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Review Article

Certain Aspects of Drug Therapy for Older Patients

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Abstract

The number of persons older than 60 years are growing yearly across the globe. Older and elderly patients take a considerable number of medications (8 drugs on average). However, drug therapy for older patients must be implemented with special caution. Age-related changes lead to reduction of excretion rate, increased half-life of a drug, inadequate drug response, affecting toxic effects of therapy in general. Because the use of a medication may cause adverse effects per se, one must consider potential effects and symptoms of overdose on certain medications in geriatrics clinical practice.

Keywords: *Older Age; Geriatric Syndromes; Adverse Effects of Drug Therapy*

Introduction

The number of persons older than 60 years are growing yearly across the globe. It is expected that this number would increase from 962 mln. to 2,1 bln. people by 2050 and up to 3,2 bln. people by 2100 [1].

The incidence rate in the older persons group (65 - 74 y.o.) is twice as high as among younger people. The rate in the elderly group (75 y.o. and older) is six times the rate among younger people. Ageing leads to increase in chronic and other diseases and prejudices the body's natural ability to respond to endo- and exanthropic causes [2].

Older and elderly patients take a considerable number of medications (8 drugs on average in case of epilepsy and 8,6 - in case of the Parkinson's disease). Most of these drugs are often prescribed without any medical indications (up to 40% of prescribed medications) [3]. However, drug therapy for older patients must be implemented with special caution.

Age-related changes lead to reduction of excretion rate, increased half-life of a drug, inadequate drug response, affecting toxic effects of therapy in general. Because the use of a medication may cause adverse effects per se, one must consider potential effects and symptoms of overdose on certain medications in geriatrics clinical practice [4].

Geriatric syndrome and potential effects of certain drugs: There are three main groups of geriatric syndromes [5]:

1. Somatic (malnutrition syndrome, pressure ulcers, gatism, gait disorders, vertigo and ataxy, pain syndrome, hearing and vision impairment and faintness);

2. Psychic (dementia, depression, delirium, behavioral and adaptation disorders);

3. Social (loss of ability for self-service, dependency on outside assistance, social isolation, susceptibility to violence, severance of family bonds).

In vivo, all three groups are collectively referred to as senile asthenia syndrome (SA) that manifests itself in more than 85 symptoms. The most common symptoms are general weakness, sluggishness and/or unintentional weight loss. SA is accompanied by the reduction in physical activity level and functional fitness, depletion of the adaptation and reparative reserves and leads to dependency on outside assistance and the loss of ability for self-service in daily life [6].

Older patients are assumed to be at high risk of cardiovascular diseases. Such patients are usually prescribed with 2 - 3 antihypertensive drugs, peroral antidiabetic medications, statins and allopurinol [7]. The combination of these drugs substantially increases the risk of unwanted effects and adverse reactions [8]. A therapist must be familiar with potential high-risk combinations of certain cardiovascular drugs (Table 1) [9].

Interacting Drugs		Kinetics and Dynamics
MAOI/tricyclic antidepressants	Epinephrine, norepinephrine, phenylephrine, ephedrine, tyramine, amphetamine, cocaine, amphepramone, caffeine, products containing thiamine, etc.	Increased amines excretion rate and slow-down of endogenous and exogenous amines inactivation lead to higher levels of toxicity and arousal of different CNS' systems, hypertensive crisis, tachycardia, severe headaches (hypertensive encephalopathy), loss of consciousness and cerebral hemorrhage.
	Reserpine, guanethidine, levodopa, methyldopa, clonidine	Cardiotonic effects, tachycardia, repolarization, perverted effect on blood pressure (sharp increase), increased hypoglycemic effect.
Digitalis	Aminoquinolines	Increase in blood digoxin level and cardiotoxicity
	Anti-arrythmia drugs (tiracizine, quinidine, amiodaron, etc.), calcium antagonists (verapamil, diltiazem)	Acute manifestation of cardiotoxicity (increased negative dromo- and chronotropic effects), decreased conductivity, arrhythmogenic effects
	Thiazide and loop diuretics	Hypoglycemia, increased toxicity, increased chances of overdose on heart glycosides
	Adrenomimetics (epinephrine, norepinephrine, orciprenaline), sympathomimetics (ephedrine), methylxanthines (caffeine, theophylline)	Mutual increased of arrhythmogenic effects period (increased heterotrophic arousal)
Nitrates	Sildenafil	Increased vasodilatory and anti-aggregate effect
Adrenostimulants	Halothane	Pacing disorders (extrasystolia, etc.)

Table 1: *High-risk combinations of cardiovascular drugs.*

In geriatrics, even mono-drug therapy can lead to occurrence of new pathological conditions. For instance, the use of uretic drugs, beta-adrenergic blocking agents, calcium channel blockers, antidepressants, NSAIDs, opioids, or sedatives increases the fall risk [10].

Another factor affecting a drug therapy for older patients is the presence of cognitive disorders. These disorders are usually caused by aging changes and the progression of neurodegeneration processes. However, another cause of such disorders could be the adverse ef-

fects of drug therapy [11,12]. A therapist must remember that cognitive disorders and associated conditions may be caused or worsened by intake of neuroleptics, benzodiazepines, antidepressants, barbiturates, opioids, anti-Parkinson and antiepileptic medications, antitumoral drugs, diuretics, corticosteroids and glycosides.

Cholinolytic agents may adversely affect memory function [12]. Such agents can be found in creams, and SARI drugs. Although some drugs are not considered cholinolytics as such, these drugs may possess cholinolytic properties. For instance, prednisolone, digoxin, nifedipine and ranitidine have atropine-like effects. This group of medications may cause the following side-effects: confusion, disorientation, hyperarousal, hallucinations and delirium, dry skin and mucous membranes, vision impairment, loss of balance, tachycardia and other pacing disorders, and urinary retention. One of the diagnostic signs that cognitive disorders and associated conditions were caused by the intake of cholinolytics is the improvement of a clinical picture after the withdrawal. However, cholinolytic-caused is often mistaken with the Alzheimer.

In recent years, anticonvulsants have been frequently prescribed to patients with chronic pain, sugar diabetes and migraine. There is no scientific evidence that this group of medications adversely affect cognitive functions. However, older patients may develop various disorders, including dementia, during the intake of topiramate, carbamazepine, lamotrigine and valproates [13]. Topiramate adversely affects speech and calculus functions, short-term memory. Valporic acid drugs may cause dementia and cerebral atrophy (prseudoatrophy).

Lithium is used in geriatrics to treat depression, delusional and affective disorders [14]. Older patients may develop muscle weakness, early fatigue, muscular twitching, sluggishness, lethargy, drowsiness, coarse tremor, ataxy, muscle hypertone, increased deep tendon reflexes, mutism, confusion, catatonia, epileptiform attacks, articulation disorder, attentional focus impairment, headaches, visual hallucinations, early extrapyramidal disorders, benign intracranial hypertension. These symptoms are often attributed to dementia or other cognitive disorders and may look like onset of the Creutzfeldt-Jakob disease. Patients with long term intake of lithium for preventive purposes demonstrate so-called "autopilot syndrome". These patients mainly complain of emotional dampening, a feeling of depersonalization or loss of creativity and in some cases demonstrate memory impairment and perception disorder.

Long term intake of neuroleptics and antidepressants may lead to dementia [15] with the development of a neurovisualized cerebral atrophy. The chances of dementia misdiagnosis are higher when there is no expression of extrapyramidal side effects. Changes in cognitive functions may persist for 2 - 3 months after neuroleptic's or antidepressant's withdrawal. It is recommended that therapists avoid prescribing drugs with cholinolytic properties (e.g. tricyclic antidepressants) in treatment of depression of older people. Prescription of selective serotonin reuptake inhibitors is more reasonable.

Benzodiazepines (diazepam, phenazepam, nitrazepam) are commonly used in geriatrics [16,17]. Benzodiazepines' potential side effects include frontal lobe syndrome, drowsiness and confusion.

Corticosteroids and antitumoral drugs. The adverse effect of corticosteroids and antitumoral drugs is linked to their effect on hippocampus [18]. Patients may often develop psychosis, whereas patients with demyelinating diseases intaking may experience memory dysfunction after pulse-therapy with methylprednisolone. Patients who intake methotrexate, cisplatin, cytosine, arabinoside or other antitumoral drugs may develop cognitive disorders and leukoencephalopathy. Diagnosed dementia is usually subcortical, the patients often demonstrate walking and pelvic impairment, and less often, epileptic seizures. The cognitive disfunction is progressive, however, spontaneous improvements of clinical picture are not uncommon.

Aging processes affect pharmacokinetics and pharmacodynamics. In older patients, all pharmacokinetic processes are slowed down which leads to an increased blood concentration of outbound agents. The number of specific receptors decreases, but their sensitivity to medication increases and perverts, when delivery of a medical agent is impaired. Low physical activity, lesser consumption of nutrients and vitamins, dehydration, constipation, impaired blood circulation and CNS arousal contribute to the occurrence of perverted reactions

[19]. This explains why older patients usually need less than standard average doses of medications. When a therapy goal is reached the dosage is further decreased and maintenance dose is prescribed (this is dose is also lower than that used in treatment of middle-age patients). It is recommended that older patients limit intake of psychoactive medications and neuroleptics (including sedatives, sleeping pills, tranquilizers and antidepressants).

Signs of incorrect dosage of certain medications

The signs of incorrect dosage of and overdose on drugs are myosis, bradycardia and dysuria. These symptoms are collectively referred to as mediator toxic syndromes (or mediator toxindromes). Early identification of mediator toxindromes is crucial for diagnosis and adequacy of the treatment (Table 2) [20,21]. We analyze the side-effects of overdose on the most-commonly prescribed antihypertension drugs in greater detail below.

Syndrome	Signs	Potentially Causing Drugs
Adrenergic	Mydriasis (no changes in pupils); arterial hypertension, bradycardia (α-adrenergic systems arousal); tachycardia (β-adrenergic systems arousal); hear sounds are loud, the gallop rhythm; pale and moist skin (α-adrenergic systems arousal); decline in intestine motor function, muscle hypertone; rhabdomyolysis in severe cases	Sympathomimetics, antidepressants, flu medications, adrenomimetics, amphetamines, phosphodiesterase inhibitors (aminophylline (Euphylin)), caffeine, phencyclidine, thyroid hormones, naloxone
Sympatholytic	Myosis, arterial hypotension, bradycardia, heart sounds are muffle and split; respiratory distress; decline in intestine motor function; muscle hypotone	Sympatholytics, clofeline, Beta-blockers, Calcium channel blockers, reserpine, quinidine, opioids and homologous drugs.
Cholinergic	Myosis, accommodation spasm; bradycardia or tachycardia, heart sounds are muffle, bronchorrhea; crepitations in lungs; diarrhea; moist skin and mucous membranes; lacrimation; salivation; profused defecation and urination; myofibrillation; convulsions	Cholinomimetics, anticholinesterase medications, cholinosensitivity enhancers, alcohol, heart glycosides, opiates and opioids, benzodiazepines
Anticholinergic	Arousal, delirium; mydriasis, accommodation paralysis, tachycardia, amplified heart sounds; dry skin and mucous membranes, decline in intestine motor function; urine outflow obstruction	Antihistamine drugs, antidepressants, neuroleptics, sedatives, cholin blockers, belladonna alkaloids

Table 2: *Classic mediator syndromes.*

We analyze the side-effects of overdose on the most-commonly prescribed antihypertension drugs in greater detail below.

Angiotensin-converting enzyme inhibitors (perindopril, ramipril, lisinopril, quinapril, cilazapril, enalapril, etc.)

The overdose on angiotensin-converting enzyme inhibitors causes cough (particularly rough among smoking patients) that prevents effective treatment. Other side-effects (e.g. skin reactions, adverse effects on blood chemistry and CNS) are uncommon [20]. Patients with hyponatremia and hyperthermia often demonstrate sharp drops of blood pressure. The toxic effects of medications are more related to accompanying diseases (e.g. proteinuria in patients with renal arteries stenosis), rather than the dosage as such.

The severity of the toxic effects associated with the overdose is related to orthostatic conditions, found in patients who:

1. Intake cardio-depressants (including cytostatics);
2. Intake diuretics;
3. Undergo dialysis;
4. Suffer from hyperhidrosis; or
5. Dehydration caused by GI tract pathologies.

One should keep in mind, that only captopril and lisinopril are considered direct effect medications. The pharmacodynamics of other drugs involves a biotransformation stage at which the prelate agent is activated. The pharmacodynamics explains delayed development of intoxication.

Mild overdose

The symptoms of include moderate hypotension, and, less often, bradycardia and mild hyperkalemia (during long term intake of medications). Patients with a complicated anamnesis (chronic renal failure, renal arteries stenosis) may develop oliguria, a condition that often leads to misdiagnosis.

Moderate overdose

The symptoms of moderate overdose include manifested hypotension, in particular, in patients with hypernatremia (displayed during intake of diuretics, carbamazepine, azithromycin, chlorpropamide, cisplatin and other agents causing disproportionate secretion of antidiuretic hormone).

Mediator syndrome is absent; however, patients may experience dry mucous membranes (intestine peristalsis is present, serving a diagnostic sign of overdose). Further, the level of potassium may be higher than 5,7 mmol/L (manifested hyperkalemia).

High overdose

The symptoms are extreme hypotension, hyperkalemia, arrhythmia, oliguria, edema and CNS oppression syndrome.

The patients may experience side-effects affecting other functional systems (blood chemistry, skin reactions) at any overdose level.

Beta-adrenergic blocking agents (propranolol, metoprolol, nebivolol, betaxolol, bisoprolol, pindolol, sotalol, etc.)

The overdose on beta blockers usually affects cardiovascular system; metabolism and lung breathing. The toxic effect of beta blockers is always dose dependent. The severity of the side-effects is linked to the symptoms of the beta adrenergic blocking syndrome:

1. Bradycardia;
2. Hypotension;
3. Vertigo;
4. Hyperhidrosis;

5. Hypoglycemia;

6. CNS oppression with present intestine peristalsis.

Hemodynamics, pacing disorders and hypoglycemia may be accompanied by complications, particularly dangerous to older patients and patients with sugar diabetes. Side effects affecting the GI tract are less expressed. This group of medications induces withdrawal syndrome that may provoke acute coronary syndrome [21].

Mild overdose

The symptoms are mild bradycardia, that may develop without initial drop in blood pressure. Patients complain of general weakness, drowsiness (in particular, during the intake of lipophilic drugs), diaries, constant feeling of cold and feet chilliness. These conditions are associated with hypoglycemia. Asthmatic components are present during chest auscultation.

Moderate overdose

The symptoms are manifested bradycardia, AV-block, hypotension, hypoglycemia that is difficult to correct in patients with sugar diabetes and alcohol dependency.

Massive overdose

The symptoms include extreme bradycardia, Type I(II) Mobitz blocks, cardiogenic shock, asystole and convulsions. Severe intoxication may lead to coma (usually in cases of overdose on membrane depressants).

ECG: Early cardiotoxic effect (increased electric systole, increased P-R intervals with normal QRS complex in case of severe intoxication).

Calcium channel blockers (CCB) (verapamil, diltiazem, phenygidin, nimodipine)

CCB shall not be prescribed to patients with:

1. Sinus node weakness syndrome;

2. Atrial-ventricular conductivity impairment;

3. Lung hypertension;

4. Hypertrophic obstructive cardiomyopathy.

The CCB therapy for patients intaking heart glycosides, beta blockers, diuretics, disopyramide, quinidine, lithium shall start with small doses. The cardiovascular system's response mush be monitored, in particular, when prescribing a slow-release drug.

Most commonly, the overdose on CCB adversely affects cardiovascular system (calcium ion channel impairment condition) and endocrine system (galactorrhea, oligomenorrhea). High dose monotherapy with CCBs may cause tinnitus (usually within first days). This condition worsens when CCBs are combined with ototoxic drugs. CCBs intake often leads to decline in intestine motor function. Where these conditions are present, it is recommended to prescribe enterosorbents and sorbitol (or any diuretic).

Mild overdose

The symptoms include moderate hypotension, bradycardia (nifedipine causes tachycardia), mild hyperkalemia and hyperglycemia (usually during long term intake). Swollen ankles, prolactinemia (galactorrhea) are diagnosed. Mild overdose may also cause menstrual cycle irregularity linked to hypoestrogenemia.

Moderate overdose

The symptoms are manifested hypotension (in particular, during the intake of amlodipine), sinus bradycardia, arrhythmia. Amlodipine and phenygidin do not cause bradycardia. To the contrary, this medication may increase hear rate against the drop in blood pressure. Patients complain of tinnitus, vertigo, nausea and, less commonly, vomiting.

Massive overdose

The symptoms of high overdose are lasting hypotension, life-threatening pacing disorders, including complete AV-block, cerebral blood flow impairment. A transfer of the patient to intensive care unit may be necessary.

Angiotensin-converting enzyme inhibitors (ACE inhibitors) (valsartan, losartan potassium, candesartan, irbesartan, telmisartan, eprosatran, etc.)

Older patients with renal failure (including that caused by renal arteries stenosis), congestive forms of heart failure [22], hyponatremia and hypovolemia, or undergoing dialysis, or intaking thiazide diuretics are at high risk of overdose on ACE inhibitors.

A clinical picture is characterized by decrease in blood pressure and postural reactions of blood circulation that may be lasting and disappear after one-two weeks post withdrawal. Regardless of intoxication severity, patients develop anemia, urea/creatinine disbalance (azotemia), changes in lipid blood spectrum and decline in forced exhale metrics during lungs spirometry (more often to occur during losartan intake).

Mild overdose

The symptoms of mild overdose are hypotension (in the absence of tachycardia), postural reactions, “first-dose phenomenon” when dosage exceeds ED50 (more expressed for losartan, than candesartan or episartan). Patients may complain of vertigo, insomnia and during a long-term intake of drugs of migraine-like headache, a metallic taste in the mouth, decline in acuity and stuffed nose.

Moderate overdose

The symptoms include anticholinergic syndrome (dry mucous membranes, tachycardia, diplopia, decline in intestine motor function, epigastric pains, nausea and vomiting that may be linked to stomach sprain) with stable hypotension. A patient demonstrates orthostatic reactions.

Many patients also complain of swollen face and soar throat. Some patients may demonstrate cognitive disorders, mood change, deteriorating patients are diagnosed with tremors and hyperesthesia. The most common metabolic disorders is hyperkalemia (the increase in potassium levels may be sharp and intense - 0,5 mEq/L every 12 hours).

Massive overdose

The symptoms include α-adrenergic blocking syndrome that manifests itself in persistent and deep hypotension, tachycardia, hyperhidrosis, swelling, cyanosis (face, lips, nose and throat), block of the myocard impulse conduction, myocard ischemia, changes in CNS - delirium-like episodes, syncopal conditions, ischemic and acute cerebrovascular blood circulation attacks.

A therapist must remember:

1. All patients suspected to have overdose on ACE inhibitors must be tested on electrolytes and creatinine levels, nitrogen remaining concentration and blood bicarbonate level;
2. The dosage must be decreased for patients with creatinine clearance less than 30 ml/min;
3. The dosage must be decreased if patients display soar throat, enlarged lymph nodes, swallowing problems, swelling of face, lips or limps, an immediate blood testing must be conducted to assess the toxic effects of medications and/or presence of infections;
4. Patients with alkalosis or increased urine nitrogen/creatinine rate may experience a "first-dose phenomenon" and manifested hypotension [23].

Diuretics (osmotic - mannitol; thiazide - hydrochlorothiazide; potassium-sparing - triampur, loop - furosemide)

Excessive dosage of diuretics prescribed to patients with different pathologies leads to dehydration and electrolytes disbalance [24]. The most dangerous conditions caused by overdose are:

1. Intracell dehydration, ricochet syndrome that may be concurrent with brain herniation and/or secondary brain edema (mannitol);
2. Hyperkalaemia causing slow down neural impulses conductivity (myocard, muscles) that may lead to ventricle fibrillation (potassium-spearing diuretics);
3. Hypokalaemia that causes expedited spread of repolarization leading to a higher myocardial arousal and ectopia (hydrochlorothiazide);
4. Hypomagnesemia causing ventricle fibrillation that it particularly dangerous when concurrent with hypokalaemia.

Thiazide diuretics can lead to glucose uptake impairment, often in patients with sugar diabetes. Loop diuretics can cause hypochloremic and hypokalemic alkalosis.

The adverse effects of overdose (including the mild overdose) are delayed and develop over several days. The overdose symptoms overhaul a diuretic effect by up to three-four hours. The symptoms include nausea, vomiting and diarrhea followed by common intoxication symptoms: weakness, hyporeflexia, hypotension and electrolyte exchange impairment.

Hypokalemia (blood potassium level < 3 mmol/L)

The symptoms include general muscle weakness, decline in intestine motor function, stomachache, arrythmia, convulsions, soft paralysis, rhabdomyolysis (in cases of lasting and/or severe hypokalemia). More often, hypokalemia is caused by overdose on thiazide

diuretics. Acute or severe hypokalemia may lead to dehydration, atrial and ventricle fibrillation, ventricle tachycardia, hemocoagulation, ventricle extrasystoles, intestinal obstruction, clotting and acute hear failure.

Hyperkalemia (blood potassium level > 6 mmol/L)

The symptoms include bradycardia, arrythmia. Hyperkalemia is commonly caused by overdose on verospiron or other potassium-sparing diuretics). Patients often develop ventricle arrythmia, hypomagnesemia, hyponatremia, hyperchloremic alkalosis. These conditions provoke increased toxic response to other medications used together with diuretics.

Hypocalcemia and hypomagnesemia

Hypocalcemia and hypomagnesemia lead to pacing disorders and in some cases to convulsions. These conditions are displayed when a standard average dose of loop and thiazide diuretics is increased.

Hyperglycemia, hypercalcemia, hyperuricemia is often displayed in case of overdose on thiazide diuretics. Glucose exchange impairment leads to hyperglycemia and in severe cases - development of hyperosmolar nonketotic coma.

The symptoms described above would help a therapist to avoid or at least diminish the adverse effect of therapy. Given the number of new drugs registered every year, the strict compliance with prescription requirements becomes essential. When prescribing a particular drug, a therapist should consider:

- Effect on all pathogenic causes;
- Clinical evidence of effectiveness;
- Drug safety for long-term intake;
- Effect on quality of life (patience' compliance with and adherence to therapy);
- Absence of adverse combinatoric effect.

Conclusion

It is always difficult to choose a medication at the outset. Usually, the choice of a drug depends on a therapist's personal preferences and, almost never, does she consider pathogenic factors. As a result, most patients do not receive optimal drug treatment at the early stages of the disease. It is particularly true in older patients' therapy.

The presence of somatic pathologies requiring prescription of two and more medications with different pharmacokinetics and pharmacodynamics makes effective drug therapy for older patients even more difficult.

A therapist must consider the following [25]:

1. Crossing of medications' biotransformation paths leading to increase or decrease in each drug's effectiveness and, as a result, multiplication of adverse effects and unpredictable drug response;
2. Potentiation of known side-effects and increase in toxic effect, first and foremost, on GI tract, liver, kidneys and brain;

3. Occurrence of unexpected and not-known side-effect;
4. Difficulties associated with determining a correct dosage (long term treatment with below standard average doses)
5. Inflation of therapy costs.

Therefore, every therapist must abide by the following rules:

1. Any prescription must follow the diagnosis and not vice versa; a drug shall only be prescribed for known indications in strict compliance with the drug's description;
2. Strictly follow course and daily dosages, especially, of antihypertension drugs;
3. Consider potential adverse effects of certain drugs combinations.
4. Consider age-factor and existing pathologies.

One should always keep in mind, that any drug is approved based on results of risk and benefit analysis, among other things. As such, there are no risk-free medications. As such, 'do no harm' shall the guiding principle of a therapy. A therapist should always be sensible when prescribing polydrug therapy keeping in mind potential adverse combinatoric effects. A therapist shouldn't also forget that despite there is no 'one-size-fits-all' solution and any therapy must consider the patient's response to treatment, age, anamnesis, metabolism and hemodynamics.

Further, compared to treatment of young patients (when a therapist's goal is to restore the impaired functions to the degree possible) the goal of a drug therapy of older patients is a relief of symptoms and a compensation of impaired functions [17].

One may assume that the progress in genopharmacology would lead to development of new generation medications. Such medications would have all the benefits of the present generation drugs with no or decreased side-effects. Nonetheless, any drug shall be prescribed with due consideration of pharmacodynamics and cumulative pharma-effect. Not doing so put the patient's health and even life at danger.

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