Continuing Medical Education

Psychopharmacological Treatment in Older People

Avoiding Drug Interactions and Polypharmacy

Torsten Kratz and Albert Diefenbacher

Summary

Background: As the elderly population increases, so, too, does the number of multimorbid patients and the risk of polypharmacy. The consequences include drug interactions, undesired side effects of medication, health impairment, and the need for hospitalization. 5–10% of hospital admissions among the elderly are attributable to undesired side effects of medication.

Methods: This review is based on publications retrieved by a selective search in PubMed and the Cochrane Library that employed the search terms “drug interaction,” “undesired side effect,” “polypharmacy,” “pharmacokinetics,” and “pharmacodynamics.”

Results: Elderly patients are particularly at risk of polypharmacy, both because of the prevalence of multimorbidity in old age and because of physicians’ uncritical implementation of guidelines. The more drugs a person takes, the greater the risk of drug interactions and undesired side effects. Age-associated changes in pharmacokinetics and pharmacodynamics elevate this risk as well. Physicians prescribing drugs for elderly patients need to know about the drugs’ catabolic pathways, protein binding, and inductive and inhibitory effects on cytochrome P450 in order to avoid drug interactions and polypharmacy.

Conclusion: Multiple aids and instruments are available to ensure practical and reasonable drug monitoring, so that the risks of drug interactions and undesired side effects can be detected early and avoided.

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Department of
Psychiatry,
Psychotherapy and
Psychosomatics,
Evangelisches
Krankenhaus
“Königin Elisabeth”
Herzberge, Berlin:
Prof. Dr. med. Kratz,
Prof. Dr. med.
Diefenbacher, MBA

The elderly are making up an ever-increasing percentage of the overall population as part of an ongoing demographic development. There are already more than 6 million persons over age 80 in Germany now; by 2050, there will be approximately 10 million (1). Because of the growing elderly population, there are more multimorbid persons than ever before, and thus more patients who need to take multiple drugs (2). Polypharmacy, which is defined as the simultaneous use of five or more drugs, is a particular problem among persons aged 75 to 85 (2).

Polypharmacy leads to an increasing frequency of drug interactions, undesired side effects of medication (“adverse drug effects,” ADE), impaired health, and hos-

pitalization (e1). Drug interactions can lead to toxicity or to diminished therapeutic efficacy via inhibitory or inductive effects on cytochrome P450 (CYP). ADE cause increased costs in the health care system and are responsible for 5–10% of hospital admissions of elderly patients (3–6, e2). The elderly are also at higher risk of rehospitalization because of severe ADE (e3). Drugs that often cause ADE in old age include antihypertensive drugs (36%), non-steroidal anti-inflammatory drugs (NSAID) (17.8%), insulin preparations (13.9%), anticoagulants (33.3%), and psychoactive drugs (24.8%) (7, e1, e4, e5).

The uncritical use of psychoactive drugs in elderly patients, along with the altered pharmacokinetics and

Drug interactions

Drug interactions can lead to toxicity or to diminished therapeutic efficacy via inhibitory or inductive effects on cytochrome P450 (CYP).

Polypharmacy

Polypharmacy—the simultaneous use of five or more drugs—markedly increases the risk of drug interactions and undesired side effects, particularly in elderly patients.

pharmacodynamics of drugs in old age, can also increase the rate of undesired side effects. Anticholinergic drugs and sedating psychoactive drugs are risky. ADE are often hard to tell apart from manifestations of the known underlying disease or a new disease (8, 9). Undesired effects of psychoactive drugs in the elderly can have dramatic consequences: falls due to drug overdose or parkinsonoid effect; delirium, syncope, and cognitive dysfunction caused by anticholinergic drugs; bradycardia due to cardiac side effects; decompensated diabetes and heart attack or stroke due to metabolic side effects.

The rigid application of guidelines in patients suffering from multiple chronic diseases markedly increases the risk of polypharmacy and the likelihood of potentially dangerous drug interactions and ADE (10, 11). The failure to adjust drug doses because of a lack of knowledge of the pharmacokinetics and pharmacodynamics of psychoactive drugs in old age is a common cause of drug interactions and ADE (11).

The treatment of elderly patients with psychoactive drugs is important; it may be needed to sustain a good quality of life. A proper knowledge of the specific changes of pharmacodynamics and pharmacokinetics in old age can help limit the frequency of drug interactions and polypharmacy (e6). This knowledge is necessary, simple, and easily acquired. In one study, training of intensive care unit staff in this matter lowered the frequency of drug interactions from 66% to 54% and of ADE from 44% to 25% (12).

Method

This review is based on publications retrieved by a selective search in PubMed and publicly available databases.

Learning objectives

Readers of this article should acquire

- an understanding of the special aspects of the pharmacokinetics and pharmacodynamics of psychoactive drugs in the elderly,
- an acquaintance with age-associated aspects of drug resorption, distribution, elimination, and biotransformation, and
- knowledge of how to avoid polypharmacy and undesired side effects when prescribing psychoactive drugs to elderly patients who need them.

Pharmacokinetics

Pharmacokinetic interactions affect the bioavailability of a drug either indirectly (through the induction or

Pharmacokinetic interactions

Pharmacokinetic interactions affect the bioavailability of a drug either indirectly (through the induction or inhibition of CYP) or directly by an intermolecular process, e.g., by chelation.

TABLE 1

Overview of the inhibitory effects of selected antidepressant drugs on various CYP-450 isoenzymes*

Drug	1A2	2C9	2C19	2D6	3A4
Fluoxetine	+	++	++	+++	+
Sertraline	+	+	++	+	+
Paroxetine	+	+	+	+++	+
Citalopram	+	–	–	–	–
Duloxetine	–	–	–	++	–
Venlafaxine	–	–	–	+	–
Mirtazapine	–	–	–	+	–

– no inhibition; + mild inhibition; ++ moderate inhibition; +++ marked inhibition
*modified and enlarged from (e8, e28–e30)

inhibition of CYP) or directly. Pharmacokinetic changes in old age include altered resorption (through the gastrointestinal tract and across the blood-brain barrier), distribution, protein binding, renal elimination, and biotransformation (CYP) (13, e7).

Distribution

Age-associated changes include lower fluid volume, organ perfusion, muscle mass, and serum albumin concentration, and an increase in body fat (14). The consequences include altered serum concentrations, longer persistence of drugs in the body, stronger drug effects at lower doses, and increased side effects and toxicity.

The increased body fat resulting from the ongoing conversion of muscle mass to fat and connective tissue in old age leads to an increased concentration and uncontrolled deposition of lipophilic drugs in the fat depots of the body. Thus, the half-life of diazepam, a highly lipophilic drug, is twice as long in the elderly even if there is no change in creatinine clearance, and the use of diazepam in elderly patients should be viewed critically (15). Oxazepam and lorazepam are not lipophilic, do not have a prolonged half-life in the elderly, and should be used in preference to diazepam.

Protein binding

The serum albumin concentration is normally lower in old age (15, 16, e8). Drugs, however, bind to albumin, and only the free drug, not the bound drug, is pharmacologically active. Drug doses must, therefore, be adjusted to avoid excessive concentrations of free

The effects of pharmacokinetic interactions

Pharmacokinetic interactions affect resorption (through the gastrointestinal tract and across the blood-brain barrier), distribution, protein binding, renal elimination, and biotransformation

TABLE 2

Selected important drugs that induce cytochrome P450*

Drug class	Drug	affected CYP
Antibiotics	griseofulvin rifampicin	1A2, 2C8, 3A4 1A2, 2C8, 3A
Antiepileptic drugs	carbamazepine	1A2, 2C9, 3A4
Antirheumatic drugs	phenylbutazone	3A
Psychoactive drugs	hypericum	1A2, 3A4
Proton-pump inhibitors	omeprazole	1A2, 2C19
Hypnotic drugs	phenobarbital	1A2, 2C8, 3A

*modified and enlarged from (e8, e28–e30)

drug leading to undesired side effects or toxicity. Psychoactive drugs with high protein binding (> 90%), a steep dose-response curve, and a narrow therapeutic window are affected. Such situations, though uncommon, can be problematic, for example, when acetylsalicylic acid (ASA) and valproic acid are given together (interactions, bleeding tendency). ASA—e.g., given for secondary prophylaxis after stroke—can displace valproic acid from protein, leading to a rise in the serum valproic acid concentration. Agitation, confusion, or, rarely, valproic acid encephalopathy may ensue.

Elimination

Age-associated changes in renal elimination may be present on an individual basis. Renal perfusion, the number of nephrons, and the glomerular filtration rate (GFR) all decline with age. The GFR falls by as much as 1 mL/min per year, and tubular function diminishes by 1% per year after age 50 (16, 17). There may be delayed elimination of renally excreted drugs such as glycoside inhibitors and digoxin. Blood levels of drugs should, therefore, be checked more frequently in elderly patients, and drugs should be preferred that are catabolized in more than one pathway. For example, digoxin (which is renally eliminated) can be switched to digitoxin (which is eliminated via the kidneys and the liver).

Biotransformation and CYP

Biotransformation is especially important in old age. In the elderly, the liver is up to 40% smaller, its perfusion is reduced by as much as 30%, the enzymatic activity of the CYP-dependent phase I reaction is lower, and there is greater bioavailability and slower elimination of

hepatically eliminated drugs, including propranolol, metoprolol, verapamil, and nifedipine (e9).

CYP plays an essential role, because it participates in oxidation and hydrolysis in the phase I reaction of the liver. Phase I is subject to age-associated changes, while phase II (glucuronidation) is generally unchanged in old age. Particularly important isoenzymes in the treatment of elderly patients with psychoactive drugs include 1A2, 3A4, 2D6, 2C19, 2B6 and 2C9 (eFigure).

When multiple hepatically catabolized drugs are given simultaneously, the blood levels of these drugs can be either elevated or decreased. A drug combination can lead to a relevant pharmacokinetic interaction if one of the administered drugs inhibits or induces a CYP enzyme (“perpetrator drug”) while another one of them is preferentially catabolized by the inhibited or induced enzyme (“victim drug”). It is thus important to know how the various drugs being taken by a patient are catabolized, and whether they can inhibit or induce a CYP enzyme.

Inhibition of cytochrome P450 enzymes

The physician prescribing a psychoactive drug to an elderly patient must consider possible inhibition of isoenzyme 2D6, which plays a role in the catabolism of many drugs used in internal medicine as well as that of certain psychoactive drugs. Inhibiting it can lead to serious drug interactions and ADE. The antidepressant drugs paroxetine and fluoxetine are potent inhibitors. Paroxetine combined with either nebivolol or metoprolol (two antihypertensive agents) can cause severe bradyarrhythmia (18) by inhibiting the catabolism of the antihypertensive drug and thereby raising its blood level. The plasma concentration of aripiprazole also rises when a 2D6 inhibitor is given (19, 20).

Tramadol, an analgesic drug, and tamoxifen, a drug used for the hormonal treatment of breast cancer, are both given as inactive precursor stages (prodrugs) that are converted to their active forms through the activity of isoenzyme 2D6 (21). If either of these drugs is taken in combination with a strong 2D6 inhibitor, such as paroxetine, fluoxetine, bupropion, or melperone (doses >50 mg/day), its efficacy can be markedly impaired (21). In the case of tamoxifen, this can increase the mortality from breast cancer (e10).

2C19 is another relevant isoenzyme. The combination of sertraline with omeprazole can lead to ADE and serious drug interactions (22). A serotonergic syndrome can arise, because sertraline is catabolized

Biotransformation and CYP

Biotransformation is especially important in old age. In the elderly, the liver is smaller and its perfusion is reduced, the enzymatic activity of the CYP-dependent phase I reaction is lower, and there is greater bioavailability and slower elimination of hepatically eliminated drugs.

Examples of inhibition

Paroxetine inhibits isoenzyme 2D6; when given together with nebivolol (a selective β -adrenoreceptor blocker), it markedly elevates the blood level of nebivolol, causing bradyarrhythmia.

through the activity of isoenzyme 2C19, which omeprazole inhibits. Pantoprazole, which does not inhibit isoenzyme 2C19, is therefore to be preferred. In elderly patients, citalopram, venlafaxine, and mirtazapine should be used instead of sertraline. Paroxetine and fluoxetine should be avoided (*Table 1*).

Inhibition of the effect of isoenzyme 3A4 must also be borne in mind in the pharmacotherapy of elderly patients. Drugs that are catabolized through its activity can have an elevated plasma concentration and exert toxic effects. The antibiotics clarithromycin and erythromycin potently inhibit isoenzyme 3A4 (23, e11), and their use in combination with drugs catabolized via isoenzyme 3A4, such as quetiapine and aripiprazole, is problematic, as the plasma levels of the latter will rise (19, 20, 24).

Certain neuroleptic drugs, such as olanzapine, may have elevated plasma levels if given in combination with ciprofloxacin, which inhibits isoenzyme 1A2 (19, 20).

Not only psychoactive drugs, but even grapefruit juice (25) can inhibit hepatic drug catabolism, particularly via isoenzyme 3A4. Grapefruit juice can elevate the bioavailability of psychoactive drugs such as quetiapine, comipramine, carbamazepine, and buspiron three- to fivefold (25). Patients should be informed of this and instructed to avoid grapefruit juice.

Induction of cytochrome P450 enzymes

CYP induction can cause major problems in the pharmacotherapy of the elderly (*Table 2*).

Carbamazepine and St. John's wort are both potent inducers of multiple CYP isoenzymes (e.g., 1A2, 2C9, 2C19, 3A4) (26–29). Thus, the concomitant administration of either of these drugs can markedly lower the plasma level of quetiapine through the induction of isoenzyme 3A4 (19, 20).

St. John's wort is a popular mild antidepressant. If given together with a phenprocoumon, it can counteract the effect of the latter (29) by inducing isoenzyme 3A4, through which it is catabolized. The consequences can include thrombosis, heart attack, and stroke. The inducing effect of St. John's wort can also be seen when it is given concomitantly with theophylline, cyclosporines, carbamazepine, anti-infectious drugs (e.g., antiretroviral drugs against HIV), tricyclic antidepressants (TCA, e.g., amitriptyline), and oral contraceptives (29, 30).

Carbamazepine potently induces isoenzymes 1A2, 2C9, and 3A4, stimulating the catabolism of certain

BOX 1

Selected drugs with anticholinergic effects(ADE)*

- **Antidepressant drugs**
 - amitriptyline
 - imipramine
 - doxepin
 - trimipramine
 - nortriptyline
 - maprotiline
 - clomipramine
- **Antiparkinsonian drugs**
 - biperidene
 - procyclidine
 - trihexyphenidyl
- **Neuroleptic drugs**
 - chlorpromazine
 - thioridazine
 - fluphenazine
 - perazine
 - melperone
 - clozapine
- **Muscle relaxants/spasmolytic drugs**
 - orphenadrine
 - methocarbamol
- **Urologic drugs/spasmolytic drugs**
 - oxybutynine
 - tolterodine
 - solifenacin
- **Antiemetic drugs**
 - dimenhydrinate
- **Antihistamine drugs**
 - dimethidine maleate
 - diphenhydramine
- **Gastrointestinal spasmolytic drugs**
 - butylscopolamine bromide

*modified and expanded from (e31–e33) ADE, adverse drug effects

neuroleptic drugs, coumarins, cyclosporines, anti-infectious drugs, and oral contraceptives (31, 32).

Ginkgo biloba can induce CYP as well. Some preparations (25) accelerate the metabolism via isoenzyme 2C19, leading to a 50–60% drop in the plasma level of, for example, citalopram, escitalopram, TCA, pantoprazole, and omeprazole (30, 33). Ginkgo biloba may also induce isoenzyme 2C9, an important isoenzyme in the catabolism of phenprocoumones and warfarins. Thus, the use of St. John's Wort, carbamazepine, and ginkgo biloba in elderly patients should be critically reassessed.

Various foods, as well as cigarette smoking, can also lead to enzymatic induction. Smoking, meat grilled over wood charcoal, and broccoli can all induce isoenzyme 1A2, through whose activity olanzapine and clozapine, among other drugs, are catabolized (34).

Pharmacodynamics

In a pharmacodynamic interaction, two drugs that exert their effects on a single organ or regulatory circuit

Grapefruit juice

Not only psychoactive drugs, but even grapefruit juice inhibits hepatic drug catabolism. It can elevate the bioavailability of psychoactive drugs such as quetiapine, comipramine, carbamazepine, and buspiron three- to fivefold.

St. John's wort

St. John's wort is a mild antidepressant. If given together with a phenprocoumon, it can counteract the effect of the latter by inducing isoenzyme 3A4. The consequences can include thrombosis, heart attack, and stroke.

TABLE 3

Drugs that can prolong the QTc interval

Drug class	Drug
Antiarrhythmic drugs	Class Ia: quinidine Class III: sotalol, amiodarone
Antipsychotic/neuroleptic drugs	haloperidol, ziprasidone, quetiapine, sulpiride, pimozide, sertindol
Antidepressant drugs	doxepin, amitriptyline, maprotiline
Antihistamine drugs	terfenadine, astemizole
Antibiotics	erythromycin, cotrimoxazole, pentamidine, moxifloxacin
Other	ketanserin, probucol, zolmitriptan

interact either directly (by competition) or indirectly (by antagonism or synergism).

Age-associated changes

Altered pharmacodynamics in old age can promote drug interactions and adverse drug effects. A decline in neuronal density, lower receptor density, reduced transmitter synthesis, and receptor hypersensitivity all need to be taken into account. Clinical consequences can be seen in the dopaminergic, serotonergic, and cholinergic systems, including (respectively) an increased tendency to exhibit extrapyramidal motor symptoms and signs (EPMS); an elevated risk of agitation and sexual dysfunction; and a tendency toward anticholinergic side effects, such as urinary retention, glaucoma, and delirium (35, e7).

The serotonergic syndrome

This syndrome is due to heightened central and peripheral synaptic effects of serotonin, as seen, for example, in patients taking a selective serotonin reuptake inhibitor (SSRI) combined with a monoamine oxidase inhibitor (MAOI). Its main manifestations are fever, neuromuscular manifestations (tremor, hyperreflexia, myoclonus, hyperreflexia), and mental disturbances including disorientation, confusion, agitation, or euphoria, as well as vegetative manifestations (e.g., nausea, vomiting, diarrhea, hyperhidrosis, tachycardia). Combinations of substances working via different pathways to stimulate the secretion of the same active metabolite are problematic. For example, SSRI combined with triptans can induce a serotonergic syndrome (e12).

Definition of pharmacodynamic interactions

In a pharmacodynamic interaction, two drugs that exert their effects on a single organ or regulatory circuit interact either directly (by competition) or indirectly (by antagonism or synergism).

Drugs that increase the risk of falling

These include antihypertensive drugs, muscle relaxants, benzodiazepines (sedation and diminution of muscle tone), antipsychotic drugs, and antidepressants with an alpha-antagonistic and therefore blood-pressure-lowering effect. Diuretic drugs can also increase the risk of falling by lowering the blood pressure and by disturbing renal function and electrolyte homeostasis (e13). There is evidence that SSRI increase the risk of falling in demented patients in dose-dependent fashion (e14). Caution should be exercised when combining two drugs with similar receptor-binding profiles. Tricyclic antidepressants, such as amitriptyline, and neuroleptic drugs, such as promethazine and quetiapine, can cause a drop in blood pressure if combined with an antihypertensive drug. Benzodiazepines should be used with caution in elderly patients, as they may be depressogenic, in addition to their other known risks, i.e., sedation, falls, and drug dependence. The uncritical use of benzodiazepines in demented patients can cause organo-affective disturbances (36) that manifest themselves as behavioral abnormalities (37). Benzodiazepines can destroy the normal architecture of sleep and worsen any sleep disorder that the patient may already have.

Drugs with anticholinergic effects and an increased risk of delirium

Drugs that exert anticholinergic effects are problematic, as the elderly are more susceptible to anticholinergic side effects. The drugs listed in the Box as members of this group should not be given to elderly patients if this can be avoided. If these drugs need to be given and rapid cognitive worsening or delirium ensues, they must be discontinued or switched to another drug. A lack of understanding of such events often leads to the non-recognition of adverse drug effects as such, so that they are treated symptomatically with yet more medication.

The simultaneous use of multiple drugs with anticholinergic effects, such as low-potency neuroleptic drugs and eyedrops that contain atropine, should be avoided. Antiparkinsonian drugs and tricyclic antidepressants (anticholinergic effect) or neuroleptic drugs (such as olanzapine or quetiapine) can cause a central anticholinergic syndrome or delirium. Drugs given in internal medicine, such as cortisone, antiemetics (e.g., dimenhydrinate), and calcium antagonists, can also have anticholinergic effects. Urological drugs can as well.

Combinations of drugs that simultaneously affect electrolyte metabolism should be critically reassessed.

Drugs that increase the risk of falling

Antihypertensive drugs, muscle relaxants, benzodiazepines (sedation and diminution of muscle tone), antipsychotic drugs, antidepressants with an alpha-antagonistic and therefore blood-pressure-lowering effect, and diuretics

The combination of an ACE inhibitor with a potassium-sparing diuretic can lead to hyperkalemia and delirium. Serotonergic drugs, such as citalopram, can cause hyponatremia by inducing SIADH (the syndrome of inappropriate antidiuretic hormone secretion: elevated ADH secretion by the pituitary gland leads to fluid retention, with hypervolemia and dilutional hyponatremia), which can present with delirium or a dementia-like syndrome. The simultaneous administration of a diuretic drug (particularly a thiazide diuretic) and a serotonergic drug elevates the risk for hyponatremia as well.

Drugs that can prolong the QTc interval

Drugs that can prolong the QTc interval should be avoided in the elderly and should not be combined. Critical drugs in this category include tricyclic antidepressants and neuroleptic drugs such as haloperidol, ziprasidone, quetiapine, and sulpiride. Caution must also be exercised in combining these drugs with other drugs that prolong the QTc interval, such as amantadine (19, 20, e15) (Table 3).

Drugs that increase the risk of bleeding

Serotonergic drugs increase the risk of bleeding when given in combination with platelet aggregation inhibitors, newer oral anticoagulant drugs (NOAC), or phenprocoumon (e16). Serotonin increases platelet aggregation. SSRI lessen the reuptake of serotonin from the blood into the platelets and thereby leads to a bleeding tendency (e17). Ginkgo preparations can also increase the risk of bleeding when given in combination with SSRI, platelet aggregation inhibitors, NOAC, or phenprocoumon (e18). Valproic acid in combination with either ASA or an anticoagulant drug increases the risk of bleeding as well (19, 20).

Interactions with lithium

Lithium, a drug with a narrow therapeutic spectrum, plays an important role in modern psychiatric pharmacotherapy, in the elderly just as in younger patients. Nonetheless, its use for phase prophylaxis, mood stabilization, and treatment of suicidality requires a thorough knowledge of its potential drug interactions (eTable 1).

To avoid lithium intoxication, lithium should not be combined with thiazide or loop diuretics, non-steroidal anti-inflammatory agents, ACE inhibitors, or calcium antagonists (19, 20, 38, e19). The treating psychiatrists and somatic physicians must collaborate to ensure that this does not occur.

SIADH: the syndrome of inappropriate ADH secretion

The inappropriate secretion of ADH (antidiuretic hormone) by the pituitary gland leads to increased fluid retention in the kidneys, and thereby to hypervolemia and dilutional hyponatremia. Diuretics and SSRI can cause SIADH.

Interactions with mood-stabilizing drugs

Mood stabilizers can cause drug interactions as well. The simultaneous administration of valproic acid and tricyclic antidepressants raises the seizure threshold (19, 20). The combination of valproic acid with clozapine can alter the plasma levels of both drugs (19, 20). Lamotrigine and valproic acid can elevate each other's plasma levels, creating a risk of toxic epidermolysis (19, 20).

Interactions with neuroleptic drugs

Neuroleptic drugs can interact with drugs of other types. The combination of clozapine and valproic acid can cause neutropenia (19, 20). Clozapine has a strong anticholinergic effect (19, 20). Risperidone can accentuate the effect of alpha-1 inhibitors such as tamsulosin; if combined with a tricyclic antidepressant or a beta-blocker, it can induce extrapyramidal motor manifestations (19, 20).

Avoidance of drug interactions and polypharmacy

When elderly patients are treated with psychoactive drugs, the physician should choose a drug or drugs that have no anticholinergic side effects, are no more than mildly sedating, carry a low risk of inducing extrapyramidal motor manifestations, do not prolong the QTc interval, have little effect on orthostatic blood pressure, have a broad therapeutic spectrum, are well tolerated by patients with multiple diseases, have little general metabolic activity, and affect electrolyte homeostasis as little as possible.

Tricyclic antidepressants (TCA) should be avoided because of their anticholinergic and cardiotoxic side effects. If a TCA is nonetheless necessary, nortriptyline is to be preferred because of its better side-effect profile (with respect to the QTc interval, orthostasis, sedation, and anticholinergic effects) (e20, e21). Because of their inhibitory effect on CYP, paroxetine, fluoxetine, and fluoxetine should not be used, and ciprofloxacin, erythromycin, and clarithromycin should be critically reassessed. Carbamazepine, ginkgo biloba, and St. John's wort potentially induce multiple isoenzymes and should therefore be avoided. Benzodiazepines are sedating, induce dependence, and have a depressogenic effect in the elderly; they should be used for carefully chosen indications and only for a short time, if at all.

The indication for any drug given to an elderly patient (e.g., a proton-pump inhibitor or a statin) must first be assessed. If the drug is truly indicated, it should be given at first in the lowest possible initial dose and then gradually titrated upward ("start low,

Cardiac conduction disturbances

The administration of clarithromycin and quetiapine can markedly increase the risk of cardiac conduction disturbances, with potentially life-threatening consequences.

FIGURE

Flowchart for dealing with polypharmacy (modified, enlarged, and supplemented from [e34]); ADE, adverse drug effect(s)

go slow”). Drugs with short half-lives and high bio-availability are to be preferred. They should not be strong CYP inhibitors.

Drugs with a narrow therapeutic spectrum should be avoided. Drugs that can be taken easily are to be preferred, e.g., drugs that are easy to swallow and can be taken once per day. In old age, patients are subject to increasing pharmacokinetic and pharmacodynamic variability. The former can be checked by serial measurement of blood levels of the drug (Figure).

Checklists and instruments

A number of checklists and instruments are available for the avoidance of drug interactions and polypharmacy. The PRISCUS list aids in the choice of drug (8); its main limitation is that the drug assessments and

recommended alternatives and monitoring strategies that it comprises are based on expert opinion. The same holds for the FORTA concept (“fit for the aged”) (e22, e23) and the Beers list (39). It has been shown, for example, that low-potency neuroleptic drugs are, in fact, disadvantageous when used by elderly patients because they are sedating, exert anticholinergic effects, and cause orthostatic hypotension (Table 4, eTable 2, eTable 3).

Alongside these checklists, compendia (19) and internet-based tables (“drug interactions Flockhart table”; [32]) have come into increasing use. They describe the catabolic pathways and CYP-inhibitory and -inductive effects of the psychoactive drugs in current use. The potential side effects and the necessary monitoring are summarized. For patients with renal insufficiency, the internet site dosing.de (e24) is

The risk of bleeding under SSRI

Serotonin increases platelet aggregation. SSRI lessen the reuptake of serotonin from the blood into the platelets and thereby leads to a bleeding tendency.

Induction

St. John’s wort induces isoenzyme 3A4; if given together with phenprocoumon, it accelerates the catabolism of the latter, leading to a weakening or loss of the anticoagulant effect.

TABLE 4

Potentially inappropriate drugs* for elderly patients (modified from [8, e22, e23, 39])

Drug	Important risks in elderly patients	Monitoring	Alternative drugs (selection)
Antidepressants			
Tricyclic antidepressants – amitriptyline – doxepin – imipramine – clomipramine – maprotiline – trimipramine	– constipation, dry mouth – cardiac arrhythmias – lightheadedness, inner unrest – confusion, delirium – cognitive deficits – risk of falling	– bowel peristalsis (ileus) – cognitive function – risk of falling – ECG checks, incl. QTc – blood-level checks	– selective serotonin reuptake inhibitors – mirtazapine
SSRI – fluoxetine – paroxetine	– nausea, insomnia, dizziness – serotonergic syndrome – cognitive deficits and confusion in hyponatremia	– cognitive function – renal function – electrolytes	– another selective serotonin reuptake inhibitor (e.g., citalopram) – mirtazapine
MAO inhibitors – moclobemide – tranylcypromine	– hypertensive crises – hypotension – malignant hyperthermia	– blood pressure and heart rate checks – ECG checks, incl. QTc	– selective serotonin reuptake inhibitors (but not fluoxetine or paroxetine) – mirtazapine
Neuroleptic drugs			
Classic neuroleptic drugs – haloperidol – fluphenazine – levomepromazine – perphenazine	– delirium – cognitive deficits – extrapyramidal ADE (EPMS) – hypotension – sedation with risk of falling – increased mortality in demented patients	– cognitive function (anticholinergic ADE) – parkinsonoid, muscle stiffness, dysphagia (EPMS) – risk of falling – blood pressure and heart rate checks – ECG checks incl. QTc – blood count checks – liver value checks – blood level checks	– atypical neuroleptic drugs (e.g., quetiapine, aripiprazole, risperidone) – low-potency neuroleptic drugs (e.g., melperone, pipamperone)
Atypical neuroleptic drugs – olanzapine – clozapine	– anticholinergic ADE – EPMS (less than with classic neuroleptic drugs) – olanzapine: weight gain, increased risk of heart attack and stroke in dementia patients – clozapine: risk of agranulocytosis and myocarditis	– cognitive function (anticholinergic ADE) – risk of falling – blood pressure and heart rate checks – liver value checks – blood level checks – ECG checks incl. QTc – blood count checks for clozapine, differential blood count incl. troponin	– other atypical neuroleptic drugs (e.g., risperidone, quetiapine, aripiprazole) – low-potency neuroleptic drugs (e.g., melperone, pipamperone)

*This selection of drugs is based on the psychopharmacotherapy of elderly patients with antidepressant and neuroleptic drugs.

Sedatives, hypnotic drugs, and mood stabilizers are presented in eTable 2.

ADE, adverse drug effect(s); anticholinergic ADE: agitation, confusion, delirium, constipation, urinary retention, tachyarrhythmia, hypotension; EPMS; extrapyramidal motor symptoms and signs: 1. early dyskinesia (glossal or pharyngeal spasms, abnormal movements of head, neck, shoulders, gaze spasms), 2. parkinsonoid (tremor, rigidity, akinesia), 3. akathisia (distressing unrest in the sitting or standing position, irritability, anxiety), and 4. tardive dyskinesia (hyperkinetic, involuntary, stereotypic chewing, lip-smacking, and pharyngeal movements, choreiform or athetotic movements)

Classical neuroleptic drugs increase the risk of:

Delirium, cognitive deficits, extrapyramidal ADE (EPMS), hypotension, sedation with a risk of falling, and increased mortality in demented individuals

MAO inhibitors increase the risk of:

Hypertensive crises, Hypotension, and malignant hyperthermia

helpful; for those with a prolonged QTc interval, see CredibleMeds (e25).

Interactive platforms, such as www.psiac.de (40) and www.mediq.ch, are also of use (e26). Though not free of charge, they are independent of the pharmaceutical industry. They enable the physician to type in the patient's drug list and see the potential drug interactions and adverse drug effects that may be associated with it. This enables the minimization of risks associated with polypharmacy, the reassessment of drug indications, and the prevention of prescription of an excessive number of drugs. Interactive platforms are also available for smartphones, such as the independent app called "Arznei-Check," a product of the Ifap GmbH company (e27). The consistent use of these instruments and aids would help prevent the twin problems of drug interactions and polypharmacy.

Conclusion

Elderly patients are particularly exposed to the risk of polypharmacy. This is generally because of the multimorbidity associated with old age, often combined with physicians' uncritical, simultaneous application of all of the existing guidelines for each and every one of the patient's underlying illnesses. The more drugs a patient takes, the greater the risk of drug interactions and undesired side effects. The altered pharmacokinetics and pharmacodynamics of old age elevate this risk as well.

When treating the elderly patient with drugs, it is particularly important for the physician to know the pathway by which each drug is catabolized and any inducing or inhibiting effect it may have on CYP. This holds especially for drugs that are rapidly metabolized and have a low bioavailability, which have a high risk of interacting with other drugs. Numerous aids and instruments are available for clinical practice (eTable 4) that enable practical and reasonable drug monitoring (e.g., by measurement of serum drug levels) and the early detection of risks for possible interactions and undesired side effects, so that these can be effectively avoided. Knowledge of these matters as they relate specifically to elderly patients is necessary, easily acquired, and much simpler to apply in routine clinical practice than one might have expected.

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Overview

When elderly patients are treated with psychoactive drugs, drug monitoring and early risk assessment can markedly lessen the risk of drug interactions and polypharmacy.

Conflict of interest statement

Prof. Kratz has received payment from the following companies for preparing continuing medical education events; Janssen-Cilag, Lilly, and Novo Nordisk. Prof. Diefenbacher states that he has no conflict of interest.

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Corresponding author

Prof. Dr. med. Torsten Kratz
Abteilung für Psychiatrie, Psychotherapie und Psychosomatik
Funktionsbereich Gerontopsychiatrie und -psychotherapie
Königin-Elisabeth-Herzberge Krankenhaus
Herzbergstr. 79
D-10365 Berlin, Germany
T.Kratz@keh-berlin.de

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► Supplementary material

For eReferences please refer to:
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Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

Altered pharmacokinetics in old age also affects the distribution of drugs. What change can arise?

- a) lower fluid volume
- b) increased organ perfusion
- c) increased muscle mass
- d) decreased fatty tissue
- e) increased serum albumin

Question 2

What benzodiazepine drug is preferred in old age from the pharmacokinetic point of view?

- a) diazepam
- b) lorazepam
- c) bromazepam
- d) flurazepam
- e) alprazolam

Question 3

A patient already taking valproic acid is additionally treated with ASA because of a transient ischemic attack. What undesired side effect can arise?

- a) hyperglycemia
- b) bradycardia
- c) hypertension
- d) confusion
- e) hypotension

Question 4

Altered pharmacokinetics in old age also affects biotransformation. What change arises?

- a) increased activity of protein kinase C
- b) hepatic enlargement
- c) increased hepatic perfusion
- d) diminished enzymatic activity of the CYP-dependent phase I reaction
- e) altered glucuronidation

Question 5

A patient already taking the antihypertensive drug nebivolol is additionally given paroxetine to treat depression. What undesired side effect can arise?

- a) worsening of depressive manifestations
- b) nausea and vomiting
- c) loss of antihypertensive effect
- d) marked tachycardia
- e) severe bradyarrhythmia

Question 6

What drug combination in an elderly patient can cause hyponatremia?

- a) an antihypertensive drug and an antiarrhythmic drug
- b) a benzodiazepine and an antidiabetic drug
- c) a urologic drug and an antihypertensive drug
- d) a serotonergic antidepressant and a diuretic
- e) an antidiabetic drug and an antihypertensive drug

Question 7

An antidepressant drug, combined with tramadol, can lessen the analgesic effect of the latter. For which antidepressant drug is this relevant?

- a) citalopram
- b) fluoxetine
- c) mirtazapine
- d) venlafaxine
- e) sertraline

Question 8

What drug can lead to a pan-induction of cytochrome P450 and thereby to the increased catabolism of other drugs?

- a) metoprolol
- b) bisoprolol
- c) citalopram
- d) risperidone
- e) St. John's wort

Question 9

What are the typical manifestations of serotonergic syndrome?

- a) fever, tremor, disorientation, and vegetative manifestations
- b) insomnia and nocturia
- c) anorexia and insomnia
- d) delusions and tremor
- e) hypoglycemia and insomnia

Question 10

Which of the following drugs increase the risk of falling in elderly patients?

- a) antidepressants with an alpha-antagonistic effect
- b) nitrospray p.r.n.
- c) low-molecular-weight heparin
- d) raloxifen in women
- e) proton-pump inhibitors

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Supplementary material to:

Psychopharmacological Treatment in Older People

Avoiding Drug Interactions and Polypharmacy

by Torsten Kratz and Albert Diefenbacher

Dtsch Arztebl Int 2019; 116: 508–18. DOI: 10.3238/arztebl.2019.0508

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eTABLE 2

Potentially inappropriate drugs for elderly patients: sedatives and hypnotic drugs, short- and intermediate-acting benzodiazepines, Z drugs and mood stabilizers (modified from [8, e22, e23, 39])

Drug	Important risks in elderly patients	Monitoring	Alternative drugs (selection)
Sedatives and hypnotic drugs			
Long-acting benzodiazepines – diazepam – flurazepam – bromazepam – prazepam – clobazam – nitrazepam – flunitrazepam	– risk of falling – sedation and muscle relaxation – paradoxical reactions (e.g., agitation, irritability) – cognitive deficits – dependence – depression	– cognition and wakefulness – risk of falling and gait instability – psychopathology (mood, agitation, irritability) – development of tolerance	– low-dosed short-acting benzodiazepines (e.g., oxazepam, lorazepam) – sedating antidepressant drugs (e.g., mirtazapine) – low-potency neuroleptic drugs (e.g., melperone, pipamperone)
Short- and intermediate-acting benzodiazepines – alprazolam – temazepam – triazolam – lorazepam – oxazepam – lormetazepam	– risk of falling – sedation and muscle relaxation – paradoxical reactions (e.g., agitation, irritability) – cognitive deficits – dependence – depression	– cognition and wakefulness – risk of falling and gait instability – psychopathology (mood, agitation, irritability) – development of tolerance	– sedating antidepressant drugs (e.g., mirtazapine) – zolpidem (≤ 5 mg/d) – low-potency neuroleptic drugs (e.g., melperone, pipamperone)
Z drugs – zolpidem – zopiclone – zaleplon	– risk of falling – sedation and muscle relaxation – paradoxical reactions (e.g., agitation, irritability) – cognitive deficits – dependence	– cognition and wakefulness – risk of falling and gait instability – psychopathology (mood, agitation, irritability) – development of tolerance	– sedating antidepressant drugs (e.g., mirtazapine) – low-potency neuroleptic drugs (e.g., melperone, pipamperone)
Doxylamine and diphenhydramine	– anticholinergic ADE – dizziness – EKG changes	– cognition and wakefulness – risk of falling and gait instability – anticholinergic ADE – EKG checks incl. QTc	– sedating antidepressant drugs (e.g., mirtazapine) – zolpidem (≤ 5 mg/d) – low-potency neuroleptic drugs (e.g., melperone, pipamperone)
Chloral hydrate	– dizziness – EKG changes	– cognition and wakefulness – risk of falling and gait instability – anticholinergic ADE – EKG checks incl. QTc	– sedating antidepressant drugs (e.g., mirtazapine) – zolpidem (≤ 5 mg/d) – low-potency neuroleptic drugs (e.g., melperone, pipamperone)
Mood stabilizers / antiepileptic drugs			
– phenytoin – phenobarbital	– risk of falling – sedation and muscle relaxation – paradoxical reactions (e.g., agitation, irritability) – cognitive deficits – delirium	– cognition and wakefulness – risk of falling and gait instability – psychopathology (mood, agitation, irritability) – blood level checks	– other antiepileptic drugs (e.g., lamotrigine, valproic acid, gabapentin, levetiracetam)

ADE, adverse drug effect; anticholinergic ADE: agitation, confusion, delirium, constipation, urinary retention, tachyarrhythmias, hypotension;

EPMS, extrapyramidal motor symptoms and signs: 1. early dyskinesia (glossal or pharyngeal spasms, abnormal movements of head, neck, shoulders, gaze spasms), 2. parkinsonoid (tremor, rigidity, akinesia), 3. akathisia (distressing unrest in the sitting or standing position, irritability, anxiety), and 4. tardive dyskinesia (hyperkinetic, involuntary, stereotypical chewing, lip-smacking, and pharyngeal movements, choreiform or athetotic movements)

eTABLE 3

Drugs*¹ with a favorable profile for elderly patients (abbreviated and modified from the Forta list [e22, e23])²

Drugs by indication	FORTA category
Dementing diseases	
Acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) (for mild to moderate dementia of Alzheimer type)	B
Memantine (for moderate to severe dementia of Alzheimer type)	B
Depression	
Selective serotonin reuptake inhibitors:	
sertraline	B
escitalopram	B
citalopram	B
Bipolar disorder	
Lithium	B
Quetiapine	B
Insomnia/sleep disorder	
Melatonin (timed-release preparation)	B
Arterial hypertension	
ACE inhibitors (renin-angiotensin system inhibitors)	A
Angiotensin receptor antagonists	A
Long-acting calcium antagonists of the dihydropyridine type, e.g., amlodipine	A
Beta-blockers	B
Diuretics (as thiazide: indapamide preferred)	B
Congestive heart failure	
Renin-angiotensin system inhibitors (ACE inhibitors)	A
Angiotensin receptor antagonists	A
Sacubitril/valsartan	A
Beta-blockers (metoprolol, carvedilol, bisoprolol)	A
Diuretics	B
Acute coronary syndrome	
ACE inhibitors (renin-angiotensin system inhibitors)	A
Acetylsalicylic acid	A
Unfractionated heparin and low-molecular-weight heparins	A
Beta-blockers that lower the heart rate	A
Atorvastatin	A
Nitro-Spray, taken occasionally and acutely as needed	A
Clopidogrel, prasugrel	A
Thrombolytic drugs, especially rTPA (recombinant tissue-type plasminogen activator)	B
Atrial fibrillation	
Beta-blockers	A
Non-vitamin-K-dependent oral anticoagulant drugs (NOAC)	B
Except apixaban	A
Vitamin K antagonists (warfarin)	B
Osteoporosis	
Basal supplementation with calcium and vitamin D (also for prevention, from age 65 onward)	A
Biphosphonates, parenteral (e.g., injection once every three months)	A
Raloxifen for women	A

Denosumab	A
Biphosphonates, oral	B
Diabetes mellitus, type 2	
Dipeptidylpeptidase inhibitors	A
Insulin and insulin analogues for very strict indications	B
Metformin	B
Glucagon-like peptide 1 analogues	B
Chronic pain	
Paracetamol	A
Metamizole	B
Opioids with cautious titration for dose-finding, e.g., buprenorphine, oxycodone, hydromorphone	B
Nausea and vomiting	
Metoclopramide (for short-term use)	B
Constipation	
Macrogol	A
Lactulose	B
Picosulfate (for short-term use)	B

*¹The selection of drugs is derived from the psychopharmacotherapy of elderly patients and on drugs typically prescribed to mentally ill elderly patients by specialists in internal medicine and primary care.

*²www.umm.uni-heidelberg.de/klinische-pharmakologie/forschung/forta-projekt-deutsch/

Category A = the drug has already been tested on elderly patients in large-scale trials, and its benefit clearly outweighs its risks

Category B = the efficacy of the drug in elderly patients has been demonstrated, but there are some limitations with respect to safety and efficacy

eTABLE 4

Online Tools

Application	Online tools
Interactive databases	www.drugs.com/drug_interactions.php (English) www.drug-interactions.com (English) www.psiac.de (German, requires payment) www.mediQ.ch (German, requires payment) reference.medscape.com/drug-interactionchecker (English)
Internet-based tables	Flockhart Drug Interactions (English) www.medicine.iupui.edu/clinpharm/ddis/table.aspx PRISCUS List (German) www.priscus.net Forta Concept (German) www.umm.uni-heidelberg.de/klinische-pharmakologie/forschung/forta-projekt/
Renal insufficiency	www.dosing.de (German)
Prolonged QTc interval	https://crediblemeds.org/ (English)
Smartphone apps	Ifap Arzneicheck (German) www.ifap.de/mobile-loesungen/ Medscape (English) www.medscape.com/public/medscapeapp

eTABLE 1

Important information for the use of lithium in combination with other drugs

Drug used in combination with lithium	Adverse drug effect
Thiazide diuretics, loop diuretics	elevated lithium level because of reduced clearance (alternative: potassium-sparing diuretics)
Tetracyclines (antibiotics)	elevated lithium level
NSAID (e.g., diclofenac, ibuprofen)	elevated lithium level because of reduced clearance
ACE inhibitors (e.g., enalapril, lisinopril, acerbon)	elevated lithium level because of reduced clearance (arises only in 3–4 weeks)
Calcium antagonists (e.g., verapamil)	increased neurotoxicity at normal lithium levels
SSRI (e.g., citalopram) und SNRI (e.g., duloxetine)	increased risk of serotonergic syndrome
Carbamazepine	increased neurotoxicity at normal lithium levels

NSAID, nonsteroidal anti-inflammatory drugs; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors

eFIGURE 1

CYP-450 isoenzyme distribution (percent)

Psychopharmacotherapy: important isoenzymes and their distribution

Isoenzyme distribution may vary across individuals.

(Modified and expanded from [e28–e30]).