Polipharmacy in the elderly

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The geriatric patient

- Deterioration of various organs – pluripathology
- Greater propensity to get sick - vulnerability
  - Symptomatic opacity: poverty of symptoms
- Tendency to chronicity:
  - Over 70 years - ≥ 2 chronic processes
  - Impairment of the quality of life
  - Less vitality
- Inability to be autonomous – disability risk
- Receives multiple drugs: polypharmacy
  - Vulnerability of the elderly to drugs
  - More adverse reactions and drug interactions

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Ageing is associated with the development of chronic diseases

Elderly has greater predisposition to get sick (vulnerability)

Cardiovascular
- Hypertension
- Coronary and peripheral artery disease
- Atherothrombosis
- Stroke
- Heart failure
- Arrhythmias - Atrial fibrillation

CNS
- Cognitive impairment
- Mental disorders
- Affective and sleep disorders
- Parkinson and Alzheimer disease

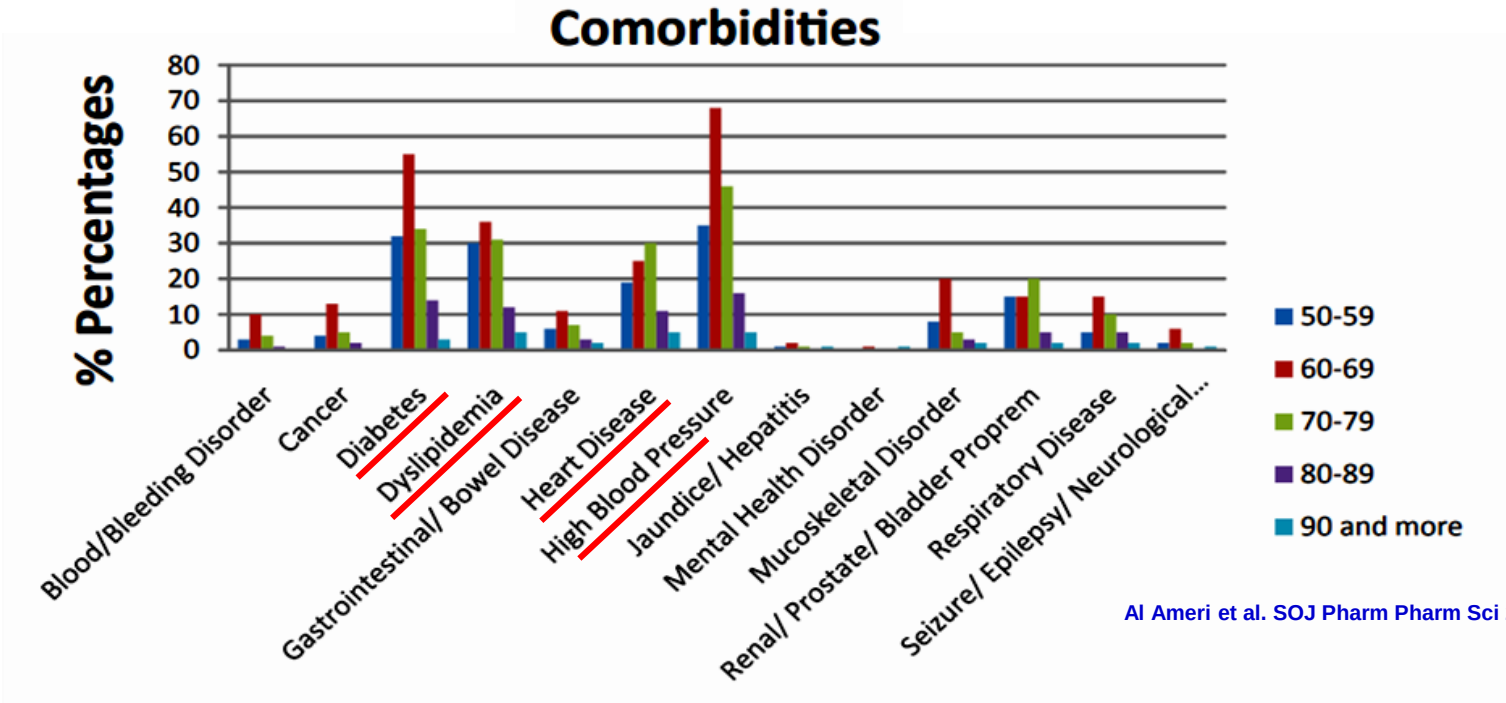
Musculoskeletal
- Osteoarthritis
- Osteoporosis
- Diminished range of motion
- Increased risk of fractures

Digestive
- Decreased peristalsis, Constipation
- Malnutrition
- Risk of dysphagia and ulcers
- Hepatic diseases

Genitourinary
- Increased risk of kidney failure
- Prostate enlargement
- Decreased tone in bladder & urethra
- Incontinence
- Urinary tract infections

Other
- Cancer
- Diabetes mellitus
- Visual impairment: cataracts
- Increased risk of respiratory infections

The distribution of co-morbidities among age groups



Al Ameri et al. SOJ Pharm Pharm Sci 2014;1:1-7

Advanced age is the most potent risk factor for CVD

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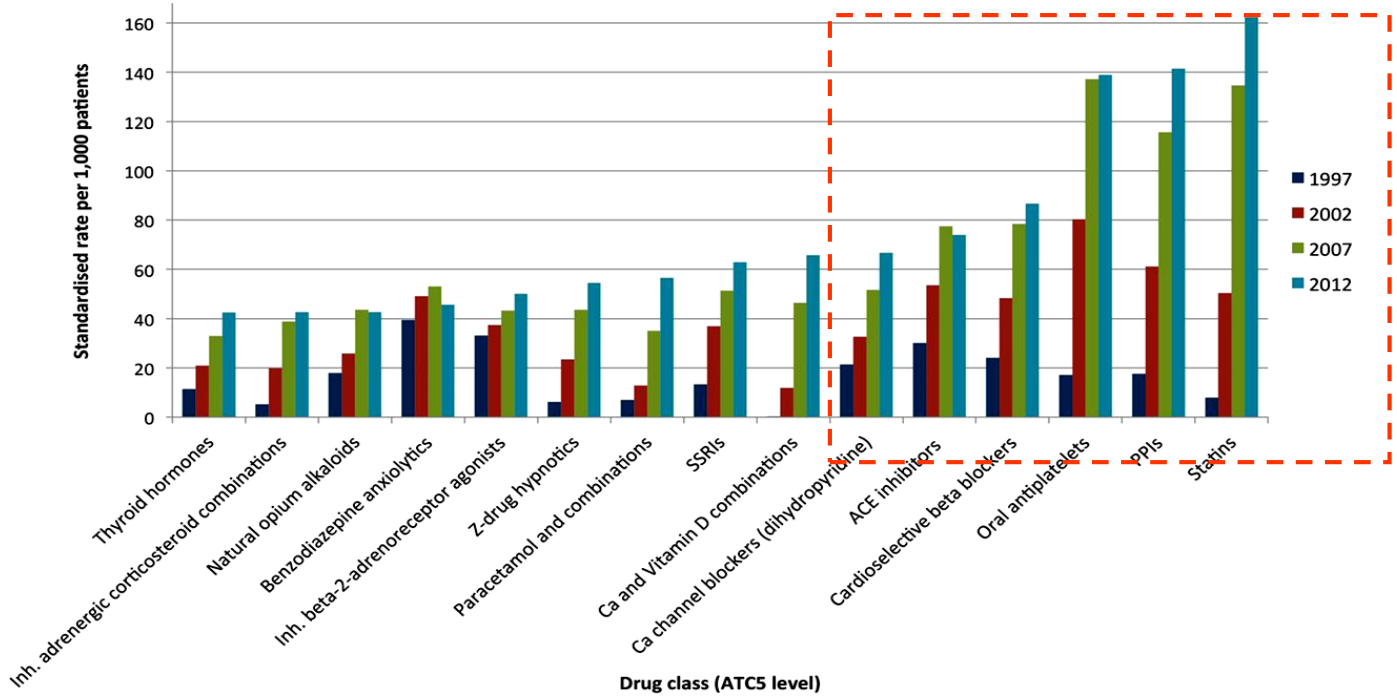
Rates of prescribing of most common regular medicines in all individuals in 2012



An increasing number of elderly patients require chronic medical therapy for their comorbidities

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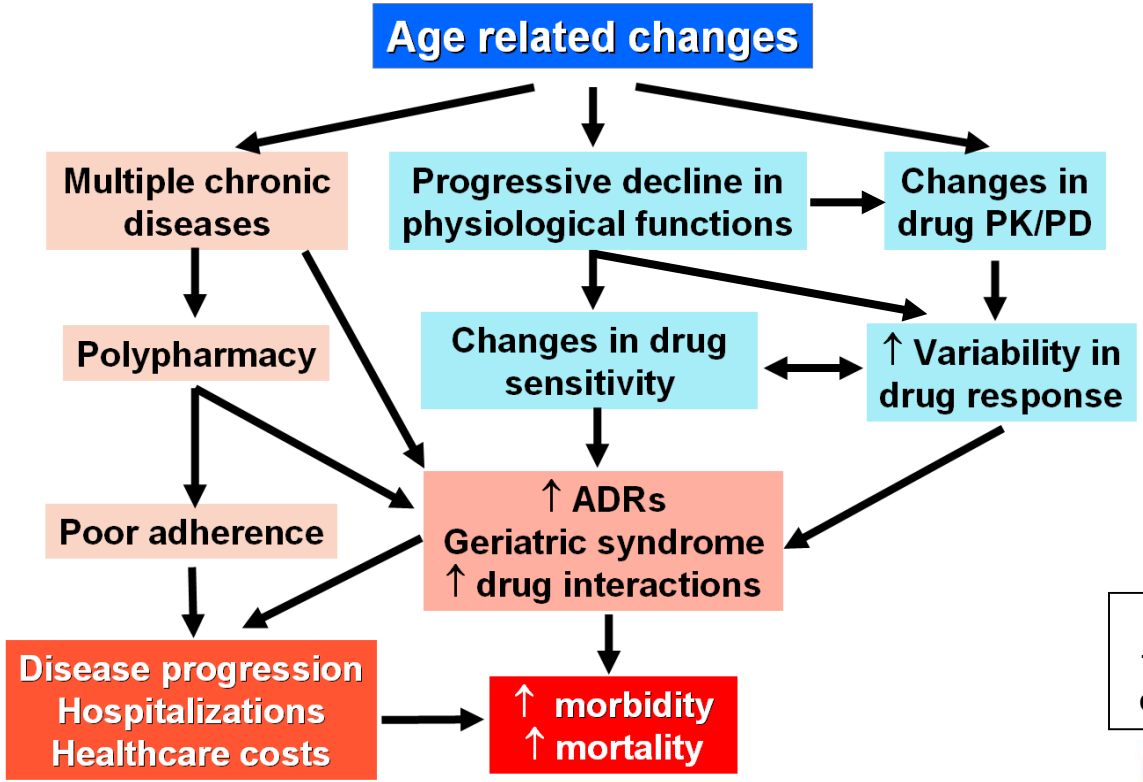
Moriarty et al. BMJ Open 2015;5:e008656

Drug treatment in the elderly is challenging



Sparse evidence from RCTs in real oldies (>75 years)

ESC GUIDELINES

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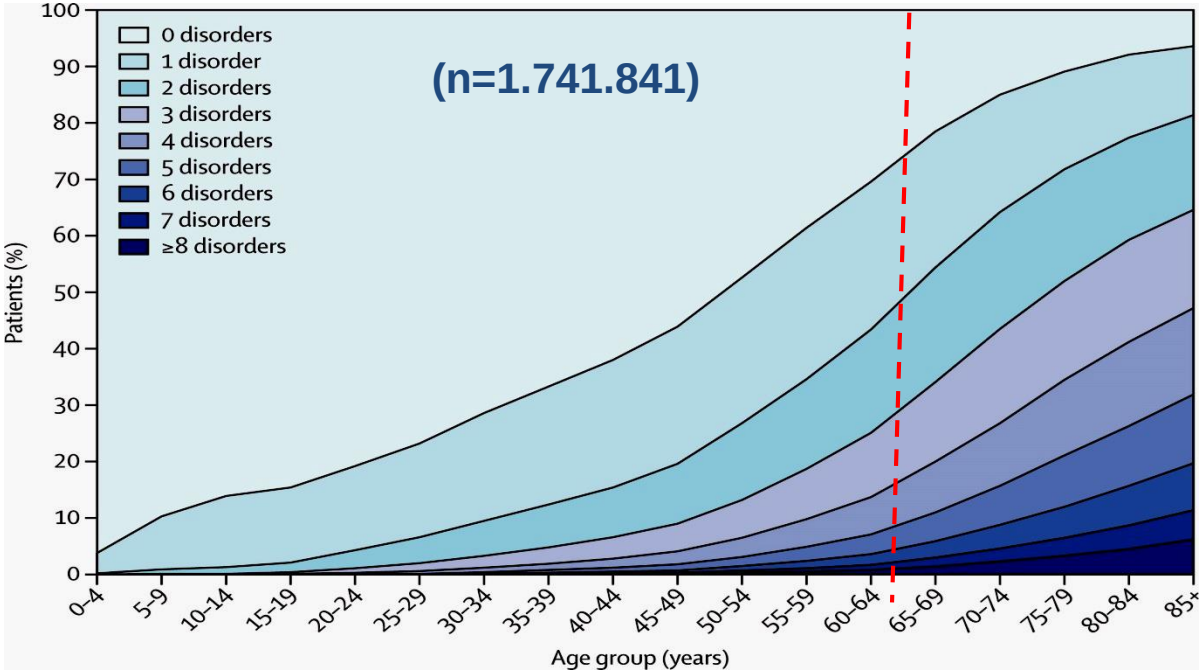
Polypharmacy - Definition

- **The use of multiple, excessive, inappropriate or ineffective medications (1)**
- **5 or more medications in non-hospitalized individuals at the same time (2,3)**
  - **Prescriptions, over-the-counter (OTC) medications and self-medication drugs, herbs, vitamins and dietary supplements**
- **75% of Europe's healthcare bill is spent on chronic diseases (€700 billion annually)**
  - **EU older adults consume ~60% of all prescribed medications (15.7 B€) and purchase 40% of OTC medications**

(1) Tjia J et al. Drugs Aging 2013;30285-307. (2) Veehof LJ et al. Eur J Gen Pract 2000;6:98–106.
(3) Maher RL e al. Expert Opin Drug Saf. 2014;13:57-65

The number of chronic conditions increases with age



- 42.2% of all patients had ≥ 1 morbidities, 23.2% were multimorbid
- 8.3% had physical and mental health comorbidity
- Multimorbidity increased with age and was present in most aged ≥65 years

Barnett K et al. The Lancet 2012;380:37-43

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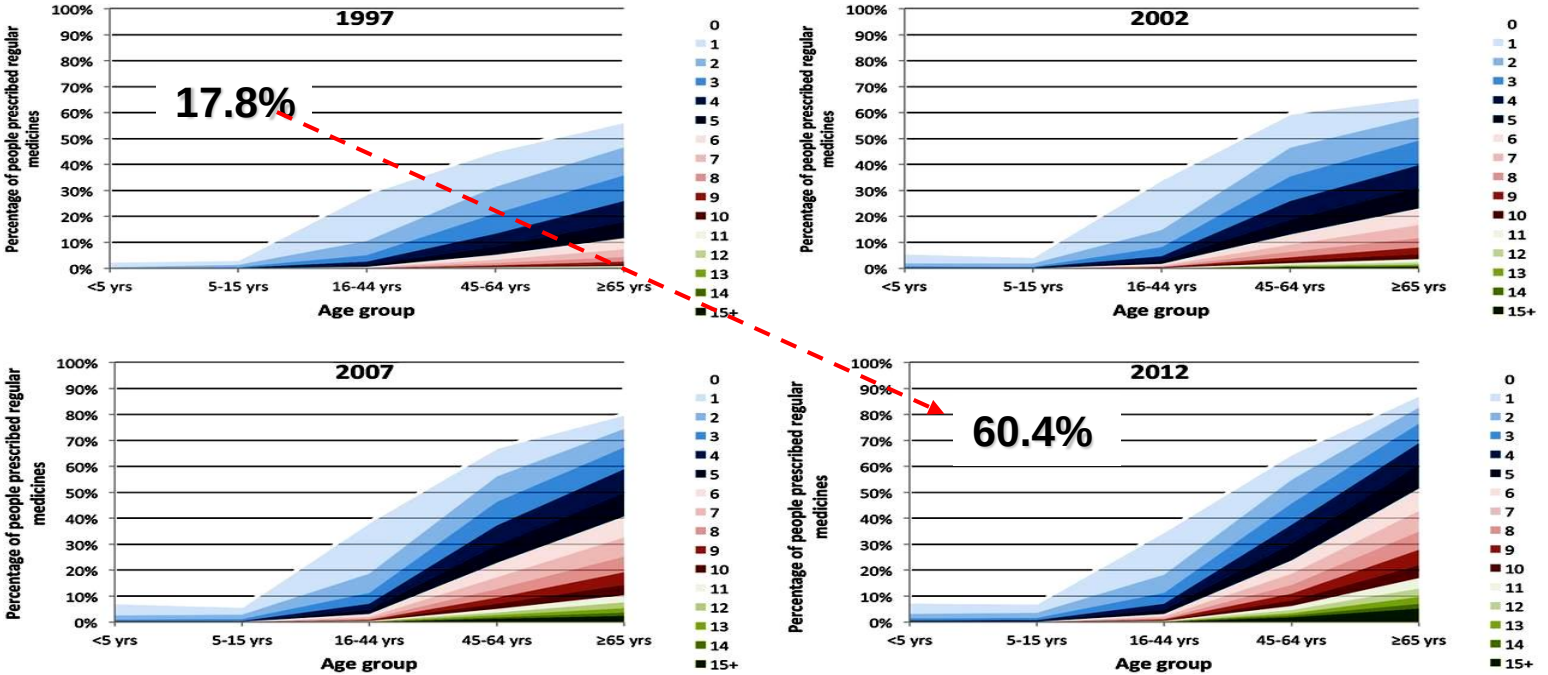
Between 1997 and 2012, there was a substantial increase in the prescripton of regular medicines, particularly in older adults (338,025–539,752 individuals)



Prevalence of Potentially Inapproriate Prescribing rose from 32.6% in 1997 to 37.3% in 2012

Moriarty F et al. BMJ Open 2015;5:e008656

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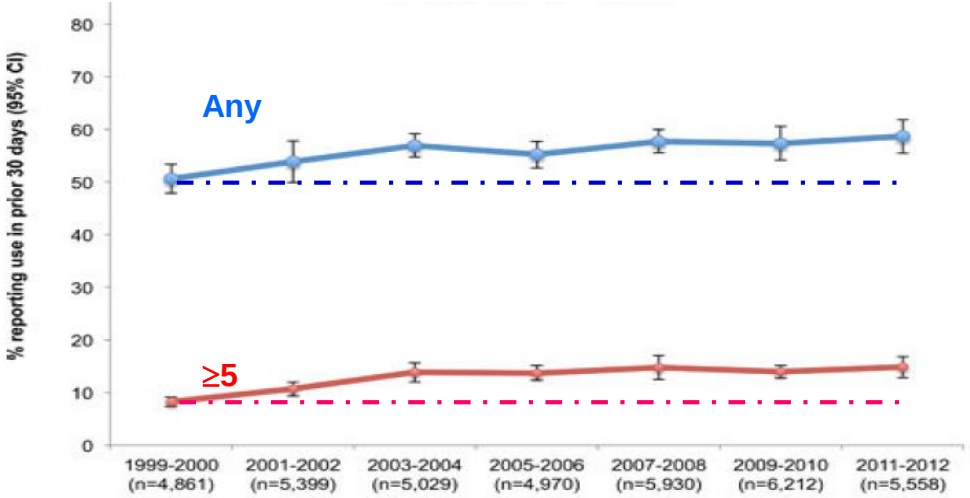
Trends in Prescription Drug Use among Adults in the US from 1999–2012 (n=37,959 non-institucionalized)



	1999-2000	2011-2012
≥5 prescriptions	8.2%	15%
Total prescriptions	51%	59%
Antihypertensives	23.6%	32.4%
ACE inhibitors	6.3%	12%
ARBs	2.1%	5.8%
β-blockers	6.0%	11%
Calcium channel blockers	6.3%	6.5%
Loop diuretics	2.5%	2.7%
Thiazides	5.6%	9.4%
Statins	6.9%	17%

The prescriptions increased also for antidepressants, proton-pump inhibitors, and muscle relaxants

Kantor ED et al. JAMA 2015;314:1818-31

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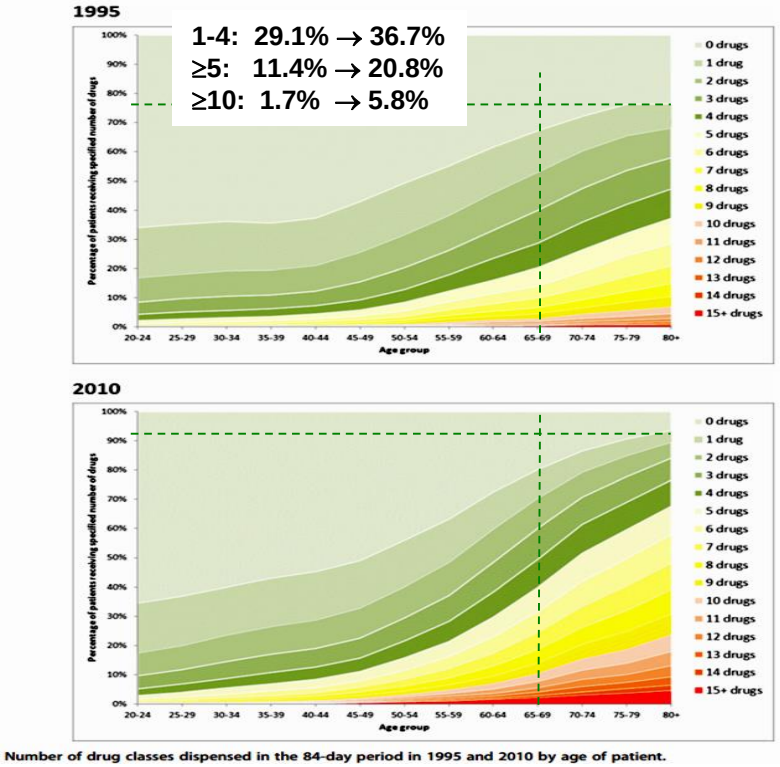
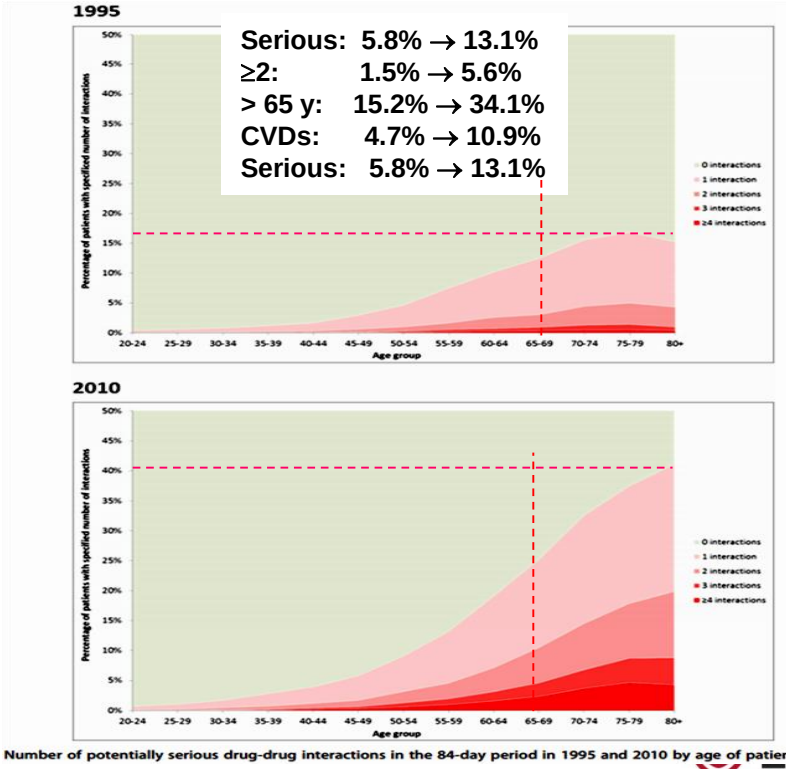
The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995–2010 (310,000 adults resident in Scotland)



Number of drug classes dispensed in the 84-day period in 1995 and 2010 by age of patient.



Number of potentially serious drug-drug interactions in the 84-day period in 1995 and 2010 by age of patients.

Guthrie B et al. BMC Med 2015;13:74

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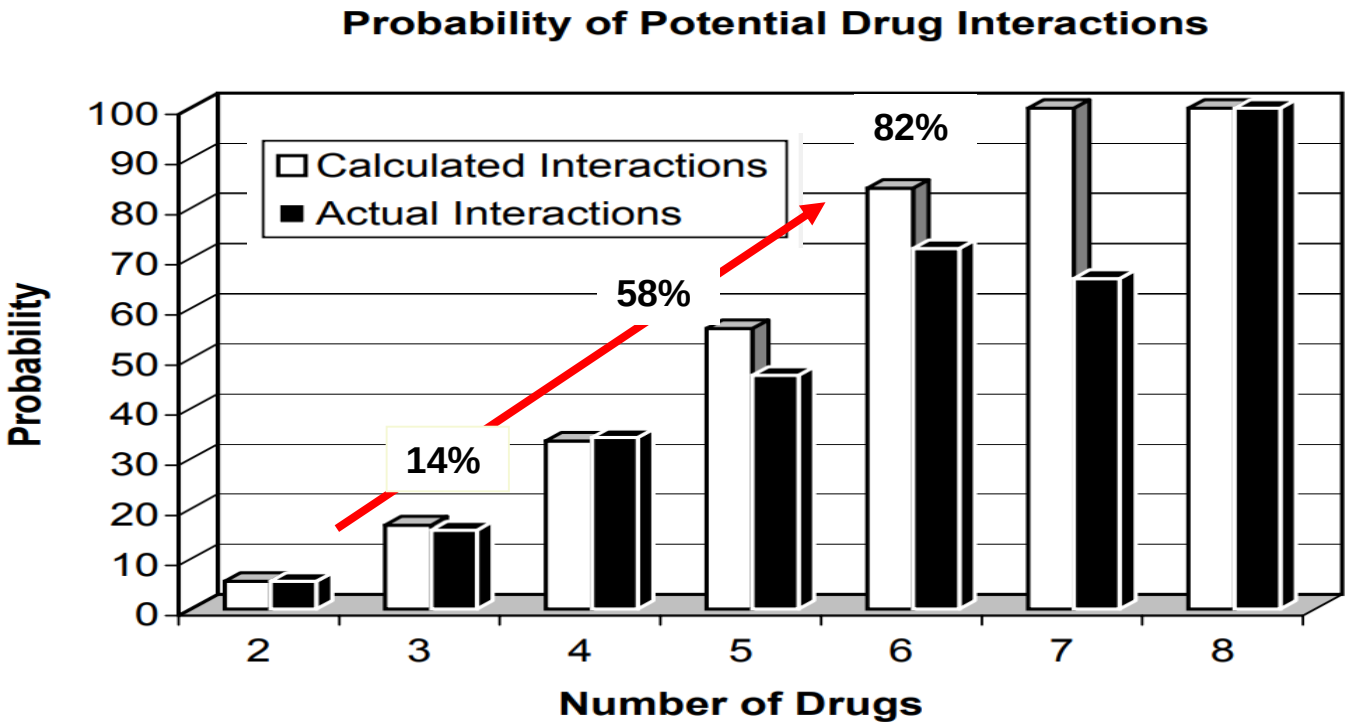
Polypharmacy in the ambulatory elderly

- Patients with 2 CVDs usually receive >5 medications (1)
  - Or more when following the ESC Guidelines
- Between 75 and 84 years (2-4):
  - 37% use ≥5 medications
  - 55% between 5-9 drugs/day
  - 14-24% take ≥10 drugs/day
- 51% were take medications not recorded in the physician's record
- >40% consume OTCs (2)
- >35% did not report the herbs and supplements they take (5,6)
- In 19 studies, 20% of patients receive inappropriately prescriptions (7)
- ADRs – 50% of patients taking ≥5 medications
  - About 50% are avoidable - deprescribing (8)

Boyd CM et al. JAMA. 2005;294:716–24. (2) Qato DM et al. JAMA Intern Med 2016. (3) Kantor ED et al. JAMA. 2015. (4) Guthrie B et al. BMC Med 2015. (5) Davies et al. Br J Clin Pharmacol 2015- (6) Jou J, Johnson PJ. JAMA Intern Med 2016. (7) Opondo et al. PLoS One 2012. (8) Hajjar e al. J Am Geriatr Soc 2005

Probability of potential drug interactions



JC Delafuente. Critical Reviews in Oncology/Hematology 2003;48:33–143

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Drugs with unclear indications

- Analgesics (NSAIDs - 63% without prescription)
- Furosemide (mild postural edema)
- Laxatives (to "regulate" the intestinal rhythm)
- Hypnotics (insomnia from nocturia, orthopnea, pain)
- Nootropics (counteract mental/physical senility)
- Expectorants/mucolytics
- Antiacids
- Multivitamins and “energetics”
- Topical anti-varicose drugs
- Herbal products

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European Heart Journal (2016) **37**, 1015–1023
doi:10.1093/eurheartj/ehv505

CURRENT OPINION

Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology

Morten Schmidt[1]*, Morten Lamberts[2], Anne-Marie Schjerning Olsen[2], Emil Fosbøll[3], Alexander Niessner[4], Juan Tamargo[5], Giuseppe Rosano[6,7], Stefan Agewall[8,9], Juan Carlos Kaski[10], Keld Kjeldsen[11,12], Basil S. Lewis[13], and Christian Torp-Pedersen[14]

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Complementary and alternative medicines (CAM)

- **15 $ billion spent each year on herbal products**
- **Self-medication (80%) - not mentioned**

Reason for Nondisclosure to Physician (Not Mutually Exclusive)	No. Unweighted (Weighted %)
Physician did not ask about CAM use	1759 (57.0)
Did not think physician needed to know	1432 (46.2)
Was not using CAM at the time	785 (26.4)
Believed that physician had less knowledge about CAM type	239 (7.6)
Did not have time to discuss CAM use with physician	142 (4.0)

CAM	Indications	Interactions
St. John's Wort (CYP induction)	Depression	P450-metabolized agents - β-blockers, Calcium antagonists, Digoxin, Statins, Warfarin
Asian Ginseng	Well-being, erectile dysfunction, hypertension, diabetes	Hypoglycemia, Increases bleeding tendency Warfarin/NSAIDS/Heparin
Gingko biloba	Dementia, tinnius, Intermitent claudication	Increases bleeding tendency Warfarin/NSAIDS/Heparin

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(1) Davies et al. Br J Clin Pharmacol. 2015;80:796-807 (2) Jou J, Johnson PJ. JAMA Intern Med 2016;176:545-6

Polypharmacy in hospitalized and nursing homes

2. Hospitalized elderlies:

- Consumption increases (1-3)
  - 41-60% take ≥ 5-8 medications, 37% ≥9 medications
- ~58% take ≥1 unnecessary prescribed drug
- In 6 European countries: 22-77% took inappropriate drug prescriptions (4)
- ADR in 10%-40% of patients: 50-70% are avoidable (1)
  - ADRs – 10-20% of all hospitalizations in Geriatric Units
- Overprescriptions at hospital discharge

Nursing Home Setting:

- In 55 Homes: average of 8 medications/patient (5)
  - Unnecessary drugs 24-58.6%, wrong dose 14%, wrong time 45%
- 2004 US Nursing Home Survey (n=13,507): 39.7% on polypharmacy (6)
- Canadian study (n=64,395): 15.5% on > 9 medications (7)

(1) Hajjar ER et al. J Am Geriatr Soc 2005;53:1518–23. (2) Nobili A et al. Eur J Clin Pharmacol 2011;67:507–19. (3) Pedros C et al. Eur J Clin Pharmacol. 2016:72:219-26. (4) Gallagher PF et al. Clin Pharmacol Ther 2011;89:845–54. (5) Barber ND et al. Quality & Safety in Health Care 2009;18:341–6. (6) Dyer L et al. Am J Geriatr Pharmacother 2009;8:62-72. (7) Bronskill S et al. JAMDA 2011:309:e15–e21

Negative consequences of polypharmacy[1-4]

- Exposure to potentially inappropriate or unnecessary drugs
- Adverse drug reactions and drug interactions
- Occurrence of geriatric syndromes:
  - Orthostatic hypotension, instability → falls/fractures
  - Urinary incontinence
  - Cognitive impairment (depression, confusion, restlessness, behavioral disorders, extrapyramidalism)
- Poor medication adherence (~50%)
  - Inversely correlated with nº of medications, complexity and costs
  - Disease progression, poor symptom control, treatment failure, hospitalizations, and even death
- Reduces functional capacity and QoL
- Greater health costs

(1) Zed PJ. CMAJ 2008;178:1563-9. (2) Shah BM, Hajjar ER. Clin Geriatr Med 2012;28:173-86. (3) Farrell B. Can Fam Physician 2013;59:1257-8. (4) Gnjidic D et al. J Clin Epidemiol 2012;65:989-995

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Polypharmacy is associated with unplanned hospitalization (n=180,815)

Numer of clinical conditons	% of patients with one or more unplanned admissions (n)
0 (38.1%)	1.8% (1254)
1 (23.3%)	3.6% (1509)
2 814.9%)	6.2% (1678)
3 (9.5%)	9.4% (1612)
4-5 (9.5%)	14.8% (2542)
≥6 (4.7%)	26.5% (2233)

Number of medications	% of patients with one or more unplanned admissions (n)
0 (53.3%)	2.8% (2736)
1-3 (25.2%)	5.2% (2356)
4-6 (11.0%)	10.3% (2043)
7-9 (5.9%)	15.4% (1647)
≥10 (4.6%)	24.8% (2046)

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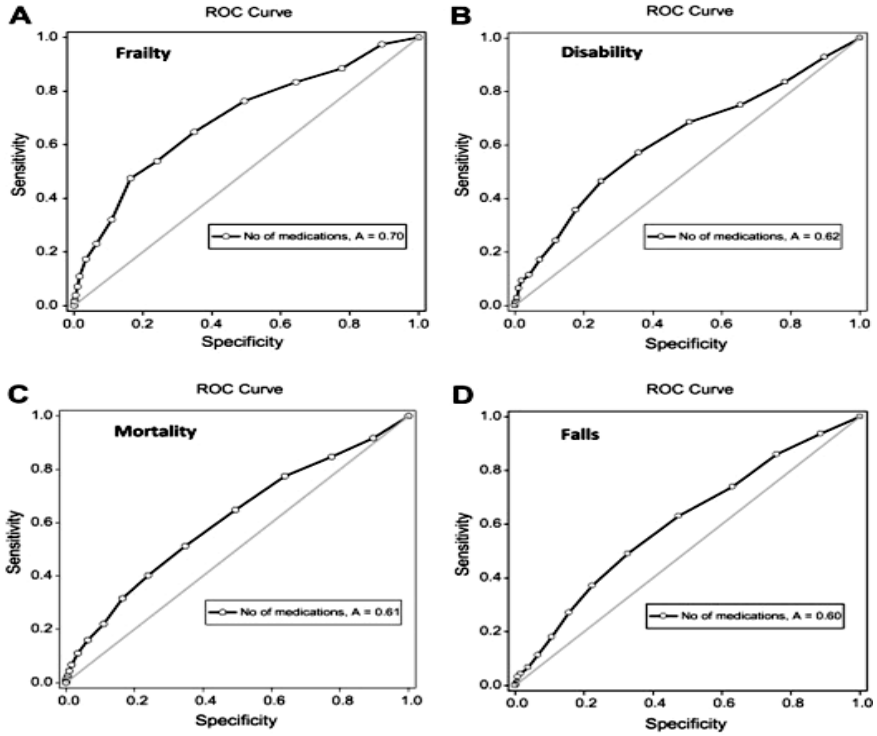
Payne RA et al. Br J Clin Pharmacol 2014;77:1073-82

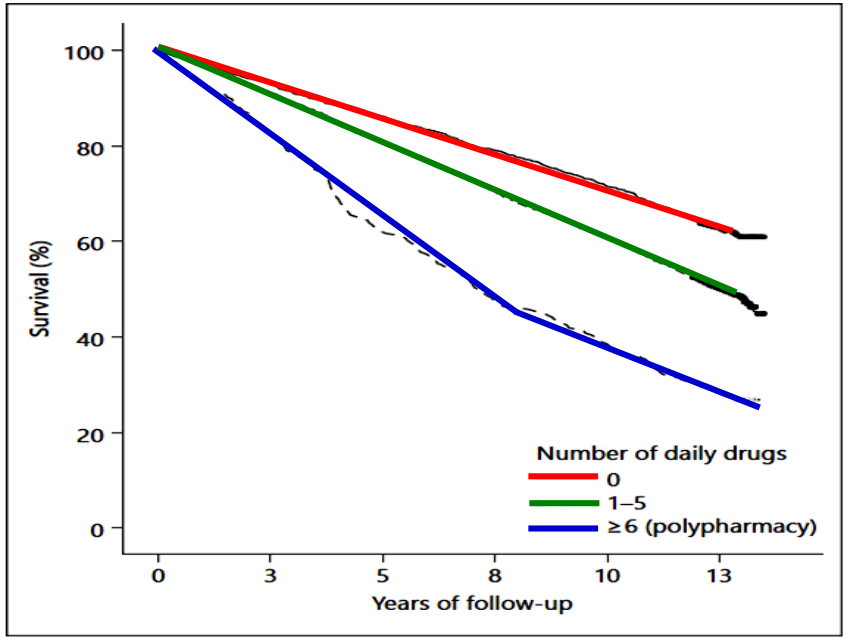
≥5 medications increase the risk of frailty, disability, mortality, and falls



N = 1,705 ≥70 years

Gnjidic D et al. J Clin Epidemiol 2012;65:989-995

Polypharmacy increases the mortality risk in elderly people



N = 5,052 ≥65 years

Gómez C et al. Gerontology 2015;61:301-9

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The prescribing cascade

An ADR is misdiagnosed as a new medical condition, and treated with a potentially unnecessary drug

Arthritis (NSAID) ✹ HTN ✹ CCB ✹ ankle swelling ✹ diuretic ✹ hyperuricemia/hyperglycemia ✹ allopurinol and an oral antidiabetic
Amlodipine ✹ Leg edema ✹ diuretic ✹ increased urination, fall risk and electrolytes changes
Unspecific pain ✹ NSAID ✹ heartburn ✹ PPI ✹ muscle weakness ✹ fractures
Depression ✹ Tricyclic antidepressants ✹ constipation ✹ laxative use
Antisychotics/metoclopramide ✹ extrapiramidal syndromes ✹ anti-Parkinson drugs ✹ orthostatic hypotencions, delirium ……..
Dementia ✹ cholinesterase inhibitors ✹ diarrhea, urinary incontinence ✹ anticholinergic therapy ✹ constipation, urinary retention

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Aging-associated physiological changes that affect pharmacodynamics

Physiological changes	Pharmacodynamic effects
Decreased cardiac reserve	↑ propensity to HF (class I and IV AADs)
Decreased LV compliance	Decreased cardiac output with β-blockers
Increased total and peripheral vascular resistance and vascular stiffness	Decreased cardiac output
Decreased baroreceptorreflex activity	↑ postural hypotension and falls with CCBs, vasodilators, nitrates, α-adrenergic blockers
Decreased cardiovascular responsiveness to β-agonists/antagonists	Decreased sensitivity to these drugs
Decreased repolarization reserve	↑ risk of drug-induced proarrhythmias
Increased sensitivity to anticoagulants	↑ risk of bleeding with warfarin and NOACs
Sino-atrial and AV nodal dysfunction	↑ risk of bradycardia and AV block with class II and IV AADs or digoxin
Brain receptors become more sensitive	↑ sensitivity to psychiatric drugs
Concurrent comorbidities and associated polypharmacy	• Increased drug–disease interactions • Increased drug–drug interactions

AADs: antiarrhythmic drugs. CCBs: calcium channel blockers.

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Sensitivity to certain CV drugs is modified in the elderly

Drug	Pharmacodynamic effect
Anticoagulants Warfarin	↑ risk of bleeding ↓ protein binding, ↑ inhibition of synthesis of vitamin K-dependent clotting factors
Antihipertensives	↓ baroreceptor response, orthostatic hypotension, falls
β-blockers/agonists	↓ effective (↓ receptors, alterations in signal transduction)
Digoxin	↑ serum levels and risk of toxicity
Thiazides and loop diuretics	↓ effective (impaired tubular secretion of the drug) Hypotension, falls, ↑ electrolytic/metabolic adverse effects
NonDHP-CCBs	↑ antihypertensive effect, bradycardia and PR prolongation
NSAIDs***	↑ GI bleeding, renal impairment, worsening of HF
Opioids	↑ analgesic effect and respiratory depression
RAAS inhibitors	↑ risk of hypotension, renal insufficiency
Statins	↑ myopathy, ↓ physical activity, falls in old-old

↑ = increase; ↓ = decrease. *** OCTs. HF: heart failure. RAAS: renin-angiotensin-aldosterone system

Main adverse reactions

Drugs	Adverse reactions
Antiarrhythmics	Bradycardia, AVB, proarrhythmia, HF, hypotension, falls
Antihypertensives*	Hypotension, instability (falls), headaches
Anticoagulants	↑ hemorrhages. warfarin – multiple interactions
β-blockers*	Bradycardia, AVB, mild sedation, delirium, falls Worsening depression (Meto, Prop), asthma/COPD and PVD
Dihydropyridine CCBs*	Peripehral edema, headache/flushing, hypotension, falls
Digoxin	Nausea, confusion, brady/tachyarrhythmias
Glucose-lowering drugs	Hypoglycaemia, confusion, falls
Nitrates*	Postural hypotension
NSAIDs*, COX2 inhibitors	GI bleeding, poor BP control, worsening CHF, nephrotoxicity, hyperkalemia
RAAS inhibitors*	Hyperkalemia, hypotension, renal failure, cough (ACEIs)
Statins	Myalgia, myopathy
Thiazide and loop diuretics*	Hypotension, falls, poor sleep, dehydration, electrolyte and metabolic disturbances, renal failure. A problem if poor mobility and urinary incontinence
Verapamil, diltiazem*	Bradycardia, AVB, constipation, hipotension (falls)

* Patients need to be educated about postural hypotension

CNS active drugs - Main adverse reactions

Drug	Caution
Anxiolytics	Sedation, drowsiness, instability → falls, urinary incontinence, hypotension, constipation, delirium
Anticholinergics (~23%): - 1st generation antihistamines - Antipsychotics - Antidepressants (TCAs) - Bladder antimuscarinics - Muscle relaxants - Sedative hypnotics	Dry mouth, constipation, urinary retention, blurrred vision, aspiration pneumonias, tachycardia Cognitive and psychomotor impairment, dementia, delirium, drowsiness, confusion, parkinsonism, instability, falls, hip fracture, loss of independence Precipitate acute glaucoma and urinary retention (BPH) ↑ hospitalizations, length of stay and mortality *Can´t see, can´t pee, can´t spit, can´t sh*t*
Benzodiazepines	Drowsiness, delirium, confusion, falls, hip fracture
Antidepressants (22%): TCAs, SSRIs	Confusion, dizziness, falls, urinary retention, falls Cardiotoxicity, increased risk of stroke and HF
Anti-psychotics	Cognitive impairment, sedation, cardiac arrhytmias, parkinsonism, increased risk of stroke and HF, hip fractures, falls, osteoporosis, disability ↑ risk of death in patients with dementia
Opiates	Constipation, respiratory depression, delirium

↑: increase. SSRIs: selective serotonin reuptake inhibitors. TCAs: tricyclic antidepressants

Potentially inappropriate prescriptions in people ≥75 ys

ACEIs/ARBs	Increased risk of hyperkalemia
Amiodarone	AF: not first choice unless HF or LV hyperthrophy
Anticoagulants, Antiplatelets	Increased risk of bleeding
Antihypertensive, Vasodilators	Orthostatic hypotension, risk of falls
Aspirin	Lack of evidence of benefit in adults ≥80
BBs + Verapamil	Bradycardia, AV block
Calcium channel blockers	Chronic constipation
Dabigatran, Prasugrel	With caution in ≥75
Digoxin	Avoid doses >0.125 mg/day for AF and/or HF
Diltiazem/Verapamil	NYHA III-IV HF
Loop diuretics	• For ankle edema, i.e. no clinical signs of HF • As first-line therapy of hypertension
Non-selective BBs	COPD
Spironolactone	>25 mg/day, Increased risk of hyperkalemia
Thiazides	History of gout (diabetes, hyperlipidemia)
Warfarin	• For first, uncomplicated DVT for longer than 6 months • For first, uncomplicated PE for longer than 12 mo

AGS BEERS CRITERIA 2015

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COPD: chronic pulmonary pulmonary disease. DVT: deep venous thrombosis. PE: pulmonary embolism.

American Geriatrics Society 2015 Beers Criteria Update Expert Panel. J Am Geriatr Soc205;63:2227–46

Tools to conduct a periodic medication assessment

- **BEERS Criteria. Drugs that should be avoided or adjusted because they are either ineffective or present unnecessarily high risk for older persons and a safer alternative is available**

American Geriatrics Society Beers Criteria® Update Expert Panel. J Am Geriatr Soc 2019; 67:674

- **STOPP – Screening Tool for Older Persons Prescriptions**
  - **Identify potentially inappropriate prescribing**
- **START – Screening Toll to Alert Doctors to Right Treatment**
  - **Helps to recognize potential prescribing omissions based on a patient's history**

Hill-Taylor et al. J Clin Pharm Ther. 2013;38:360-372

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Why is polypharmacy so widespread?

1. Ageing population; advances in medical management of diseases; and increasing use of preventive medications
2. Physicians tend to follow the guidelines: prescribe all the drugs recommended for each of the multiple diseases of the elderly

- However, guidelines are based on RCTs that:
  - Investigate a disease, not the individual patient
  - Very old, frail and those with co-morbidities are clearly under-represented/excluded
  - Hardly take into account polypharmacy in the context of multi-morbidity (CAD, DM, HF and COPD)
  - Focus on reduction of 'hard' clinical outcomes (MI, stroke, death)
  - Less attention to symptom relief and QoL, which might be of greater concern in the elderly
  - They may not pick-up ARs or interactions that occur in older people

A stepwise approach to prescribings in the elderly

- **Regular review of all drug treatment - Trust but verify "brown-bag check-ups"**
  - **Prescribed, nonprescribed, OCT, herbal products, dietary supplements**
  - **Screen for diet and nutritional state**
- **Define overall care goals: functional status, QoL, estimated life expectancy**
- **Are all drugs taken indicated and effective for the condition? (BEERS, START/STOPP tools)**
  - **Discontinue ineffective, unnecessary, incompatible or repeated medications**
  - **Are essential drugs actually prescribed?**
- **Are you following the treatment correctly?**
  - **Dosage, frequency, formulation, route of administration and duration**
  - **Simplify the treatment: 1/day, easy to swallow (liquids), medications with dual indications**
- **Provide drug information/education**
  - **Simple verbal/written instructions) for every medication to patients/caregivers at each visit**
- **Screen for ADRs and drug interactions when patient experience a new symptom**
  - **Evaluate its cause and severity - 50% are deemed preventable**
- **Communication between hospital and community care providers is essential**
- **Adopt a multidisciplinary approach (GPs, pharmacists, nurses…..)**

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Conclusions

- Polypharmacy is common in the elderly due to the need to treat the various disease states (pluripathology) that develop as a patient ages
- Polypharmacy is required to improve clinical outcomes in the elderly
  - When inappropriate: decreases the QoL and increases AEs, drug-interactions, morbidity, mortality and healthcare costs
- RCTs and Clinical Guidelines forget the elderly patient with multi-morbidity and polypharmacy
- More training in managing complex multi-morbidity and polypharmacy in the elderly is required
  - Use tools to optimise medicines use

We dislike polypharmacy as much as it is possible, and we would never exhibit a remedy of any kind unless we had a scientific reason for so doing and unless we were prepared to defend our method of treatment

W. Newnham, Provincial Medicial and Surgical Journal, 1848