SPECIFICITIES OF PHARMACOTHERAPY IN PATIENTS OF SENIOR AGE

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- Demography of pharmacotherapy
- Why change prescription in geriatric medicine?
- How to change prescription in geriatric medicine?
- Drugs potentially unsuitable at senior age
- Drug mistakes in geriatric medicine

Demography of pharmacotherapy

- Seniors over 65 account for 14% of population HOWEVER they consume 35% of medicines
- Younger seniors 60 – 64 yrs.....83% of persons consume drugs
- Medium seniors 65 – 74 yrs.....89% of persons consume drugs
- Old seniors over 75.....91-98% of persons consume drugs
- Average number of consumed drugs increases with age
  - Outpatient seniors on average 4-6 drugs
  - Hospitalized on average 5-8 drugs

Sickness rate at old age

- Increase of total prevalence with age
- Changed spectrum of diseases – more chronic and degenerative diseases, more frequent acute decompensation and hospitalisation
- High invalidising potential of disease
- Important social component

Most frequent diseases in elderly persons:
Cardiovascular diseases (IHD, hypertension)
Locomotory system diseases (osteoporosis, arthritis)
Metabolic diseases (diabetes mellitus)
Gastrointestinal and respiratory diseases

Specific characteristics of old-age morbidity I

- Organs lose their functional reserve
- Lower adaptation to changes of both internal and external environment
- Easy decompensation of organ functions and organism as a whole
- Health state assessment is difficult – discrepancy between objective and subjective condition
- polymorbidity (concomitant diseases – unrelated; chain of causes: Immobilisation → phlebotrombosis → pulmonary embolism → pressure sores, urinary incontinence → sepsis)

Specific characteristics of old-age morbidity II

- Microsymptomatology – asymptomatology
  no fever, leucocytosis, silent myocardial ischemia
- Mono(oligo)symptomatology
  tachyfibrilation (thyreotoxicosis)
  - Non-specific symptoms
    fatigue, dysorexia, weight loss
- Secondary affection syndromes
  symptoms in other than the affected organ – the lowest reserve (brain – delirious state, kidneys)
- Catenating of symptoms (cascade reaction)
- Atypical drug reactions

Health disorders, invalidity, incompetency, disability

Criteria and definition:

The persons who are unable to perform activities corresponding with their age are considered to suffer from health disorders.

Geriatric patient requires a complex approach + individualization of therapy

- Age associated changes
- Polymorbidity
- Drug – drug, drug – disease interactions
- Chronic pharmacotherapy – changes in efficacy and safety with time, revision of medication every 6 months
- Course and results of treatment –

  – increased variability
- Safety of treatment

Complications of pharmacotherapy at old age

- Chronic diseases
- Disability
- Increase in post-medication reaction
- Polypharmacy
- Potentially inappropriate medicaments for elderly patients
- Non-compliance
- Change in pharmacokinetics
- Change in pharmacodynamics

Adverse post-medication events at old age

- 5–35% of outpatient seniors show post-medication reactions
- In 5.7–16.2% of patients these post-medication complications result in acute hospitalisation.
- Many of these reactions can be prevented (32–69% of cases)
- Large part of adverse events pass undiscerned – further medication prescription – prescription cascade
- Up to 70% of AEs depend on the dose, they can be eliminated via dose decrease
- Up to 30% of AEs are predictable
- Up to 20% of deaths in senior patients result from

Most frequent AEs in elderly patients

- Cardiovascular system – orthostatic hypotension, arrythmia, syncopes, falls
- Gastrointestinal system - diarrhea, constipation, sickness, vomiting
- Central nervous system - sedation, delirium, confusion, depression, extrapyramidal symptoms

Compliance decreases with old age

- Up to 60% of seniors do not take medications according to their doctor's recommendation
- Pharmacological compliance decreases with the number of drugs used and limited self-sufficiency (impaired eyesight, memory, ability, thinking)
- Social compliance - loneliness, isolation, poverty

Most frequently prescribed drugs in patients over 75 (Topinková ČR 2000)

- Vasodilators 65% of persons
- Analgesics 41% of persons
- Cardiotonics 40% of persons
- Diuretics 31% of persons
- Rheologics 28% of persons
- Calcium channel blockers 25% of persons
- ACE inhibitors 22% of persons

10 most frequently taken drugs in seniors (International study Shelter 2009 - 2011)

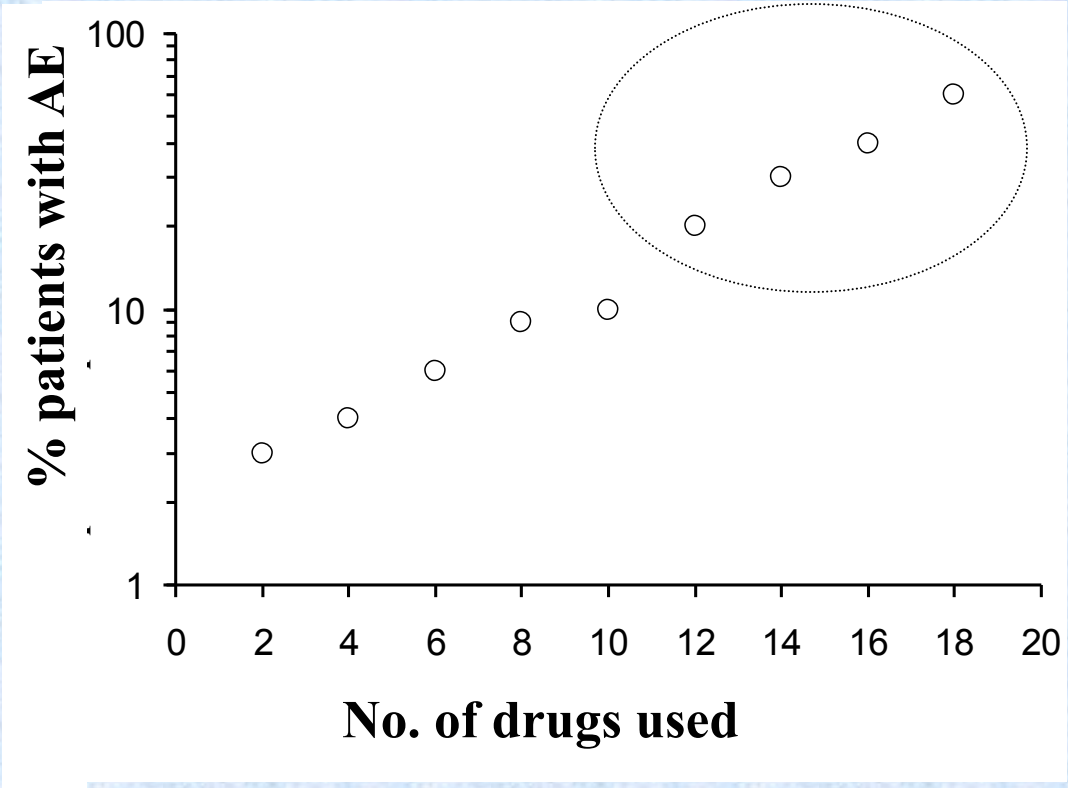
1. Laxatives 42%
2. Drugs for acid-related disorders 41%
3. Antiaggregatory drugs 38%
4. Benzodiazepines 36%
5. Antidepressants 36%
6. Diuretic stimulants 35%
7. Analgesics 34%
8. Antipsychotics 26%
9. ACE inhibitors 23%
10. β-blockers 23%

Polypharmacy

- Concurrent use of multiple drugs in a risky combination or in excess (clinically unnecessary)
- Usually 4 and more drugs
- Increases with age and polymorbidity

Adverse drug reactions

- A distinct factor of increased occurrence is the **number of concurrently used medications**



Polypharmacy

- Drug reactions often qualify a state considered to be a manifestations of ageing:

imbalance
giddiness
falls
nervousness
incontinence

somnolence
tiredness
asomnia
malaise
depression
confusion

Some may be indicative of a psychiatric treatment
→ with psychotropic drugs

Inappropriate prescription (most frequent mistakes)

- Insufficient treatment (underprescribing)

  Doctors do not prescribe drugs with demonstrable benefits (statins, antidepressants, ACEi)

- Redundant treatment with no indication (overprescribing)

  Hypnotics, benzodiazepines, peripheral vascular dilators, nootropics

- "Imperative drugging"

  A drug is prescribed for every single disease

- Prescription with a risk of interactions

- Prescription of high-risk profile medications

  Drugs that are counter-indicated for comorbidities (β-blockers + COPD)

Why change prescription in geriatrics?

AT OLD AGE

Changed pharmacodynamics

!

Changed pharmacokinetics

PHARMACOKINETICS at old age

- Influenced by age-related changes

Age-related changes in drug pharmacokinetics and their clinical consequences - ABSORPTION

Decreased splanchnic and periphery perfusion,

Decreased GIT motility,

Absorption area decay (atrophy of mucosa and villi)

Increase in ventricle pH

Prolonged absorption after p.o. / i.m. administration

Delayed reactions to medications

Age-related changes in drug pharmacokinetics and their clinical consequences - DISTRIBUTION

1. Decrease in total body water
2. Increase in body fat
3. Hypoalbuminemia

1. Increase in plasmatic levels for hydrosoluble medicines (↓ Vd)

2. Risk of cumulation of liposoluble medicines – toxicity, prolonged elimination

3. Increase in free fraction of medicines with albumin linking (frequent malnutrition)

Age-related changes in drug pharmacokinetics and their clinical consequences - METABOLISM

Decrease in weight and liver perfusion

Decrease in CYP3A4 function

Decrease in glucuronidase in very old persons

Slight slow-down in biotransformation

Increased risk of AE of drugs – drug interactions in polypharmacy

Age-related changes in drug pharmacokinetics and their clinical consequences– ELIMINATION

Decreased renal blood flow

Decreased glomerular filtration – physiological characteristic of old age

Decreased tubular secretion

Decreased excretion of drugs that are eliminated by kidneys

Prolonged T1/2 (amiodarone, digoxin, fluoxetine, alprazolam)

Danger of toxicity

Pharmacokinetic changes at old age

- **ABSORPTION** – increase in gastral pH, decrease of absorption area, decreased splanchnic perfusion, decrease in GIT motility
  - Slightly prolonged absorption phase in both oral and i.m. administration of drugs (delayed reaction to medications)

DISTRIBUTION – decrease in total body water, increase in total body fat (alteration of the body fat/water ratio), hypoalbuminemia

Less water ➔ smaller distribution volume for polar drugs (AMG, digoxin), increase in plasmatic levels of hydrosoluble drugs and risk of toxicity at cumulation of liposoluble medicines in fat tissue (phenytoin, BZD), increase in free (active) fraction of drugs with albumin linking

Pharmacokinetic changes at old age

METABOLISM – decrease in the weight of liver, in liver blood flow, in CYP 3A4 function, decreased glucuronidation in very old persons

- Slight slow-down in biotransformation, increased risk of AE mainly due to drug interactions in polypharmacy

ELIMINATION – Decrease in renal blood flow and in glomerular filtration, decreased tubular secretion

Prolonged drug effect, danger of toxicity already with physiological, i.e. age-related decrease in glomerular filtration of medicines excreted by kidneys

PHARMACODYNAMICS at old age

- Deterioration of homeostatic mechanisms
- Changes cause an increased risk of adverse and unexpected reactions
- Changes at receptor levels cause changes in tissue receptivity

Frequent clinical problems of seniors in relation to changes accompanying ageing: Drugs with a negative impact I

- Orthostatic hypotension (centrally effective antihypertensives, diuretics, β-blockers, tricycl. antidepressants, benzodiazepines)
- Postural instability (same drugs as with ort. hypotension)
- Extrapyramidal symptoms, dyskinesia (metoclopramide, classic antipsychotics, haloperidol)
- Decrease in cognitive functions, behavioural disorders, delirium (centr. sympatholytics, tricyclic antidepressants, barbiturates, benzodiaz., analgesics-anodynes, antiparkinsonian agents, antihistaminics, H2-blockers, theofyline, digoxin, indometacin)

Frequent clinical problems of seniors in relation to changes accompanying ageing: Drugs with a negative impact II

- Constipation, subileus (anodynes, tricycl. antidepressnats, antihistaminics, spasmolytics)
- Urinary incontinence (diuretics – loop, anticholinergics)
- Increased risk of hypothermia (sedatives, hypnotics, antipsychotics, vasodilatants, myorelaxants)
- Risk of hyponatremia, susceptibility to dehydration (chlorpropamid, diuresics, SSRI)
- Susceptibility to erectile dysfunction, gynaecomastia (α1-sympatholytics, sedatives, urin. tract spasmolytics, spironolaktone, digoxin)

Frequent clinical problems of seniors in relation to changes accompanying ageing: Drugs with a negative impact III

- Increased risk of bleeding (increased sensitivity to warfarin, heparin)
- Increased sensitivity to digoxine – AE already at therapeutical concentrations

General PRINCIPLES of pharmacotherapy in geriatric medicine

- **Is pharmacotherapy necessary?**
- **Which medication to choose?** Inappropriate: BDZ with a long half-life (or no BZD, amitriptyline, barbiturates (obsol.), indomethacine)
- **Opt for the smallest number of medicines possible.** Risk of AE, LI, non-compliance
- **Which drug form is to be used?** Syrup and suppositories are better
- **Modification of doses.** Dose and dose interval; start with a lower dose
- **Which AE can be expected?**
- **Is the patient capable to take the drug/s) himself/herself?**

General PRINCIPLES of pharmacotherapy in geriatric medicine

- Know the effects of changes caused by ageing on the effects of medicines
- Try to contribute to optimization of compliance (adherence)
- Know the drugs that are better to be avoided in geriatric medicine

Mark H. Beers, 54, Expert on Drugs Given to Elderly, Dies Feb 28, 2009

Beers' List

— Potentially Inappropriate Medications for the Elderly

It is not about counterindications at administration, however utmost care is required!!!

Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. ***Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts.*** *Arch Intern Med. 2003;163:2716-2724*

New Beers' criteria (modified) 2012, 2015!!!

BEERS' LIST – for instance:

Medicament/drug group	Note, risks
Tricyclic antidepressants	Significant anticholinergic effect, risk of sedation, orthostatic hypotension and arrhythmias. SSRI are a safer alternative.
Barbiturates (nowadays obsolete)	Significant sedation, habit-forming, especially those with short-term effect are inappropriate.
Benzodiazepines	Risk of sedation, habit-forming, drugs with a long half-life are inappropriate (diazepam, flurazepam, chlordiazepoxid); benzoadiazepine (oxazepam) with a short-term effect is more suitable, or nowadays these are not recommended at all!
Meprobamate	Sedation, habit-forming, induces delirium,

Drugs potentially inappropriate at old age according to Beers‘ criteria of 2003

- benzodiazepines
- (barbiturates)
- fluoxetin
- central anorectics
- digoxin
- methyldopa
- amiodaron
- ticlopidin
- indometacin, naproxen, piroxikam
- promethazin
- laxatives

General PRINCIPLES of pharmacotherapy in geriatric medicine

- Know the effects of changes caused by ageing on the effect of medicines
- Try to contribute to optimization of compliance (adherence)
- Know the drugs that are better to be avoided in geriatric medicine
- Know the **7 fundamental principles** of prescribing drugs in geriatric medicine

Seven fundamental principles of drug prescription in geriatric medicine

1. Remember a drug can cause a pathological symptomatology (disease)
2. Seek for establishing the diagnosis prior to prescription
3. Know the pharmacology of the prescribed drug well
4. Start „low" and proceed slowly; better still: start „low" and stay „low“

„Start low, go slow.“

„Start with a low dose
and increase it slowly.“

Seven main principles of drug prescription in geriatric medicine

1. Remember a drug can cause a pathological symptomatology (disease)
2. Seek for establishing the diagnosis prior to prescription
3. Know the pharmacology of the prescribed drug well
4. Start „low" and proceed slowly; better still: start „low" and stay „low“
5. Be aware of other medications of the patient
6. Be careful about compliance
7. Regularly check the list of drugs taken

How to change prescription in geriatric medicine?

Low-dose regimes

„Start low, go slow“

Appropriate introductory dose = ½ of adult dose

Drugs with confirmed efficacy at lower doses:

omeprazol: half of plasmatic clearance, double t1/2 already after the 1st dose, recommended doses for the elderly=10 mg)

atorvastatin (10 mg)

enalapril (2.5-5 mg 2x day),

diclofenak (75mg/day)

ibuprofen (200 mg 3-4x day)

ranitidine (100 mg 2x day)

fluoxetine (2.5 – 10mg/day or every other day)

metoprolol (50mg/day)

Adverse drug interactions

- Drug – drug interaction:

– warfarin + sulfonamide (competition for a linkage to plasm. proteins)

– alprazolam + zolpidem (drugs of the same group, potentiation of reaction)

– anticholinergics + drugs with a high absorption capacity, antacids (slowed resorbence)

- Drug - disease interaction:

- verapamil + impulse transfer disorder (heart rhythm disorder)
- opiates, anticholinergics + dementia (delirium)

- Drug – food

- grapefruit juice (CYP3A4 inhibitor)
- Herbaceous vegetables (vit. K – decreases the effect of warfarin)
- chinolons + minerals (decreased absorption of chinolons)

Expert recommendations for geriatric pharmacotherapy

- Expert consensus for the CR 2012
- Recommended approach: Geriatric medicine for general practitioners 2010
- Beers' criteria of 2003 (USA)
- Laroche 2007 (France)
- STOPP/START 2008 (Ireland) take into account (in)appropriateness of drugs at simultaneous assessment of patient‘s chronic diseases
- New Beers' criteria 2012

Potentially inappropriate medications at old age

PIMs – potentially inappropriate medications
- the term coined by Beers in 1991 (USA)

= Drugs the potential **risk** in seniors over 65 **overtops expected benefit** at long-term treatment, or the efficacy of the medication is inadequate or inadequately verified

- Indication unsupported with scientific evidence
- Higher risk of post-drug reactions
- Low cost effectiveness
- A safer alternative is available in the market

AGS Beers' criteria for application of PIMs (potentially inappropriate medications) in seniors American Geriatric Society – updated 2012

- Interdisciplinary panel of 11 experts
- Systematic overview and recording of adverse effects and post-drug reactions in elderly patients
- The list includes 53 drugs or drug groups
- 3 categories:
  1. Medications that should not be used in senior patients
  2. Medications that should not be prescribed to seniors suffering from certain diseases and syndromes
  3. Medications that should be used cautiously with senior patients

- „Less is more approach“

Journal of American Geriatric Society 2012

(Expert consensus for the CR 2012)

- Recommendations created on the grounds of consensus of a multidisciplinary panel of experts in geriatric, internal medicine, GP, clinical pharmacy and clin. pharmacology
- The list of potentially inappropriate includes altogether 71 medications
  - Inappropriate medications (part I)
  - Drugs/drug groups inappropriate for seniors in specific situations/ with specific comorbidities (part II)
    - Drug-disease interaction (68 items)
    - Duplicate prescription (1 item)
  - Recommended drugs/procedures (part III)
    - Beneficial for patients and omitted from prescribing (22 items)

(Expert consensus for the CR 2012)

The list is NOT a prohibition of prescription
BUT
a recommendation to limit the prescription of these drugs inappropriate for seniors, and not to prescribe these drugs as medications of first choice. In case of their prescription their effect and adverse effects have to be carefully monitored

http://www.prolekare.cz/prakticky-lekar-clanek/potencialne-nevhodna-rizikova-leciva-u-senioru-expertni-konsensus-pro-ceskou-republiku-2012-37322

STOPP and START criteria (Ireland 2008)

- Listed according to physiological systems

STOPP criteria – cardiovascular system

- digoxin – Dosed 0.125 mg/day on a long-term basis in decreased kidney function (Kr/S > 150 μmol/l and GF < 50ml/min)
- Loop diuretics with oedemas without signs of heart failure (unverified efficacy; suitable compression of extremities
- Loop diuretics in monotherapy treating hypertension (safer and more efficient alternatives)
- thiazide diuretics with gout (danger of causing an attack)
- non-CS β-blockers with COPD (risk of bronchospasm)
- diltiazem or verapamil with hearth failure NYHA III-IV (risk of retrogression)
- Ca channel blockers with chronic constipation
- ASA + warfarin without protection against GIT bleeding (H2 antagonists, proton pump inhibitors)
- dipyridamol in secondary prevention of CVS in monotherapy
- ASA dosed > 150 mg/day (unsubstantiated efficacy)
- ASA with missing history or symptoms of IHD
- warfarin unsubstantiated benefit of treatment longer than 6 months with uncomplicated deep vein thrombosis)
- warfarin longer than 12 months in uncomplicated pulmonary embolus

STOPP criteria–
CNS and psycho-active drugs

- Tricyclic antidepressants:
  - Patients with dementia (risk of cognitive deficit)
  - Patients with glaukoma (risk of acute glaukomatous attack)
  - Patients with heart conduction disorder (proarrythmogennic effect)
  - Constipation (worsening)
  - In combination with opioides or Ca channel blockers (constipation)
  - Benign prostatic hyperplasia or retention of urine (risk of retention)
- Long-term (> 1 month) treatment with benzodiazepines in hypnotic indication (hypotension, falls, confusion, extrapyram. sy)
- Long-term (> 1 month) treatment with antipsychotics at parkinsonism (worsening of extrapyramid.sy)
- fenohtiazine antipsychotics (chlorpromazin, levopromazin) – decrease threshold of attack
- SSRI at hyponatremia (Na < 130 mmol/l)

STOPP criteria– gastrointestinal system

- Diphenoxylate, loperamid, codein
  - Therapy of diarrhoea without inquiring into cause
  - At infectious gastroenteritis
- metoclopramide at parkinsonism
- Proton pump inhibitors in VCHGD therapy exceeding 8 weeks in full ther. dose

STOPP criteria– respiratory system

- theofylin in monotherapy of COPD (narrow (low) therapeutical index)
- System corticoids in maintenance therapy of COPD instead of inhalatory therapy
- ipratropium in nebulized form at glaukoma (risk of inducing an attack)

STOPP criteria– musculoskeletal system

- NSA with history of VCHGD or GIT bleeding without concurrent preventive treatment with gastroprotectives
- NSA long-term treatment in excess of 3 months to treat mild dolour at osteoarthritis
- Combination of NSA and warfarin
- Long-term treatment with NSA and colchicine in chronic gout therapy if allopurinol is not contra-indicated

STOPP criteria – urogenital system

- Musculotropic spasmolytics (antimuscarinic drugs)
  - Anticholinergic AE – confusion, agitated state
  - chron. glaukoma – danger of glaukomatous attack
  - Prostatic hyperplasia (risk of urine retention)
- Alpha blockers
  - In benign prostatic hyperplasia (risk of ziko pollakisuria, incontinence)
  - With bladder catheter indwelling longer than 2 months

STOPP criteria– endocrine system

- glibenclamide in type II DM (risk of prolonged hypoglycaemia)
- β-blockers in DM (risk of hypoglycaemia, risk of masking the symptoms)

STOPP – patients with a history of falls

- benzodiazepines
- Antipsychotic drugs
- 1st gen. antihistamine drugs
- Vasodilatants
- Opioids

STOPP – analgesics

- Strong opioids (morphine, fentanyl)
- Long-term use of opioids (longer than 3 months), if laxatives are not used simultaneously, there is a risk of worsening cognitive deficite (exception: paliative therapy, severe chronic pain)

START criteria – cardiovascular system

- warfarin in patients with chronic atrial fibrillation
- ASA in patients with chronic atrial fibrillation, if warfarin is contraindicated
- ASA or clopidogrel in proven ischemic disease (of heart, brain, periph. arteries)
- Antihypertensives in BPsyst > over 160 mmHg
- Statines in secondary prevention, in active seniors with life expectation > 5 years
- ACEi in chron. heart failure
- ACEi after acute myocardial infarction
- β-blockers in chronic stable angina pectoris

START criteria - endocrine system

- metformin in type II DM with/without metabolic syndrome (with preserved renal functions (Kr/S < 150 µmol/l and GF > 50ml/min)
- ACEI or blockers for AT1 in diabetic patients with nephropathy – proteinuria or microalbuminuria (> 30 mg/24 hr) +/- biochemic signs of renal failure
- Statines in diabetic patients with presence of 1 and more CVS risk factors (hypertension, hypercholesterolemia, nicotinism)
- Antiagregation therapy in diabetic patients with presence of 1 and more CVS risk factors (hypertension, hypercholesterolemia, nicotinism)

START criteria - continued

Gastrointestinal system:

Proton pump inhibitors in GERD (gastroesophageal reflux disease), peptic oesophageal stricture

Musculoskeletal system:

Supplementation with calcium and D vitamin, in dg. osteoporosis, after osteoporotic fracture, with osteoporotic dorsal cyphosis

bisphosphonates using systemic corticosteroids

Disease modifying drugs (DMARDs) in active medium severe to severe RA lasting > 12 weeks

CNS:

L-DOPA in idiopatic Parkinson disease with functional limitation and disability

antidepressants in patients with medium severe to severe depression lasting > 3 months