

A Comprehensive Protocol to Mitigate Inappropriate Medication in the Elderly

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Elderly

- Increasing population (by 2050 – 30% >65)
- Longer life expectancy
- Many chronic diseases
- Many different drugs
- New drugs coming to the market
(investment in chronic diseases)
- Higher rates of drug related morbidity and mortality



Medication Therapy Problems

- Drug use without indication; polypharmacy
- Indication without drug use
- Dose too low / too high
- Adverse drug reaction
- Drug interaction
- Inappropriate drug
- Lack of adherence or compliance
- Medication error



Adverse Drug Events (ADEs)

- Responsible for 5-28% of acute geriatric hospital admissions
- > 95% of ADEs in the elderly are considered predictable and approximately 50% are considered preventable



- “The desire to take medicine is perhaps the greatest feature which distinguishes man from animals.”
- Sir William Osler, in H. Cushing, *Life of Sir William Osler* (1925)



Inappropriate prescribing in the elderly

- Ranges from 20–79% depending on the study population, setting, country, specific tools used
 - Prescribing medications with potentially serious DDIs
 - Underuse
 - Overuse
 - Misuse (PIMs, inappropriate dose, inappropriate duration)



Screening Tools

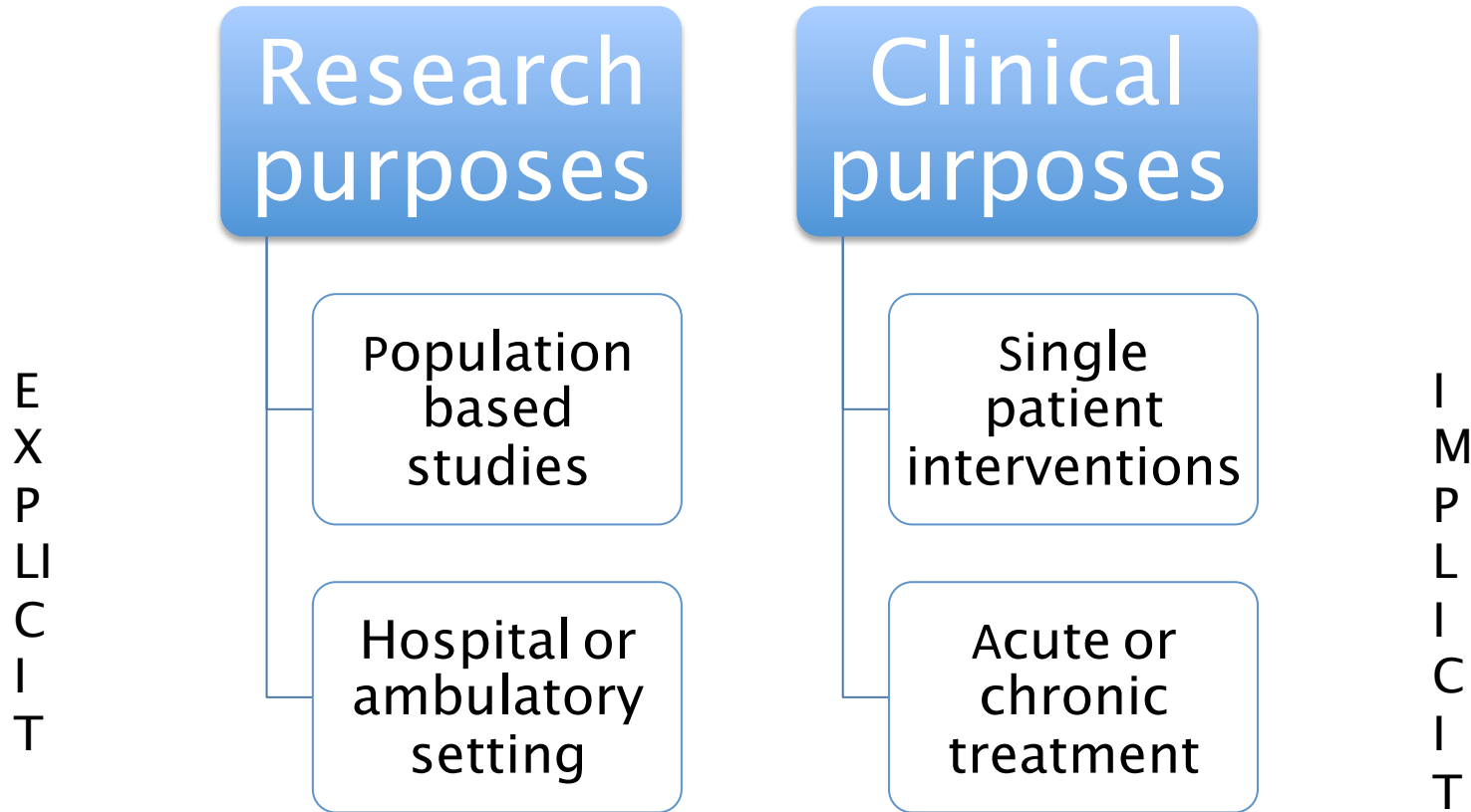
- Aim to improve medication appropriateness and / or avoid potentially serious ADRs
- Different degree of comprehensiveness and complexity
 - Explicit – criterion based
 - Developed from published reviews, expert opinions, consensus techniques. Can be applied with no clinical judgement
 - Implicit – judgement based
 - Patient specific, depend on users' knowledge, experience , attitude, time consuming
 - Combination
 - Explicit guidelines serve as background to supply user's clinical judgement of patient's medication
 - Implicit questions provide a patient specific approach



- Beers (1991,1997, 2012) USA
- McLeod (1997) Canada
- Naugler (2000) Canada
- Fick (2003) USA
- Laroche 2007 (France)
- Barry (2007) Ireland
- Gallagher (2008) Ireland
- Rognstad (2009) Norway
- Holt (2010) Germany
- Renom-Guiteras (2015) EU(7) PIM list
-



Tools



Combination
(computerized
decision support)



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REVIEW ARTICLE

Potentially inappropriate medications in the elderly: a comprehensive protocol

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Comprehensive protocol

1. Unfavorable risk / benefit ratio
 2. Drugs with questionable efficacy
 3. Drugs to be avoided with certain diagnoses / conditions
 4. Potentially serious DDIs
- suggests alternative therapeutic solution



Drugs with unfavorable benefit/risk ratio

DRUG	POSSIBLE ADVERSE EFFECTS	POSSIBLE THERAPEUTIC SOLUTIONS
Analgesics		
Indomethacin	Severe CNS side effects	Short-term use of a weak NSAID (e.g., ibuprofen) or acetaminophen or a weak opioid (e.g., tramadol)
Concomitant use of 2 or more NSAIDs	No enhancement of efficacy, increased risk of ADRs	Short-term use of only one weak NSAID (e.g., ibuprofen)
Long-term use of full-dosage, longer half-life NSAIDs: naproxen, piroxicam	Increased risk of GI bleeding, renal failure, high blood pressure and heart failure	Short-term use of a weak NSAID (e.g., ibuprofen) or use of acetaminophen or a weak opioid (tramadol, codeine)
Drugs with anticholinergic properties		
Antidepressants : amitriptyline, maprotiline	Muscarinic-blocking side-effects, cardiotoxicity when overdosed	SSRIs (except fluoxetine) or SSNIs
Antipsychotic drugs : fluphenazine, levomepromazine	Muscarinic-blocking side-effects	Atypical antipsychotic drug with less anticholinergic activity (e.g., olanzapine, risperidone, quetiapine)
Antihistamines : diphenhydramine, dimenhydrinate	Muscarinic-blocking side-effects, sedation, drowsiness	Antihistamines without anticholinergic activity (e.g., cetirizine, levocetirizine, loratadine, desloratadine)
Concomitant use of drugs with anticholinergic properties	Enhanced anticholinergic ADRs	Avoid drugs with anticholinergic activity in general
Sedative or hypnotic drugs		
Long- acting benzodiazepines : diazepam, bromazepam, nitrazepam, flurazepam	Prolonged sedation and drowsiness, increased risk of falls	Short-acting benzodiazepines given in doses \leq half the dose in younger adults
Short-acting benzodiazepines, dose > half the dose in younger adults (lorazepam > 3 mg, oksazepam > 60 mg, alprazolam > 2 mg)	Increased risk of ADRs without increased efficacy	Short-acting benzodiazepines given in doses \leq half the dose in younger adults
Meprobamat	Very sedative properties, addictive with prolonged use	Short-acting benzodiazepines given in doses \leq half the dose in younger adults



Drugs with unfavorable benefit/risk ratio

Antihypertensives		
Methyldopa	Bradycardia, exacerbation of depression	
Clonidine	Orthostatic hypotension	Other antihypertensive drugs, except the ones listed here (i.e., diuretics, calcium channel blockers [except short-acting ones], ACE inhibitors, AT1 blockers)
Moxonidine	Headache, vertigo, asthenia	
Nifedipine, short-acting	Postural hypotension, myocardial infarction, stroke	
Doxazosine	Hypotension, dry mouth, urinary incontinence	
Antiarrhythmics		
Amiodarone	Prolonged QT interval, risk of «torsade de pointes», reduced efficacy in the elderly	Other antiarrhythmics, depending on the type of arrhythmia (e.g., propafenone, beta blockers, calcium channel blockers)
Disopiramide	Negative inotropic and anticholinergic properties	
Digoxine > 0.125 mg	Reduced renal clearance and increased risk of ADRs	Digoxine < 0.125 mg, with serum concentrations 0.5-1.2 ng/ml
Antiplatelet drugs and vasodilators		
Ticlopidine	Blood and liver adverse effect	Clopidogrel, aspirin
Dipiridamole	Vasodilation and postural hypotension, questionable efficacy	
Drugs used to treat gastrointestinal disorders		
Cimetidine	CNS adverse events, confusion, common drug interactions	Other H ₂ -antagonists or proton pump inhibitors
Scopolamine	Muscarinic-blocking agent, no proven efficacy	Mebeverine
Long-term use of stimulant laxatives: bisacodyl, sennosides	Worsening of irritable bowel syndrome	Osmotic laxatives (e.g., lactulose)



Drugs with unfavorable benefit/risk ratio

Long-acting sulfonylureas		
Chlorpropamide, glibenclamide	Protracted hypoglycaemia	Short- or immediate-acting sulfonylureas (e.g., glipizide, gliclazide)
Muscle relaxants		
Baclofen	Drowsiness, amnesia, fall	Thiocolchicoside, mephenesine
Opioid analgesics		
Pentazocin	More CNS adverse effects, including confusion and hallucinations; mixed agonist and antagonist	Other opioids, with more favourable risk/benefit profile (e.g., tramadol, oxycodone)
Meperidine	Not an effective oral analgesic in doses commonly used. May cause confusion	
Other		
Ferrous sulfate >325 mg/d	Increased incidence of constipation	Dose <325 mg/d
Nitrofurantoin	Can induce renal insufficiency, pneumopathy, peripheral neuropathy, allergic reaction	Other type of antibiotics, depending on microbiology results
Methyltestosterone	Potential for prostatic hypertrophy and cardiac problems	Avoid testosterone substitution
Estrogens only (oral)	Carcinogenic potential and lack of cardioprotective effect	If necessary, combination of estrogens with progestagens. HRT to be used for the shortest time possible.
Thioridazine	Greater potential for CNS and extrapyramidal adverse effects	Atypical antipsychotic drug with less extrapyramidal adverse effects (e.g., olanzapine, quetiapine)
Daily fluoxetine	Long half-life of drug and risk of producing excessive CNS stimulation, sleep disturbances, and increasing agitation	Other SSRI or SSNI



A drug with unfavorable benefit/risk ratio in the elderly is:

1. diazepam
2. warfarin
3. azithromycin
4. simvastatin



A drug with unfavorable benefit/risk ratio in the elderly is:

1. Diazepam

Long-acting benzodiazepines (bromazepam, nitrazepam, flurazepam) may cause prolonged sedation and drowsiness, increase the risk of falls.
Alternative: short acting bzd in half dose

2. warfarin

3. azithromycin

4. simvastatin



Drugs with questionable efficacy

DRUG	POSSIBLE ADVERSE EFFECTS	POSSIBLE THERAPEUTIC SOLUTIONS
Cerebral vasodilators		
Dihydroergotoxine		
Gingko-biloba		
Pentoxifylline		
Piracetam	No really proven efficacy while there is risk of postural hypotension, falls, headache or stomach upset	Therapeutic abstention
Betahistine (except in the indication of Meniere syndrome and vestibular vertigo)		
Cinarizine (except in the indication of Meniere syndrome and vestibular vertigo)		



A drug with questionable efficacy in the elderly is:

1. ACE inhibitor ramipril
2. piracetam
3. piroxicam
4. propranolol



A drug with questionable efficacy in the elderly is:

1. ACE inhibitor ramipril
2. Piracetam
has no proven efficacy
3. piroxicam
4. propranolol



Drugs to be avoided with certain diagnoses / conditions

DISEASE OR CONDITION/DRUG	POSSIBLE ADVERSE EFFECTS	POSSIBLE THERAPEUTIC SOLUTIONS
Heart failure		
Disopyramide	Negative inotropic effect	Antiarrhythmic drug without negative inotropic effect
High sodium content drugs (sodium and sodium salts [bicarbonate, biphosphate, citrate, phosphate, salicylate, and sulfate])	Potential to promote fluid retention and exacerbation of heart failure	Avoid this type of drugs
Calcium-channel blockers, except , dihydropyridines	Negative inotropic effect.	Avoid verapamil and diliazem in these patients. Depending on the underlying diagnosis (hypertension, angina), drug without negative inotropic effect should be used
Long-term prescription of NSAIDs	Potential to promote fluid retention and exacerbation of heart failure	Acetaminophen or a weak opioid (e.g., tramadol). Monitoring of cardiovascular function.
Hypertension		
Pseudoephedrine	May produce elevation of blood pressure secondary to sympathomimetic activity	Avoid OTC cold and cough medications containing this substance.
Long-term prescription of NSAIDs	May produce elevation of blood pressure secondary to salt and water retention	Acetaminophen or a weak opioid (e.g., tramadol). Monitoring of blood pressure.
Chronic renal failure		
Long-term prescription of NSAIDs	May reduce renal blood flow and worsen renal failure	Acetaminophen or a weak opioid (e.g., tramadol). Monitoring of renal function.



Drugs to be avoided with certain diagnoses / conditions

Gastric or duodenal ulcers		
NSAIDs	May exacerbate existing or produce new ulcers	Acetaminophen or a weak opioid (e.g., tramadol). If use of NSAID is deemed unavoidable, use NSAID with less gastrointestinal risk (e.g., ibuprofen) in combination with proton pump inhibitors.
Aspirin	May exacerbate existing or produce new ulcers	Use in combination with proton pump inhibitors
Seizures or epilepsy		
Clozapine, thioridazine	May lower seizure threshold	Atypical antipsychotic drug without proconvulsive effect and with a favourable risk to benefit profile (e.g., olanzapine, risperidone, quetiapine)
Bupropion	May lower seizure threshold	SSRI (except fluoxetine) or SSNI
Blood clotting disorders or receiving anticoagulant therapy		
NSAIDs	Increased potential for bleeding	For analgesia use acetaminophen or a weak opioid (e.g., tramadol)
Aspirin	Increased potential for bleeding	If the combination is deemed unavoidable, use with extreme caution and regular monitoring of the patient
Clopidogrel		
Cimetidine (those taking warfarine)	May elevate INR values and increase potential for bleeding	Other H ₂ -antagonist or proton pump inhibitor
Bladder outflow obstruction		
Anticholinergics	May decrease urinary flow, leading to urinary retention	Use drugs without anticholinergic activity
Stress incontinence		
Alpha blockers (doxazosin, urapidil)	May induce or worsen incontinence	Use alternative antihypertensives (e.g., ACE inhibitors or AT1 blockers), antidepressants (SSRI or SNRI) and sedative/hypnotics (e.g., short-term use of short-acting benzodiazepines). Avoid anticholinergics.
Anticholinergics		
Tricyclic antidepressants		
Long-acting benzodiazepines		



Drugs to be avoided with certain diagnoses / conditions

Arrhythmias		
Tricyclic antidepressants	Concern due to proarrhythmic effects and ability to produce QT interval changes	SSRI (except fluoxetine) or SSNI
AV block		
Tricyclic antidepressants	May worsen heart block	SSRI (except fluoxetine) or SSNI
Digoxine	May worsen heart block	Avoid digoxine, non-dihydropyridine calcium channel blockers, beta blockers and antiarrhythmics
Verapamil		
Insomnia		
Decongestants	Concern due to CNS stimulant effects	Short term topical application
Theophylline		Inhaled bronchodilators
Methylphenidate		Avoid this type of drug
MAO inhibitors		Another type of antidepressant
Parkinson disease		
Metoclopramide	Concern due to their antidopaminergic/ cholinergic effects	Another antiemetic drug
Conventional antipsychotics (fluphenazine, haloperidol)		Atypical antipsychotics with less D2-blocking activity (e.g., quetiapine or clozapine)
Acetylcholinesterase inhibitors (donepezil)		Memantine for treatment of dementia
Depression		
Long-term benzodiazepine use	May produce or exacerbate depression	Short-term benzodiazepine use
Methylphenidate		Avoid this type of drug
Sympatholytic agents: methyldopa and reserpin		Another type of antihypertensive drugs (including beta blockers)



Drugs to be avoided with certain diagnoses / conditions

Anorexia and malnutrition		
CNS stimulants (methylphenidate)	Concern due to appetite-suppressing effects	Avoid this type of drugs
Fluoxetine		Use cautiously another type of SSRI or SNRI with
Syncope or falls		
Short- to intermediate-acting benzodiazepines	May produce ataxia, impaired psychomotor function, syncope, and additional falls	Avoid benzodiazepines
Long-acting benzodiazepines		Avoid benzodiazepines
Tricyclic antidepressants		SSRI (except fluoxetine) and SNRI
Conventional antipsychotics (fluphenazine, haloperidol)		Atypical antipsychotics with less alpha blocking activity (e.g., quetiapine, ziprasidone, aripiprazole)
SIADH/hyponatremia		
SSRIs	May exacerbate or cause SIADH	Most antidepressants and antipsychotics linked to SIADH. Consider stopping the treatment or use a drug with a different pharmacological profile and monitor serum sodium levels. Consider concomitant treatment with demeclocycline.
Obesity		
Olanzapine	May stimulate appetite and increase weight gain	Atypical antipsychotic drug without proconvulsive effect and with a favourable risk to benefit profile (e.g., olanzapine, risperidone, quetiapine)
COPD or asthma		
Long-acting benzodiazepines	May exacerbate or cause respiratory depression	Short-term use of short-acting benzodiazepines
Beta blockers - nonselective		Cardioselective beta-blockers



Drugs to be avoided with certain diagnoses / conditions

Chronic constipation		
Calcium channel blockers	May cause constipation	Other types of antihypertensives, except centrally acting, or another types of antianginal drugs (e.g., beta blockers, nitrate)
Anticholinergics		Avoid anticholinergics.
Centrally acting antihypertensives		Other types of antihypertensives, except calcium channel blockers
Opioid analgesics		Concomitant use of osmotic laxatives
Gout		
Thiazide diuretics	May precipitate or worsen gout	Use different type of antihypertensive (e.g., AT1 blocker losartan or a calcium channel blocker amlodipine)
Diabetes		
Corticosteroids	May precipitate or worsen diabetes	If corticosteroid therapy is unavoidable, use smallest dose possible and monitor blood glucose
Narrow-angle glaucoma		
Anticholinergics	Acute-angle glaucoma risk increased	Use drugs without anticholinergic activity
Osteoarthritis		
Long-term prescription of NSAIDs	May cause gastropathy, bleeding and salt and water retention	Acetaminophen or a weak opioid (e.g., tramadol). NSAIDs to be used for the shortest time possible (considering gastrointestinal risk of an individual NSAIDs)



Drugs to be avoided with certain diagnoses / conditions

Extrapyramidal effects of antipsychotic drugs		
Anticholinergics (e.g., biperiden)	May cause agitation, delirium and impaired cognition	Atypical antipsychotic drug with less extrapyramidal adverse effects (e.g., olanzapine, quetiapine)
Dementia		
Anticholinergics	May worsen cognitive impairment	Avoid all anticholinergics
Biperiden		Avoid and use other antiparkinson drug
All benzodiazepines		Short-term use of low dose benzodiazepines
Barbiturates		Avoid this type of drugs
Conventional neuroleptics		Atypical antipsychotics: risperidone, olanzapine, aripiprazole
Postural hypotension		
Thioridazine	May worsen postural hypotension	Atypical antipsychotic drug without alpha blocking properties (e.g., olanzapine, risperidone, quetiapine)
Tricyclic antidepressants		SSRI (except fluoxetine) or SSNI
Raynaud disease or peripheral vascular disease		
Long-term prescription of beta blockers	May worsen the underlying condition	Calcium channel blocker



Long term NSAIDs use should be avoided in the elderly with

1. Chronic renal failure
2. Pheriperal vascular disease
3. Hypertension
4. Gout



Long term NSAIDs use should be avoided in the elderly with

1. Chronic renal failure
May reduce blood flow and worsen renal failure
2. Pheriperal vascular disease
3. Hypertension
May produce elevation of blood pressure secondary to salt and water retention
4. Gout



Potentially serious DDIs

Clinically significant pharmacokinetic drug-drug interactions

(arrow indicates the influence of the second (interacting) drug on the concentration of the first, object drug)

Antiarrhythmics

Disopyramide - Cimetidine ↑
Disopyramide - Macrolides (except azithromycin) ↑
Procainamide - Amiodarone ↑
Procainamide - Cimetidine ↑
Procainamide - Trimethoprim ↑
Quinidine - Cimetidine ↑
Quinidine - Fluvoxamine ↑

Antiepileptics

Carbamazepine - Danazol ↑
Carbamazepine - Diltiazem ↑
Carbamazepine - Macrolides ↑
Carbamazepine - Verapamil ↑
Phenytoin - Amiodarone ↑
Phenytoin - Cimetidine ↑
Phenytoin - Fluoxetine ↑
Phenytoin - Isoniazid ↑
Phenytoin - Omeprazole ↑
Quinidine - Phenytoin ↓
Theophylline - Phenytoin ↓
Warfarin Phenytoin - PT-INR ↓

Other drugs with low therapeutic index

Digoxin - Clarithromycin ↑
Digoxin - Amiodarone ↑
Digoxin - Propafenone ↑
Digoxin - Quinidine ↑
Digoxin - Verapamil ↑
Lithium - ACE inhibitors ↑
Lithium - Diuretics ↑
Lithium - NSAIDs ↑
Procainamide - Cimetidine ↑
Salicylates - Probenecid ↑
Theophylline - Cimetidine ↑
Theophylline - Erythromycin, clarithromycin ↑
Warfarin - Amiodarone ↑
Warfarin - Macrolides ↑
Warfarin - Quinolones ↑
Warfarin - Sulfamethoxazole ↑

Potentially serious DDIs

Drug-drug interactions having greatest clinical importance (pharmacokinetic and pharmacodynamic)

Benzodiazepines – Azole antifungal agents
Cyclosporine – Rifampin
Ergot alkaloids – Macrolide antibiotics (except azithromycin)
MAO inhibitors - sympathomimetics (dopamine, ephedrine, phenylephrine, pseudoephedrine)
Meperidine - MAO inhibitors
Methotrexate - Trimethoprim
Nitrates - Sildenafil
SSRIs - MAO inhibitors
Theophyllines - Fluvoxamine
Theophyllines - Quinolones
Thiopurines - Allopurinol
Warfarin - Fibrin acid derivatives
Warfarin - Nonsteroidal anti-inflammatory drugs
Warfarin - Cimetidine
Warfarin – Thyroid hormones
Warfarin - Barbiturates

Other clinically important drug-drug interactions (pharmacokinetic and pharmacodynamic)

Atorvastatin/simvastatin - Amiodarone
Potassium – Potassium-sparing diuretics
Clopidogrel – Proton pump inhibitors (PPIs)
Levodopa - MAO inhibitors
SSRIs - Metoclopramide
SSRIs – Tramadol
HMG Co-A reductase inhibitors - Gemfibrozil
HMG Co-A reductase inhibitors - Macrolide antibiotics



Potentially serious DDIs

Clinically significant pharmacodynamic drug-drug interactions		
Object Drug/Drug Class	Interacting Drug/Drug Class	Outcome
ACE inhibitors	Potassium-sparing diuretics	↑ Potassium level
ACE inhibitors	Potassium supplements	↑ Potassium level
Anticholinergic	Anticholinergic	↑ Anticholinergic effect
Antihypertensive	NSAIDs	↓ Antihypertensive effect
CNS agents (eg, diazepam)	CNS agents (eg, codeind)	↑ CNS effect
Diuretics	NSAIDs	↓ Diuretic effect
NSAIDs, Aspirin	Cortikosteroids	↑ Peptic ulcer risk
Verapamil	Beta blockers	↓ Heart rate
Warfarin	Antiplatelet agents	↑ Risk of bleeding
Antiplatelet agent	Antiplatelet agent	↑ Risk of bleeding



Combination of verapamil and beta blockers may:

1. cause QT prolongation
2. induce hypoglycemia
3. decrease heart rate
4. cause angina pectoris



Combination of verapamil and beta blockers may:

1. cause QT prolongation
2. induce hypoglycemia
- 3. decrease heart rate**
4. cause angina pectoris



Comprehensive protocol

- Tested in real life environment – in relation to hospitalization for ADRs
- Acutely ill elderly patients admitted to hospital (2009 –2010)
- 454 consecutively admitted to the Department of Medicine at the University Hospital Osijek



Comprehensive protocol

- PIMs identified in 44% pts
- ADRs causing admission in 50 pts (11%)
- PIMs causing ADRs in 22 pts

- Potential DDIs found in 32%
- DDIs responsible for admission in 2 pts



Comprehensive protocol

- Tested in ambulatory setting
- County Primorsko-goranska in 2010
- All pts prescribed >5 drugs simultaneously
- ≈ 30.000 prescriptions analyzed



Comprehensive protocol

- 62% pts received at least one PIM
- Every tenth medication was inappropriate
- F_>M; benzodiazepines, antidepressants, NSAIDs
- M: theophylline, ACEi, amiodarone
- Limitation: Outcomes unknown



Principles of Prescribing in the Elderly

- Avoid prescribing prior to diagnosis
- Start with a low dose and titrate slowly
- Avoid starting 2 agents at the same time
- Reach therapeutic dose before switching or adding agents
- Consider non-pharmacologic agents



Prescribing Appropriately

- Determine therapeutic endpoints and plan for assessment
- Consider risk vs. benefit
- Avoid prescribing to treat side effect of another drug
- Use 1 medication to treat 2 conditions
- Consider drug-drug and drug-disease interactions
- Use simplest regimen possible
- Adjust doses for renal and hepatic impairment
- Avoid therapeutic duplication
- Use least expensive alternative



Preventing Polypharmacy

- Review medications regularly and each time a new medication started or dose is changed
- Maintain accurate medication records (include vitamins, OTCs, and herbals)



Non-Adherence

- Rate may be as high as 50% in the elderly
- Factors in non-adherence
 - Financial, cognitive, or functional status
 - Beliefs and understanding about disease and medications



Enhancing Medication Adherence

- Avoid newer, more expensive medications that are not shown to be superior to less expensive generic alternatives
- Simplify the regimen
- Pill organizers or drug calendars
- Educate patient on medication purpose, benefits, safety, and potential ADEs



- “One of the first duties of the physician is to educate the masses not to take medicine.”
- Sir William Osler, Aphorisms from his Bedside Teachings (1961) p. 105.



Suggested reading:

- Renom_Guiteras et al. Eur J Clin Pharmacol 2015;71:861-875
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- Popović et al. Eur J Clin Pharmacol 2014,70:737-744



- Not all diseases have a drug to be treated with
- Not all drugs have a disease to treat

