No	reference	
	Yes	3.18 (3.08-3.28)	1.15 (1.01-1.31)

* During the previous 12 months. ** Crude: Monthly. ***Adjusted by age, race, region, comorbidities included in Charlson Index

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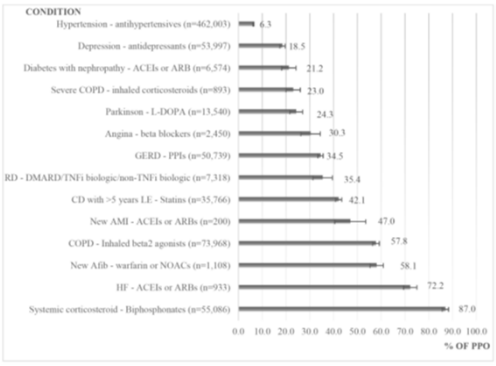
PIP in Medicare: PPO



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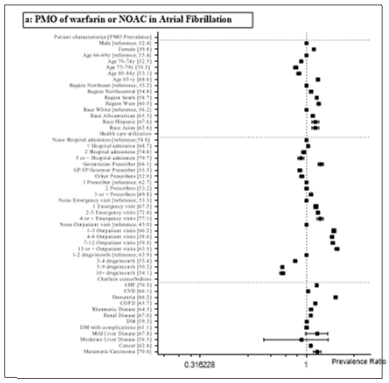
PIP in Medicare: PPO



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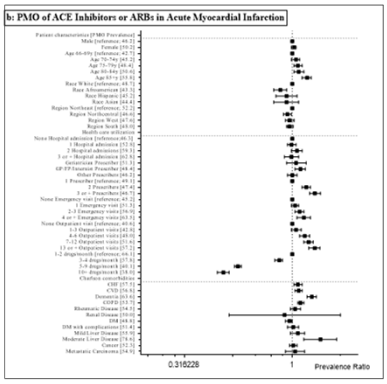
PIP in Medicare: PPO



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Conclusions PIM in Medicare

- At any point in time 1 in 5 older US adults receives at least one PIM
- PIM prevalence using STOPP Criteria lower than using Beers Criteria 2012
- PIM highest for drugs that adversely affect falls and musculoskeletal system
- Predictors of PIM
  - Age ≥80 years
  - At least one emergency visits, hospitalization, or outpatient visit during the previous 12 months

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Conclusions PPO in Medicare

- Prevalence ranges between 6% and 90%
- PPO not a good term given that we are looking at dispensed prescriptions (vs. prescribed)
- Interesting, often neglected aspect of PIP
- Predictors of PPO
  - Dependent on condition
  - Difficult to summarize in single manuscript
  - Probably best done condition specific

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Off-Label Drug Use

- Use of drugs for
  - Unapproved indications
  - Unapproved subpopulations
- May originate from
  - Presumed drug class effect
  - Extension to milder forms
  - Extensions to related conditions (organ, symptoms, pathophysiology)
- Spectrum:
  - Guideline recommended
  - Plausible
  - Last resort (finally: crazy)

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Off-Label Drug Use

- Common (antipsychotics, antidepressants, epo)
- Often not supported by strong data
- Physician free to prescribe off-label
- Potential advantages:
  - Last resort
  - Earlier access
  - Orphan conditions
- Potential disadvantages:
  - Efficacy and safety (benefit to harm) not evaluated
  - Expensive (often newer, expensive drugs)

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Off-Label Drug Use

- Supplemental NDA to add indication to label
  - Risky
  - Generics
- FDA policy currently prohibits the direct promotion of products for unapproved uses
- Areas of ambiguity
  - Sponsoring of CME
  - Distribute journal articles about off-label use

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Pharmacoepidemiology of Off-Label Drug Use

- Important public health issue
- Easy to study prevalence in claims databases
- Provide first/only evidence on benefit to harm balance
- Influence payors' decisions
  - E.g., France: off-label use tolerated but not reimbursed by universal health insurance

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