Guideline for General Practitioners
Developed by General Practitioners

Multimedication

Recommendations for Treating Adult and Geriatric Patients on Multimedication

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Why do we need multimedication guidelines for general practitioners

Physicians treating patients often fail to receive information from other physicians and clinicians involved in the treatment, not only regarding drug prescriptions but also regarding diagnostic procedures and treatment concepts [1]. On average, more than one third of patients with multimorbidities reported visiting at least 4 specialists [2].

The result is that specialists make diagnoses and prescribe treatments without knowing the prescriptions patients may be receiving from the other physicians or clinicians involved in the treatment. It results in uncoordinated multimedication, which is a severe problem that is not being dealt with seriously until now.

Chronically ill patients with multimorbidities need regular, comprehensive treatment that is coordinated with specialists. General practitioners are best fitted to coordinate the treatment as they are the doctors who see the patients regularly mostly over many years. Accordingly they are the ones who are able to bring together the information on diagnoses and all medications prescribed by other doctors and nurses involved in the treatment as well as nonprescription drugs bought by the patient. To monitor and to review these multimedication therefore should belong to their field of duties. But this is a complex and difficult task of important responsibility, that needs to be taken seriously.

In this situation, GPs need careful considered multimedication guidelines that shall provide helpful support in achieving knowledge and competence in monitoring and reviewing multimedication prescribed by physicians and nurses belonging to the ambulatory medical care network of chronically ill patients.

A key topic of a multimedication guideline for GPs in this situation is:

How to collect, record and review complete information on all medications prescribed by different specialists as well as on the patient’s OTC drugs including dosages and administration?

The Netherland’s medical care system puts much emphasis on GPs and primary pharmacies and requires all persons with medical insurance to register with a GP and a pharmacy. Both GPs and primary pharmacies share the task of monitoring and reviewing the medications of a patient.

Motivated by the Netherland’s example statutory health insurance, companies in Germany are seeking to foster general practice-centered care in order to better collect, review, and coordinate multimedication.

Why should such guidelines be prepared by general practitioners themselves?

Today it is standard practice for specialist societies to develop guidelines. Hence most guidelines focus on problems that arise in the specialized fields of their respective authors and the guidelines address key problems of the respective specialists.

But the situations encountered by general practitioners differ markedly in many aspects from those seen by other specialists and hospital clinicians. This is why a multimedica-
tion guideline for general practitioners must be prepared by general practitioners themselves.

GPs are the only physicians who have experience being the center of treatment networks for multimorbid patients. In contrast to other specialists they do not only treat individual illnesses but monitor and evaluate the entire treatment process of chronically multimorbid patients.

In this sense, GPs are also specialists – for multimedication introduced by other physicians whether in private practice or in clinics. A multimedication guideline developed by and for GPs provides recommendations for multimedication and specific drug combinations as well as for the management of the whole medication process.

Liselotte von Ferber

References


Previously Published Guidelines (some not yet updated):

- Anticoagulation
- Bronchial asthma and COPD
- Heart failure
- Diabetes mellitus type 2
- Lipometabolic disorder
- Geriatrics part 1: general geriatrics
- Geriatrics Part 2: specialized geriatrics
- Patient consultations for general practitioners
- Hypertension
- Cardiovascular prevention
- Palliative care
- Psychosomatics
- Pain
- Stable angina pectoris
- Venous thromboembolism

The Guideline Group of Hesse was founded in 1998 to create guidelines for general practitioners on selected topics for work in pharmacotherapy circles. The Guideline Group is responsible for the contents.

The multimedication guideline was drawn up in cooperation with members of the Standing Guidelines Commission of the German Society for General and Family Medicine (DEGAM), the only professional academic society for general medicine in Germany.

The PMV Research Group at the University of Cologne was responsible for the moderation of Guideline meetings, academic supervision, and guideline conception.

The Agency for Quality in Medicine (ÄZQ, Berlin) undertook a systematic study of literature in preparing the guidelines.

The guidelines have been published regularly on the websites of the Agency for Quality in Medicine (www.leitlinien.de) and of the PMV research group.

The guideline authors want to thank the Verein zur Förderung der Arzneimittelanwendungsforschung (chaired by Dr. L. von Ferber) for its financial support while preparing the guidelines.

In 2012, the polypharmacy guidelines were awarded the vdek Future Prize.

The authors wish to thank D. Bonfiglio (Cologne) for his sensitive translation of the guideline.
Responsibility

Composition of the Guideline Group

The members of the Guideline Group of Hesse for Pharmacotherapy in General Practice are practicing general practitioners in the Association of Statutory Health Insurance (KV) Physicians of Hesse, and have been active for more than 20 years as moderators of pharmacotherapy circles for general practitioners (GP). The members are in charge of developing guidelines for selected therapeutic areas pertinent to GP. This Multimedsication guideline was part of the project Quality Circles for General Practitioner Pharmacotherapy. It serves to train moderators and participants in pharmacotherapy circles. The guideline has been published in print (KVH aktuell – Pharmakotherapie) and online (www.leitlinien.de, www.pmvforschungsgruppe.de).

Aims and method

The GP Guideline Group of Hesse approaches guidelines as an aid for orientation and decision-making for patient care in primary practice. The guidelines contain therapeutic recommendations for typical symptoms and treatments (the normal case); patients with atypical presentation must be treated based on their particular conditions. Whenever possible, the recommendations have been supported by studies and strength of evidence (see below). The Guideline Group puts particular emphasis on non-pharmaceutical, patient-activating measures. The relatively low strength of evidence for such measures does not mean that they are less relevant; it only shows that these methods are less suited for the standard investigation of evidence-based medicine (such as randomized clinical studies or double-blind methods) and that it is difficult to find sponsors to fund such studies. The guidelines have merged from a careful study of existing guidelines and guideline-relevant research. Whenever evidence-based guidelines on the subject existed, we adopted relevant recommendations for primary care pharmacotherapy. When relevant studies were missing, practicing doctors of the Guideline Group arrived at consensus recommendations based on their therapeutic experiences. For several specific issues, we sought expert opinion. This pragmatic approach not only made these GP-recommended guidelines possible; it conserved scarce resources.

Autonomy

The work of the Guideline Group is autonomous and independent of outside influence. The members of the Guideline Group of Hesse all serve on a volunteer basis and have been active without compensation for out-of-pocket expenses from KV Hesse since 2009. KV Hesse does not send members to the Guideline Group nor does it submit guidelines to them before publication. There are no financial or material links between the GP Guideline Group of Hesse and any other institution or interested party.
Dear Colleagues,

Why have we created this Multimedication guideline?

For almost 20 years we have been establishing primary care guidelines with the goal of providing you the support you need to treat patients based on evidence and good medical practice. Over the years you will have noted that, as your patients become older, they take more and more medications. You have certainly seen this as a cause for concern. And you are right; so have we. But you might wonder: what if these medications are exactly what are needed and recommended for a particular set of diseases? This is a valid question. The problem is that most existing guidelines do not provide therapy recommendations for patients with multimorbidity. We have to carefully assess whether guideline recommendations are also suitable for patients with multimorbidity. We have to identify which problems are more important and require a medication-based treatment and which do not. These decisions should not be made by the doctor alone, but jointly with the patient, whose personal preferences should be factored into decisions.

Pharmacotherapy is a great responsibility. And new challenges are always emerging, especially with patients on multiple medications. As GPs we must question, monitor, and examine the course of treatment. Which medications are still needed? What can be eliminated? Has anything new come to light? We must also critically reconsider our well-worn habits and sometimes throw them overboard to give patients up-to-date medical treatments and keep them from harm’s way. This can mean eliminating one substance when prescribing a new one to avoid unpredictable cocktails or dangerous interactions.

But all this is predicated on doctors being able to inform themselves quickly about current medications.

Being a pharmaceutical guideline group, we are primarily concerned with the question of how to safely manage pharmacotherapy. What should be considered when patients take several medications concurrently? This guideline provides several forms of aid to help you in treating patients with multimorbidity correctly and according to their needs. It is also meant to remind you that you are not alone.

We also hope that the recommendations contained within will awaken in you a newly found interest for the subject.

Please feel free to send us your comments and criticism.

Sincerely,
The Guideline Group
Summary

Multimorbidity is usually accompanied by multimedication. But multimedication brings with it risks: the potential for interactions and misuse increases demands on patients as well as on the GP in his or her work as medication coordinator. A basic requirement for the safe treatment and medication management of patients on multimedication is an up-to-date medication record.

The Guideline Group differentiates between necessary multimedication and undesirable multimedication. The latter has many causes: uncoordinated treatments, self-administered medication, continuation of acute treatments, and undetected prescription cascades, to name just a few. They all provide some starting points for reducing the number of medications a patient is taking.

The guideline recommendations are based on an analysis of medication review studies. These studies were not performed in settings comparable to primary care practice in Germany and come to contradictory findings. Nevertheless, the Guideline Group recommends a medication review, since it has been proven to identify treatment problems, and to increase drug safety and the quality of life.

Prescription process

To optimize and ensure the safety and quality of drug treatment, the entire prescription process must be considered. This guideline identifies the following steps:

- **Initial patient evaluation:** First and foremost is a medical history of the symptoms and concerns of the patient and his current medications. Nonspecific complaints can be side-effects from existing medications. The basis of the evaluation for patients is the description of the medication by the patient themselves and the medication record. With patients who are suffering from treatment problems and are on multimedication, doctors should perform an annual review of all medications, including self-medications. The patient evaluation should also include determining whether the patient is adhering to the medication regimen and identifying problems with medication use.

- **Medication review:** The central component of prescription decisions is the critical review of existing medication. Key questions exist for helping doctors make prescription decisions. The Guideline Group recommends using the questions proposed by the Medication Appropriateness Index (MAI) [62]. These questions cover indications, contraindications, dosage, appropriateness, and the economic viability of the treatment.

- **Coming to an agreement with patients:** Before deciding on a prescription, the doctor must come to an agreement with the patient about their needs and expectations from the drug treatment.

- **Prescription decision:** In addition to prescribing a new drug, doctors can decide not to write a new prescription or discontinue a treatment based on the MAI assessment. The termination of treatment can also follow a joint decision by doctor and patient to discontinue indicated medications due to issues relating to quality of life or therapy management. The guidelines also provide information on screening for unmet medical needs despite multimedication.
• **Communication**: Patients must be well informed about their treatment, about their current medication record, and about their dosage and administration for successful treatment and the reduction of drug-related problems. The guideline indicates minimum requirements for medication records and recommends the medication safety program (AMTS) of the German Coalition for Patient Safety.

• **Drug dispensing**: In most cases, pharmacies dispense prescription medication. Patients on multimedication are advised to choose a primary pharmacy that can check for drug-drug interactions, issue an electronic medication record including self-medication and also note possible interactions of self-medication in the plan.

• **Drug administration**: Safe drug administration can be fostered by a variety of professions and institutions (doctors, medical assistants, pharmacies, nurses) as well as by written material.

• **Monitoring**: Each instance of monitoring (assessing treatment results, identifying adverse drug reactions (ADRs), etc.) represents a new evaluation (see above). The guidelines recommend monitoring frequencies for certain critical groups of drugs.

**General measures for reducing undesirable multimedication**

• Consult the central points of the MAI for aiding the medication review

• Do not introduce treatment without first taking a medication history (asking about cases of past intolerance, instances of self-medication and medication prescribed by other doctors; reviewing the medication record).

• Involve patients in decisions about medications (do not assume that a patient has a medication preference; do not fulfil every preference).

• Determine whether a pharmacotherapy is necessary and promising.

• Consider long-term benefits of treatment when deciding on a medication.

• Discontinue pharmacotherapy when no longer necessary; do not follow long-term treatments out of habit.

• With new patients, after hospital stays, or when additional doctors become involved always recheck and discuss the patient’s medication record.

• Screen for adverse drug reactions (give patients advice for when side-effects occur; check whether new symptoms are ADRs.)

The authors of the guideline describe the general framework – electronic and financial support – for carrying out a comprehensive medication review.
Aim and target groups of the guideline

This guideline is designed to help general practitioners systematically assess medication therapies when making prescription decisions. In this way, the guideline helps

- prevent inappropriate medications and unintended prescription cascades [119],
- avoid adverse drug-related effects,
- detect imprecise dosing and misuse,
- identify unmet medical needs even in cases of multimorbidity,
- choose suitable medication in cases of multimorbidity,
- keep the number of medications for patients manageable,
- provide advice for necessary prioritizing, and
- monitor for physiological changes (e.g., influence on pharmacokinetics in old age).

The guideline is designed for older patients as well as for general patients on multimedication. The recommendations do not apply to medical treatments used for palliative care. They are designed to help identify, prevent and eliminate problems arising from multimedication.

Note

The guideline applies to men and women alike, though masculine pronouns are occasionally used to avoid awkward phrasings.

Explanation

The very high number of multimorbid patients treated by multiple specialists at the same time requires a general practitioner who can assess and evaluate all the patient’s medications. To this end, the general practitioner must keep patient records with all diagnostic findings and coordinate all those involved in patient care. Electronic health cards and electronic medical records cannot take the place of these responsibilities. It is obvious that patients on a high number of medications require special attention. Doctors must regularly check whether all medications are necessary or whether drug-related problems are present. A well-structured approach is necessary for individual treatment assessment. Every change in treatment requires comprehensive consultation from a doctor and thorough discussion with the patient (shared decision-making). This guideline contains helpful advice for these practices.

At the time the authors began their work (fall 2011) there were no guidelines for multimedication available. In May 2012 the Dutch Association of General Practitioners, in cooperation with other professional associations, published Multidisciplinaire richtlijn Polyfarmacie bij ouderen [109], which set parameters for multimedication in patients older than 65.
Key questions for general practitioners

How do I identify a patient’s medications?

- How do I find out about all the medications (including self-administered medication) used by the patient?
- How do I get information about the treatments prescribed by other medical practitioners?
- How do I detect problems faced by patients with drug administration? How do I assess their possible resistance to drug treatment?
- How do I recognize medication administration errors and non-adherence?
- How can I simplify the drug administration schedule?
- How do I perform a medication check in an acceptable period of time?

How do I identify the risks and dangers of multimedication?

- How do I make the necessary dosage adjustments in cases of multimedication (especially with older patients or with restricted renal and liver function)?
- Which medications have an increased risk of adverse reactions in old age?
- Which specific problems can be observed with specific patient groups (e.g., children, pregnant women, patients with addictions)?
- Which check-ups are necessary in cases of multimedication and how often should they be performed?
- What aids can I use to identify interactions?
- How do I avoid complications if an acute illness requires the use of a short-term medication in addition to a prior long-term medication?

How do I detect symptoms?

- What adverse reactions can be expected when discontinuing a drug?
- How do I detect drug-related adverse reactions?
- How do I distinguish between side-effects from treatment and symptoms of disease?

How do I prevent/reduce unnecessary multimedication?

- How do I prioritize for individual cases? Is it possible to set preferences in discussion with patients/family members to reduce the number of medications?
- How do I evaluate the necessity of a current therapy or its continuation?
- What value do symptomatic and causal therapeutic aims have with individual patients?
- How can I assess the individual benefit of therapies (even if evidence based) for the patient?
- How do I detect unmet medical needs despite multimedication?
- What are the criteria for continuing to prescribe medications recommended after hospital discharge?
- Does multimedication indicate incorrect treatment (e.g., prescription cascades, see Figure 1)?
- How do I assess an individual’s risk of side-effects and interactions?
- How can patients be motivated to take active, non-pharmaceutical measures?
Introduction

Epidemiology of multimorbidity

The treatment of patients with multimorbidity taking a variety of medications simultaneously is the daily bread of the general practitioner. Depending on the study, the prevalence of multimorbidity varies between 9% and 80% among adult patients under the care of general practitioners [3, 21]. The numbers are dependent on the age of the patient and the type and number of diseases that constitute the multimorbidity. The prevalence figures are difficult to appraise without this data. Frequently, only chronic or serious illnesses are considered when determining the presence of multimorbidity. However, almost every study on multimorbidity ever published uses its own criteria, which makes comparisons between studies and findings difficult. There is no generally accepted definition for multimorbidity.

According to the Guideline Group
- multimorbidity is the copresence of 2 or more chronic or acute diseases [1] in a patient;
- multimorbidity consists of all of a patient’s illnesses that exist at the same time.

What is undisputed is that the number of chronic diseases and the number of new diseases increases markedly with age:

According to a telephone health survey (GStel03) [118] about half of people over the age of 65 in Germany show 3 or more relevant chronic diseases.

According to a Dutch study carried out in general practices, the prevalence of multimorbidity (defined as the copresence of 2 or more chronic diseases) in men 19 or under is 11% and in men who are 80 is 74%. For women in the same age groups, it is 9% and 80%, respectively [1].

According to a Berlin study of the elderly – a representative cross-sectional study of subjects over 70 – the percentage of multimorbidity is even higher: its researchers found that 88% of the elderly have at least 5 illnesses at the same time [141].

Compared with prevalence figures given in a population-based study, general practitioners see considerably more multimorbid patients. Multimorbidity causes significant problems in daily practice, and these problems have been given inadequate attention in guidelines and clinical studies. Even in treatment studies, multimorbid subjects are usually underrepresented or excluded, which limits the validity of studies for many patients under primary care [21; cited in 44].

How is multimedication defined?

Multimorbidity is usually accompanied by multimedication. Multimedication increases in older age groups, but also occurs in younger patients [100]. Like multimorbidity, there is no scientific standard for defining multimedication (synonym polypharmacy). Here too the spectrum ranges from multiple medications (> 1) in a period to a determination of a certain number of different medications prescribed at the same time (e.g., > 5 – 10) [104]. The range of reported frequency data for multimedication is correspondingly large.
How frequently and to what extent does multimedication occur?

In 2010, persons over 65 years of age insured with the German statutory health insurance funds (27.2% of the total population) took on average 3.6 daily doses of medication as part of a long-term treatment. 66% of all medications are prescribed for this age group [33].

With regard to the frequency of multimedication among the elderly in Germany, Thürmann et al. [151] found in 2012 that 42% of patients over 65 are on “cumulative multimedication”, defined as the prescription of 5 or more medications within a quarter. Schuler et al. [133] determined that around 58% of elderly patients (> 75) in Austria, who have been admitted to an internal medicine ward are on multimedication with > 6 medications. This was associated with females, need of nursing care, and a high number of discharge diagnoses.

Necessary multimedication

Even when prescriptions are part of a considered approach, the treatment plan agreed on collectively with the multimorbid patient often includes more than 5 medications. Does this represent a worse treatment since it exceeds the recommended aim of no more than 5 medications? In our opinion no, assuming that the multimedication is sensible and warranted.

Treatment must be carefully monitored; general, nonspecific, and specific complaints must be recorded. A possible relationship between new complaints and current medications – especially newly introduced substances and dosage changes – should be checked, e.g., through trial withdrawals. In many cases this will improve the patient’s quality of life. This requires constant observation and possible treatment adjustments after taking into account interactions, dosage reductions, and any medication synergies. The last involves the combination of several substances to reduce the dosage of individual medications and to reduce the risk of side-effects. (For more, see the section on the prescription process.)

The goal should always be: as few medications as possible, as many medications as needed. Necessary medical treatments should not be avoided for the sake of having no more than 5 medications.

How does undesired multimedication occur?

- Undesired multimedication can occur when a patient suffers multiple diseases, each subject to its own guidelines. Because most guidelines are designed for a single disease, serious complications can arise in multimorbid patients when no general strategy exists [23]. With many chronic diseases, multiple medications need to be combined; 5 – 10 different medications are common [21, 55].
- Undesired multimedication can occur when a patient is treated by different doctors (e.g., general practitioner, neurologist, orthopedist) who are not informed or only partially informed about the medications prescribed by their colleagues. The prescription of incompatible medications can lead to iatrogenic symptoms. Example: A patient suffering from headaches receives acetaminophen from his general practitioner, triptans from his neurologist, diclofenac from his orthopaedist for neck pain, ibuprofen from his pharmacist (over-the-counter (OTC)) and aspirin from his neighbour, “because none of that helps.”
- Undesired multimedication can occur when side-effects emerge that are not identified and that lead to the introduction of new medication and not to the adjustment of the medication causing the side effect, bringing about a prescription cascade [119]. Below is an example of a possible prescription cascade with a standard treatment involving three drugs (Figure 1).
- Undesired multimedication can occur when treatment recommendations from the hospital are adopted without a critical assessment of long-term outpatient treatment. Since inpatient stays are be-
coming shorter, the intended and adverse reactions of drugs, especially their interactions, often do not present themselves until after hospital discharge.

- Undesired multimedication can occur when patients try medications they see in ads or that friends and relatives recommend. With common symptoms such as sleep disorders or indigestion, patients self-administer medications (OTC) without their treating physicians being notified. Because many medications that once required a prescription – triptans, proton-pump inhibitors, nonsteroidal anti-inflammatory drugs – are now available without prescription at pharmacies, the potential for adverse drug reactions has grown.

- Undesired multimedication can occur when patients use so-called anti-aging compounds or purportedly safe and dubiously effective herbal medications. These substances can also trigger interactions.

- Undesired multimedication can occur when new treatments and medications are introduced over time, but previous measures or ineffective drugs are retained, leading to an accumulation of medications.

- Undesired multimedication can occur when effective therapies are continued after the treatment goal has been reached (e.g., proton pump inhibitors for acid reflux).

- Undesired multimedication can occur when opportunities to reduce the number of medications or the dosage are not taken due to a lack of monitoring after the steady state has been reached.

- Undesired multimedication can occur when medications are continued after risk factors (e.g., weight reduction, smoking cessation, dehydration) or the clinical symptoms change.

- Undesired multimedication can occur when discount agreements change, and the patient loses track of his medications, taking identical compounds from different manufacturers concurrently.

- Undesired multimedication can occur when the elderly forget to take their medications. Especially when cognitive deficits are present, patients tend to take too many or too few tablets [36].

- Undesired multimedication can occur when doctors have certain expectations, such as when they believe that a patient wants a particular medication.

In sum, undesired multimedication can arise through many different factors, including patient behavior, doctor behavior, medical practice organization and at points of contact (see [97]). If pharmaceutical treatment is to be safe, it must be understood as a management task and must take into account these factors along with the participants involved. For this, good communication between doctor, patient and the other treating physicians and consultants is indispensable, as is a thorough medication review (see below).

**Risks and dangers of multimedication**

The presence of many different medications often causes concern for the treating physician (and for the patient), especially due to the increased risk of interactions and the difficulty of keeping tabs on the bigger picture.

Multimedication can bring about a variety of side-effects, which can feign new illnesses or a worsening of an already diagnosed disease. In particular:

- With every new medication the risk of adverse drug reactions (ADRs), medication errors or drug interactions increases [111, 152].

- Multimedication frequently causes non-specific complaints such as fatigue, loss of appetite, vertigo, states of confusion, tremors or falls and can lead to functional disorders whose causes are difficult to
identify [29], resulting in the need for further medication (prescription cascade; see Figure 1).

- Adherence decreases as the number of medications increases and, as a result (prescription cascade, see Figure 1), drug instructions become more complex [15], easily confusing patients. In addition, motivation to cooperate can sink when patients have misgivings about the treatment due to the amount of medications they are taking.

- Paradoxically, multimedication can lead to important diseases not being treated properly (undertreatment), and can be an indication of an inadequate and an uncoordinated therapy [83].

- Patients on multimedication have an increased likelihood of undergoing inpatient treatment. Around 6.5% of all hospitalizations are the result of ADRs, and of these up to 80% are categorized as serious (cited by [82]; also see [63, 152]).

- The costs of treatment increase. In Germany, the additional healthcare expenses caused by ADRs amount to around 400 million euros annually [130].

- Generally, the effects, interactions and ADRs of medications stop being predictable when patients take more than 5. The rule here: less is more.

In sum, patients who are undergoing long-term treatment with multiple medications represent a risk population for adverse reactions and treatment problems. Some challenges to be addressed by therapy management are:

- accounting for potential interactions from additional medication for an acute illness (antibiotics, short-term use of pain medication),
- accounting for contraindications,
- preventing double prescriptions by multiple doctors, or as a result of discount agreements,
- accounting for patient self-administration of medication,
- monitoring for physiological changes in elderly patients and selecting appropriate medications for the elderly,
- selecting a viable treatment regimen,
- ensuring adherence and avoidance of drug administration errors,
- regularly updating medication records and regularly assessing entire treatment regimen.

Patients on multimedication require special attention. Drug-related problems can be expected in particular [108]:

- when patients regularly take 5 or more medications,
- when the medications have a narrow therapeutic range or need constant monitoring,
- when problems occur in treatment implementation (safety caps, dropper bottles, injections, aerosols),
- when patients are cognitively unable to keep up with a treatment regimen,
- when patients receive medical consultation from different doctors,
- when patients do not understand the treatment.

To ensure the safety and success of drug treatment, it is necessary to take a methodical approach to prescriptions. The following sections describe this approach and include helpful information on medication reviews.
Prescription process

Overview

Doctors typically see prescription writing as a routine process that can affect the quality of treatment and drug safety. Ideally, this process takes places in close coordination with the patient and the other treating physicians. In 2008, Bain et al. [9] divided the prescription process into the following stages: patient evaluation – medication review – identifying and coordinating treatment goals – proposing a medication – communication – prescription dispensing – drug administration – monitoring. The last stage involves another patient evaluation and begins the process anew (Figure 2).

Step 1. Patient evaluation – collecting information

The process begins with the presentation of the patient’s situation. The doctor must record the patient’s problems, his preferences and treatment aims, review his medical history and if needed carry out a physical examination. These findings provide the basis of treatment indications.
The doctor should review the patient’s records and ask the following questions:

- Are there relevant pre-existing conditions? Have all complaints and diagnoses been recorded?
- Have special problems (allergies, anticoagulant treatments) and recent blood tests (renal function) been recorded?

The patient evaluation also includes an evaluation of the patient’s medication history and current medication. In doing so, doctors should ask the patient about their experiences and problems (including management problems).

The patient evaluation can be performed with different levels of intensity and can take place either at the doctor’s practice or during a house visit:

- Stage 1: The first level is unstructured and occurs as part of a normal doctor’s consultation, with existing patients and without being prompted by medication problems. It consists of a review of the current medication record and an inquiry about other medications the patient is taking, including self-administered drugs. The doctor performs the review.
- Stage 2: The second level involves a targeted review of new prescriptions or refills. It consists of a review of the current medication record and an inquiry about other medications the patient is taking, including self-administered drugs. The doctor performs the review in the case of new medications. When indicated, doctor’s assistants can perform the review in the case of refills. They can check whether the medication is already included in the medication record, whether the interval between prescriptions and the amount of medication are appropriate and whether laboratory tests are necessary.
- Stage 3: Targeted review after receipt of a medical report from a specialist or after hospital discharge. It consists of a comparison with existing medications, a determination of the treatment duration, updating the medication record and setting treatment check-ups. The doctor performs the assessment.
- Stage 4: With new patients or with existing patients on multi-medication, a structured medication review (e.g., using MAI; for more see below) should be performed at least once a year or whenever treatment problems arise. Doctors should arrange a separate appointment to which the patient (or a contact) brings all medications (including self-administered medications) and package inserts from home. This is referred to in the literature as the brown bag method, because of how the materials are commonly submitted (i.e., in a brown bag). This approach seeks a complete survey of medication. The medications can be easily recorded in practice using any common brand of scanner. In this way, medications can be recorded in the patient’s records, interaction checks performed and medications kept up to date. House visits are also a good opportunity to get a sense of existing medications and their management (daily provision of medication, administration problems).

Checking for adherence

Likewise, the adherence to treatment regimens should be checked and deviations and problems with implementation discussed [37]. Around half to one third of the medications prescribed for chronic illness are not taken as instructed [107, 167], and the number of deviations increase with the number of medications [12]. In a study of general practices in Hesse, almost all investigated patients were affected, admitting that they did not take prescribed medicines, changed the dosages, took them outside the prescribed times, or took medications of which their general practitioners were unaware [105]. Frequent reasons for these deviations are problems with record keeping (medication records are not updated), the existence of prescriptions from other treating doctors and the use of OTC medications [128].

Today, the term for following a prescribed treatment is adherence. The previous common term for this – compliance – reflected a paternalistic model of the doctor-patient relationship in which the decision-making authority lay exclusively with the doctor. Compliance is when the patient does what the doctor says. The responsibility for not following the treatment plan is the patient’s.
By contrast, the concept of adherence emphasizes the active cooperation of the doctor and the patient in making decisions and setting treatment goals. Patients are actively asked for their opinion and involved in treatment planning [78, 167].

If the patient does not adhere to the previously arranged treatment, or if the patient does not follow the previously arranged treatment in its entirety, one speaks of non-adherence [135]. Nonadherence is not a problem of the patient, however; it usually comes from a combination of a failure to create sufficient acceptance for the medication and insufficient support of its administration. Two basic categories of nonadherence are distinguished:

- Advertent nonadherence (patient consciously decides not to implement the recommendations of the treating doctor).
- Inadvertent nonadherence (patient follows the recommendations but has problems with its use or lacks understanding for the treatment [107]).

Within these categories nonadherence can take on a variety of forms [161] (Table 1).

### Table 1. Based on [16].

<table>
<thead>
<tr>
<th>Types of nonadherence</th>
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</thead>
<tbody>
<tr>
<td>Omitting (forgetting) doses, or one-time daily applications.</td>
</tr>
<tr>
<td>Deviations from prescribed administration times and dosage intervals.</td>
</tr>
<tr>
<td>Pauses in medication; patients initiate drug holidays (≥ 2 successive days).</td>
</tr>
<tr>
<td>Termination of treatment/administration.</td>
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<tr>
<td>Lower dosage than prescribed; more frequent than overdose.</td>
</tr>
<tr>
<td>Morning administration is more regular than evening administration.</td>
</tr>
<tr>
<td>Irregular administration is frequent in the intervals between doctor visits; regular administration shortly before or after doctor visits (known as toothbrush effect, white coat compliance).</td>
</tr>
</tbody>
</table>

The following questions serve to curb nonadherence-related problems:

- Was the patient doing well with previous medications?
- Are there problems with administering the medications, e.g., opening packaging, counting drops, swallowing tablets [125]?
- Does the patient understand why the medication has been prescribed?
- Does the patient believe that it makes sense to continue the medication?
- Does the patient raise or lower the dosage on his own accord?
- Has a trial withdrawal been performed?
- Has the patient organized his medication for the day or week so that nothing is forgotten or taken twice?
- What does a patient do when he forgets to take a medication?

Try to create an environment in which patients are not embarrassed to admit when they don’t understand something or have doubts about the treatment regimen or have practical problems. Find out possible reasons for nonadherence and obtain the patient’s consensus for all measures, including regular check-ups.

The guideline “Medicine Adherence” by the National Institute for Health and Clinical Excellence (NICE Guideline 76 [107]) gives more information on how to improve patient adherence.

### Step 2. Medication review

A central component in making decisions about prescriptions is the examination and review of existing medications for each patient. Depending on the complexity of the patient situation (multimedication, treatment problems) the process varies in intensity: from the routing check-up to a comprehensive medication review and, if needed, a prioritization of medications.

- Generally, patients on multimedication (e.g., ≥ 5 medications ≥ 3 chronic illnesses – an evidence-based recommendation is lacking here) should undergo a comprehensive evaluation and medication review at least once a year [136].
With patients who don’t show current signs of medication problems, multimedication should be observed carefully. A regular review of the medication record is recommended.

Comprehensive medication review and evaluation

For the review, central questions for guiding prescription decisions are helpful. In the literature, different methods and instruments have been described [37, 126] for making methodical decisions such as VASS [158], the Medication Appropriateness Index (MAI) [62], NoTears [92], and START-STOPP [49, 50]. The Guideline Group recommends using the Medication Appropriateness Index (MAI) [62]. The MAI has been tested and evaluated on various occasions [42, 127, 140]. It consists of guiding questions for identifying unnecessary medications, increasing application safety and improving treatment quality (on MAI see below). The questions must be ticked off one by one for the current medication. This systematic collection of information forms the basis for prescription decisions.

A medication review is also recommended for:
- patients with worsening health,
- patients with signs of administration problems (adherence, management, cognitive limitations),
- new patients on multimedication,
- patients on multiple psychotropic drugs,
- patients with complicated medication records or medications with high interaction potential and or narrow therapeutic range (e.g., anticoagulants and antiplatelet drugs),
- patients with nonspecific symptoms,
- patients who have problems with the treatment regimen.

The MAI does not provide for an individual prioritization. This occurs only after MAI has been performed and in special situations. (For more, see the section below on prioritization.) In many cases, the number of medications decreases after performing MAI. The MAI does not contain explicit criteria, or whether individual substances are indicated and appropriate and whether special risks arise. For this, additional instruments (such as PRISCUS or the START-STOPP criteria; see below) must be used in addition.

The Medication Appropriateness Index is a recommended instrument for medication review to enable targeted interventions.

As shown in Figure 3, the target groups and their medication reviews are represented in order of increasing intensity.

The MAI review begins by looking at the indications for already prescribed medica-
Next, it checks whether there is sufficient proof of the medication’s effectiveness, whether there are new findings and whether expert opinion on already existing studies has changed. Furthermore, it screens all patient medications for possible interactions, side-effects, and redundancies and ensures that patients adhere to proper dosages and durations.

The medication review includes a yes/no review (without total score), which the treating physician reviews to identify the next steps to take (discontinuation, dosage adjustments, etc.).

In the following sections, we look more closely at the individual MAI steps.

Figure 4. Medication Appropriateness Index (MAI) (as modified by Hanlon [62]).
Checking for indications and evidence

Questions when reviewing indications:

- Is the diagnosis still valid?
- Have the circumstances or risk factors changed (as with hypertonia or diabetes)? Does a medication for risk prevention make sense in view of patients with limited life expectancy (such as in the case of patients with high age or the seriously ill)?
- How long ago did the event (breast cancer, osteoporosis, thrombosis, heart attack, stroke) take place? Which treatment is still required? Do studies support lifelong treatment or one of limited duration (e.g., 3-year treatment with bisphosphonates [38])?
- Has a new illness arisen in which an existing medication is contraindicated?
- Has a medication been prescribed for treating an adverse reaction?
- Are clinically irrelevant parameters (e.g., asymptomatic hyperuricemia, hypercholesterinemia without significant increase of risk) or minor complaints (malaise) being treated?

Is there evidence supporting the effectiveness of the selected medication for the presented indication?

Evidence can be found in:

- Cochrane Reviews
- Evidence base guidelines (e.g., NICE, SIGN)
- Country specific information systems for evidence based medicine (e.g., Guidelines from Medical Associations)
- Independent Drug Bulletins (International Society of Drug Bulletins; Drug and Therapeutic Bulletin)

It should be noted that the absence of studies on a medication’s effectiveness does not necessarily mean that it has no benefit.

Checking for contraindications

Frequently, doctors speak informally of “absolute” and “relative” contraindications, but such a distinction does not exist in Germany’s comprehensive drug registry (known as the Rote Liste®) and in the medically and legally binding Summary of product characteristics (SPCs). An “absolute” contraindication for a medication is referred to as a contraindication in the Rote Liste® and in the SPCs (4.3). In addition, the Rote Liste® provides information on use restrictions. These restrictions are presented in more detail in the SPCs under section 4.4 “Specific Warnings and Precautions for Use”. Section 4.2 of the SPCs “Dose, Type, and Duration of Use” should also be noted carefully; it contains information on contraindications or precautionary measures for specific patient groups (elderly, children, patients with restricted renal function, etc.). As a rule, only the information provided in the officially approved SPCs is legally binding. (German-language SPCs can be found at: www.fachinfo.de).

The check for contraindications is an indispensable part of the prescription process. Mistakes can have direct legal consequences. The prescription of a drug when it is contraindicated in the SPC is only permitted when the patient is informed about the contraindication and provides his written consent. Such a scenario is unlikely, as almost all contraindications have alternative medications as options.

- Exceptions are substances such as metformin, which is contraindicated when the creatinine clearance is < 60 mL/min; yet this strict threshold value is controversial (many overweight type 2 diabetics would surely benefit from treatment, but because their creatinine clearance is < 60 but > 50 mL/min they are not eligible). Germany’s National Disease Manage-
Prescription process (NVL) recommend the use of metformin in accordance with patient information on out-of-label use with a creatinine clearance over 30 mL/min, provided regular check-ups are performed ([28]; see also [68]).

A problem with contraindications is the vagueness of the information, especially with older medications. For instance, an unspecified condition such as liver failure (as with metformin) or liver parenchyma (as with phenprocoumon) is frequently given. With new medications, the Child-Pugh score is used as a minimum test for classifying the stages of liver cirrhosis.

Generally, the specifications of the Rote Liste® are more restrictive. Hence, it makes sense to first consult the Rote Liste® and then later the SPCs if time permits.

It should also be noted that the SPCs of different generics for the same drug can differ significantly.

It makes little sense to list the most important contraindications in this guideline, particularly because “the devil is in the details”. Everyone knows that verapamil may not be given when an AV block (second degree or greater) is present, but in medications that are rarely prescribed or given little attention, contraindications can be overlooked.

In addition, contraindications for a medication class are not always the same. For instance, what applies to ramipril does not automatically apply to enalapril.

**Summary:** The Guideline Group recommends basic restrictions to the medication portfolio so general practitioners have an easier time keeping track of the bigger picture. A reduction of patient medications reduces the number of undetected contraindications.

**Checking for interactions**

In general practice, long-term treatments can become problematic when intermittent illnesses – infections, aches and pains – arise requiring the short-term use of additional medications. Interactions must also be considered when a new long-term treatment is introduced.

Despite multiple warnings from medical software, not all interactions appear and not all of them have clinical relevance. Some combinations of drugs with interactions cannot be avoided clinically (e.g., phenprocoumon and amiodarone in the case of atrial fibrillation). The table below of collected medications/drug classes includes clinically relevant interaction risks determined by epidemiological studies.

In this situation the following strategies are available:

- using an alternative drug with fewer interactions for certain indications, e.g., pantoprazole as a PPI, pravastatin as a CSE inhibitor, azithromycin as a macrolide;
- pausing one medication if possible (such as statine while the patient is on antibiotics);
- dosage adjustment (strategy of last resort, as it is hard to steer).

**Help for interaction checks**

There is a battery of software programs for testing for interactions, some of which operate automatically. Unfortunately, their multiple warning signals can be obtrusive. Yet, switching off unfiltered warning signals has the downside that truly relevant interactions go undetected. The problem lies mainly in the fact that, increasingly, the interactions that arise from the new development of medications in vitro (through cell cultures) find their way into manufacturer warnings without clinical evidence or a clinical study. By contrast, other interaction specifications are based on individual studies (some of which are outdated) that multiply through repeated citation. Generally, the evidence for clinically relevant interactions is weak. Software should always indicate clinical relevance when reviewing medications and make recommendations on management, e.g., whether a combination should be avoided at all costs (rarely the case), whether there are alternatives, which form of monitoring is necessary, and what patients should look out for themselves.

Generally, one has to bear in mind, that low-risk interactions are not likely individually, but as a whole can lower a medication’s safety. This can become relevant if further risks emerge in the patient (infections, dehydration, changes to kidney function). At the
same time, when the number of medications is high, as tends to be the case in general practice, even rare reactions should be taken into account.

Among the available digital tools are these products and web portals:

- www.pharmatrix.de (developed by the hospital pharmacy at the University Hospital inTuebingen),
- www.hiv-druginteractions.org,

For iPhone and Android users, there is a useful application that permits quick interaction checks, even during house visits. A free registration is needed for PC and APP use (http://www.medscape.com).

Table 2 provides an overview of common interactions with dangerous consequences. The selection is based on an assessment by the guideline authors.

There are multiple interactions for grapefruit juice and medications containing St. John’s wort (OTC and prescription) but the extent of the risk depends on the source/ori-
gins (which St. John’s wort extract, which grapefruit type, time of harvest) and thus are almost impossible to predict. Hence, one should generally
- advise patients on multimedication to avoid grapefruits and grapefruit juice, even if occasional or low-level ingestion has yet to produce reliable clinical data [61, 121]. Nevertheless, a glass of grapefruit juice or a grapefruit can completely inhibit CYP 3A4 for 2 – 6 days [61, 166].
- warn against taking compounds containing St. John’s wort (OTC) when on medication and when prescribing St. John’s wort check the SPCs for interaction risks [7, 35].

While many medications can be metabolized by one or more cytochrome P450 isoenzymes, others also act as inducers or inhibitors of metabolization, which can lead to different concentrations of active agents [32]. As a result, interactions can arise that are not always predictable, especially in patients on multimedication.

Examples for interactions with cyto-

- Clarithromycin is one substance that inhibits CYP3A4. A simultaneous treat-
ment with verapamil, which requires CYP3A4 for metabolization, leads to ex-
cessive concentration of verapamil due to the shortage of CYP3A4. For many indi-
cations, amoxicillin provides an alternative with fewer interactions.
- Paroxetine requires CYP2D6 and CY-
P3A4, which are also needed by metopro-
hol for metabolization. When prescribing both at the same time, the competition can lead to an accumulation of metoprolol, since metabolism is prevented by CYP shortage. The alternative is bisoprolol.

Many substances, in addition to their main effects, also lead to anticholinergic (parasympatholytic) side-effects (e.g., tricyclic antidepressants, older H1 antihista-
mines such as hydrazine or promethazine). The main effects of spasmyotics (butylscopolamine, oxybutynin) are anticholinergic. These cause symptoms such as dry mouth, nasal congestion, and in serious cases a so-called anticholinergic syndrome can arise, characterized by confusion, vertigo, im-
paired vision, and hyperthermia. This syn-
drome is usually caused by interactions be-
tween multiple anticholinergic medications (some of which are available OTC).

Table of relevant interactions

Selected relevant medication interactions (see also [32]) (Table 2).

Prodrugs, QT prolongation

Prodrugs

Prodrugs are not effective until they are metabolized. Their effect can be diminished or strengthened by inhibition or induction of the corresponding CYP isoenzymes.

Examples for cytochrome interactions in prodrugs:
- The prodrug clopidogrel requires CYP2C19 to assume effective form. CYP2C19 and CYP3A4 are also required by omeprazole for metabolization. The combined use reduces the effect of clopidogrel.
- Tamoxifen requires bioactivation via CYP2D6 to become endoxifen. This pro-
cess is prevented by strong CYP2D6 in-
### Table 2. Selected relevant medication interactions (see also [32]).

<table>
<thead>
<tr>
<th>Medication 1</th>
<th>Medication 2 (new)</th>
<th>Effects</th>
<th>Response</th>
</tr>
</thead>
</table>
| ACE inhibitors/AT1 blockers   | NSAR/COX-2 inhibitors (e.g., diclofenac, ibuprofen, etc.) | Reduced effect of ACE inhibitors (e.g., risk of acute decompensation), additional restriction of kidney function | 1. Prevent  
2. Self-checks, e.g., blood pressure and weight  
3. Use of a different analgesic                                        |
| Diuretics                     | NSAR/COX-2 inhibitors (e.g., diclofenac, ibuprofen, etc.) | Reduced effect of diuretic (e.g., risk of acute decompensation)         | 1. Prevent  
2. Self-checks, e.g., blood pressure and weight  
3. Use of a different analgesic                                        |
| CSE inhibitors (pravastatin and fluvastatin have few relevant interactions) | Macrolides (except azithromycin), amiodarone, fluconazole, fibrates, verapamil | Mutual enhanced effects, risk for rhabdomyolysis                          | 1. Pause CSE inhibitors during antibiotics treatment  
2. Prevent  
3. If joint administration is necessary, switch to pravastatin          |
| Phenprocoumon                 | e.g., TMP, cotrimoxazole, metronidazole, doxycycline, amoxicillin/clavulanic acid, NSAR/COX-2 inhibitors, rifampicin, phenylbutazone, allopurinol, amiodarone, macrolides (all), ginseng, ginkgo | Risk of bleeding, increased or decreased effect                        | 1. Prevent  
2. Generally: if a new long-term medication is added to phenprocoumon, check INR for the first 14 days at short intervals (at least every 7 days), vice versa |
| β-blockers                    | Verapamil, diltiazem                                      | Can lead to third-degree AV block                                      | Contra-indicated                                                          |
| Glucocorticoid                | NSAIDS                                                   | Risk of bleeding in digestive tract                                     | 1. Prevent  
2. If NSAIDS are unavoidable, then add PPI                               |
| SSRIs                         | NSAIDS                                                   | Bleeding in digestive tract                                            | 1. Prevent  
2. If NSAIDS are unavoidable, then add PPI                               |
| Theophylline                  | gyrase inhibitors (all), erythromycin, clarithromycin, fluvoxamine | Increases concentration of theophylline                                | 1. Prevent  
2. If unavoidable, watch for signs of toxicity and if needed check blood levels on third day |
| PDE inhibitors for erectile dysfunction | nitrate, PENT, molsidomine                               | Untreatable, possibly lethal hypotonia                                  | Contra-indicated                                                          |
| Terfenadine, loratadine, etc. | Macrolides                                               | Prolonged QTc (terfenadine), increased effect/raised concentration (loratadine) | Terfenadine should generally not be used in cases of multimedication       |
| Dabigatran                    | ketoconazole, cyclosporin A, itraconazole or tacrolimus   | Bleeding risk, increased effect                                         | Contra-indicated                                                          |
| Rivaroxaban, apixaban         | Azole antifungals such as ketoconazole, itraconazole, and protease inhibitors, e.g., ritonavir | Bleeding risk, increased effect                                         | Contra-indicated                                                          |
| Tricyclic antidepressants     | anticholinergic spasmolytics (e.g., oxybutynin)           | Enhanced anticholinergic effects (dry mouth, vertigo, confusion)       | 1. Identify  
2. Prevent  
3. If unavoidable, observe symptoms                                          |
| Fentanyl                      | SSRI (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) SNRI (venlafaxine) MAO inhibitors (moclobemide, selegiline) | Serotonin syndrome: change of consciousness, tachycardia, unstable blood pressure, hyperthermia, neuromuscular changes, gastrointestinal symptoms (nausea, vomitus); potentially life-threatening | 1. Prevent combinations  
2. Observe symptoms  
3. Discontinue one of the medication if serotonin syndrome is suspected |
hibitors such as fluoxetine, paroxetine, or chinidin.

But for clopidogrel and for tamoxifen there is no reliable clinical data on the relevance of this interaction type. Whenever possible, these combinations should be avoided.

**Medications with risk of QT prolongation [64]**

The drug-related prolongation of the QT interval has gained much attention in recent years. These sorts of adverse reactions are feared not only with medications having cardiac indications (antiarrhythmic agents) but also with a number of medications with non-cardiac indications. Abnormal QT prolongations are also associated with potentially life-threatening ventricular cardiac arrhythmia such as torsades de pointes. The list of medications that prolong the QT interval is constantly being expanded. Numerous medication classes are affected. Class effects occur only partly; often it is only individual representatives of medication classes that lead to clinical QT interval prolongation. For the prescribing doctor, it is not simply about keeping tabs on medications that can prolong the QT interval. The list presented in Table 3 contains a striking number of neuroleptics. This is not an accident, since many of these medications carry the risk of QT prolongation. Patients on neuroleptics should be carefully watched for QT prolongation.

**Note:** Risk increases with multimedication. Women have a greater tendency for QT prolongation. Check existing treatments; carry out an ECG on patients with these medications. Patients with an already prolonged QT interval and patients with water-electrolyte imbalances should not receive these medications. The doctor who first subscribes problematic medications should perform an ECG and inform later doctors.

**Tip:** A useful source of information about the effect of new and old medications on the QT interval can be found online at [http://www.azcert.org](http://www.azcert.org). Special attention should be given to interactions, as toxic blood levels are usually not reached until other medications are introduced (e.g., terfenadine together with macrolides). The QT interval (QTc) corrected for frequency should be systematically recorded when reviewing ECG reviews to help identify cardiac side-effects early on.

**Checking dosage**

Remember that renal function can worsen significantly with age. (Glomerular filtration rate decreases yearly by ~ 1% starting at age 30.) A routine data analysis has identified medically recorded renal failure in ~ 7% of patients 60 years and older, with increasing prevalence as age increases [79]. It is estimated that 17% of frequently prescribed medications require dosage adjustments [19, 40].

To calculate renal function, it is recommended that the estimated glomerular filtra-

<table>
<thead>
<tr>
<th>Indication groups</th>
<th>Medications (examples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS drugs</td>
<td>Amitriptyline, chlora hydrate, citalopram, escitalopram, chlorpromazine, clomipramine, doxepine, felbamate, fluoxetine, flupentixol, haloperidol, imipramine, levomepromazine, lithium, methadone, methylphenidate, nortriptylin, olanzapin, paroxetine, quetiapine, risperidone, sertrindol, sertraline, thioridazine, tizanidine, trimipramine, venlafaxine</td>
</tr>
<tr>
<td>Gastrointestinal drugs</td>
<td>Granisetron, octreotide, ondansetron</td>
</tr>
<tr>
<td>Asthma medications</td>
<td>Salbutamol, salmeterol, terbutaline</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Azithromycin, clarithromycin, erythromycin, ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, trimethoprim sulfamethoxazole</td>
</tr>
<tr>
<td>Antiviral drugs</td>
<td>Amantadine, foscarnet</td>
</tr>
<tr>
<td>Antiparasitic agents</td>
<td>Chinidin, chloroquine, melofuine, pentamidine</td>
</tr>
<tr>
<td>Antimycotics</td>
<td>Fluconazole, itraconazole, ketoconazole, voriconazole</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Terfenadine</td>
</tr>
<tr>
<td>Other substances</td>
<td>Alfuzosin, phenylephrine, pseudoephedrine, tacrolimus, tamoxifen, vardenafil</td>
</tr>
</tbody>
</table>

See also: [http://www.azcert.org](http://www.azcert.org).
Prescription process

The eGFR (estimated glomerular filtration rate) can be calculated using the Cockcroft-Gault or MDRD formula, since the creatinine level in serum depends on age, sex, weight, and body type; low values do not necessarily exclude poor renal function. Laboratories provide an eGFR that is sufficiently accurate for GPs, usually using the MDRD formula, which does not require weight data. Some medications instruct doctors to adjust dosages in patients > 75 years (independent of current renal function) such as with dabigatran and prasugrel.

With patients > 65 years who have diseases threatening renal function such as diabetes mellitus (and also with younger patients who have such diseases), it is recommended that creatinine levels and eGFR be calculated once a year.

- Is there information on renal functions in the patient’s medical records?
- Is the patient taking medications that necessitate dosage adjustments?
- Is the maximally permitted dosage being kept?

The following medications should not be used when GFR is < 60 mL/min: methotrexate, enoxaparin (in treatment dosage) and lithium.

For several renal medications alternatives can be considered:
- digitoxin instead of digoxin
- rivaroxaban instead of dabigatran
- bisoprolol instead of atenolol

Further information about alternative medications and dosage reductions in the case of antidiabetics and anticoagulants when the renal function is restricted can be found in Kielstein/Keller [77].

Tips:
- Begin long-term medications in elderly patients at low levels: start low, go slow [77].
- Check dosage using www.dosing.de. This is a simple and easy-to-use portal that in just a few steps (selection of medication, entry of serum creatinine level and weight) identifies the necessary or permissible dosage for patients with renal function restrictions (open source).
- A laboratory can automatically determine the eGFR using MDRD along with the creatinine level; these values can then be added to the medical records.

Checking treatment appropriateness: STOPP, PRISCUS

With many medications, the probability of (sometimes severe) adverse drug reactions relative to benefit is considerable, especially with elderly or vulnerable patients. For over 20 years, lists of potentially inappropriate medications (PIM) have been collected for elderly patients (“Beers List” [16, 17, 148]).

Two advanced tools are suitable for practice:
- The PRISCUS list [69] reflects the prescription practice in German prescription.
- The so-called STOPP criteria (Screening Tool of Older Persons Potentially inappropriate Prescriptions) [49, 50] are grouped by organ system and describe typical situations in which a discontinuation of medication should be considered. We will return to these criteria below (Step 4: discontinuing treatment).

The PRISCUS list encompasses 83 medications on the German pharmaceutical market that a consensus of experts categorized as PIMs – drugs whose potential risks exceed their benefits – when taken by elderly patients. Frequently prescribed PIMs with elderly patients are [4, 151]:
- amitriptyline
- acetyldigoxin
- diazepam
- doxazosin
- immediate release nifedipine
- etoricoxib

The list can be downloaded free of charge at http://priscus.net/download/PRISCUS-Liste_PRISCUS-TP3_2011.pdf. (For more, see the section Multimedication in the Elderly.)

The PRISCUS list was created in a transparent process using evidence analyses and consensus building. It offers alternatives for every problematic medication. Whether they are adequate, must be checked by the prescribing doctor. Relative to previous lists, PRISCUS gives more emphasis to psychotropic drugs. In this area, presumably, the largest problems lie with inappropriate prescriptions. The PRISCUS list is comprehensive but is unable to adequately capture treatment and risk in individual cases.
Though there were many test studies on earlier lists – those for the PRISCUS have yet to be concluded –, evidence that by avoiding PIMs severe adverse drug reactions (e.g., falls, hospital stays) diminish, has not been demonstrated generally, only in subfields (psychotropic medications). Nevertheless, the PRISCUS list contains numerous high-risk and partially obsolete treatments and is thus a valuable starting point for medication reviews by GPs.

In German-speaking regions, a further tool for medication review with geriatric patients is FORTA [48]. Its basic idea is to list medications with negative risk-benefit ratios as well as those with clearly positive ratios. But here too an evaluation has yet to take place.

### Fall risk-increasing drugs

Around one third of the elderly living at home fall once a year. Up to 25% of the elderly who suffer femur breaks die from complications [29]. Most falls occur through multiple factors. All factors that make falls more likely should be eliminated preventively.

Medications are among the factors increasing fall risk that can be easily influenced [24, 30]. Several studies, especially those on patients in nursing care homes, have shown that the likelihood of a fall can be considerably reduced by adjusting medication.

The most important fall risk increasing drugs, or FRIDs, are anxiolytics, neuroleptics, antidepressants, and antihypertensive drugs [13, 29]. For all medications it is important that the start dose is low and that increases are gradual. Once again, “start low, go slow”.

Elderly patients with neurological system atrophies (e.g., Parkinson’s disease or multiple system atrophies) face particular risks. With these patients, special care should be taken when using antihypertensive drugs [29]. Table 4 shows a list of medications that increase fall risk in elderly patients. Most elderly take at least one medication from these classes (Table 4).

---

**Table 4. Fall risk-increasing drugs – FRID.**

<table>
<thead>
<tr>
<th>Medication (classes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiolytics/hypnotics/sedatives</td>
</tr>
<tr>
<td>Neuroleptics</td>
</tr>
<tr>
<td>Antidepressants (tricyclic antidepressants, SSRIs, SSNRIs, MAO inhibitors)</td>
</tr>
<tr>
<td>Antihypertensive drugs (diuretics, β-blockers, α-blockers, calcium channel blockers, ACE inhibitors)</td>
</tr>
<tr>
<td>Antiarrhythmic agents</td>
</tr>
<tr>
<td>Nitrates and other vasodilators</td>
</tr>
<tr>
<td>Digoxin</td>
</tr>
<tr>
<td>Opioid analgesics</td>
</tr>
<tr>
<td>Anticholinergic medications</td>
</tr>
<tr>
<td>Antihistamines</td>
</tr>
<tr>
<td>Antivertigo agents</td>
</tr>
<tr>
<td>Oral antidiabetic drugs</td>
</tr>
</tbody>
</table>

As modified by [29].

---

**Step 3. Agreeing with patients on treatment objectives**

Before coming to a prescription decision (see next step), doctors should explore the patient’s expectations about treatments and objectives (see the section on prioritization) and indicate them in the medication record. Adherence studies have found that whether patients adhere to a treatment depends on their attitudes to health and illness. Those who do follow treatment tend to understand why the treatment is necessary. Those who do not, often have general or specific misgivings regarding the medication’s effectiveness or risk [70, 71]. These attitudes are often hard to influence. But being aware of such attitudes can help doctors assess whether a (new) prescription is likely to be taken. The following questions offer help:

- Does the patient expect a pharmaceutical treatment? The treating physician must question his own (often unquestioned) expectations of the patient’s expectations that a medication will be prescribed.
- How much importance does the patient give to the illness and the pharmaceutical treatment?
- How does the patient conceive of the illness? Does he see himself as contributing actively to attenuating and healing his own illness and complaints?
- How does the patient value a medication slated for discontinuation?
- Are there reservations/fears about specific medications in general?
This step in the prescription process allows doctors to determine whether patients are sufficiently informed about their illness and the treatment options available to them.

**Step 4. Prescription decision**

In the above scenario we distinguish between the following options:

**Deciding against pharmaceutical treatment**

Choose non-pharmaceutical strategies whenever possible. Check together with the patient to ensure that he is able to implement medical recommendations. If the patient is already taking multiple medications, it makes sense not to treat less urgent indications, especially if general measures (i.e., conservative approaches) seem sufficient, in order to prevent drug-related problems. A decision against pharmaceutical treatment may also occur when doctor and patient prioritize limiting the number of medications. (For more, see below.)

**New prescriptions**

A new prescription might be necessary when a new illness or a new symptom arise. It might also be necessary for reasons of prevention (vaccination, prevention of cardiovascular events) or to increase treatment strength when the patient fails to respond to previous (non-pharmaceutical) treatment. To prevent unnecessary multimedication doctors need to check if any non-pharmaceutical measures suffice and whether new complaints can be traced back to an existing medication. (For more on prescription cascades, see [119].) In addition, evidence, interactions, contraindications and dosage need to be checked (MAI) and redundant prescriptions need to be eliminated. (These can occur, for instance, when medications are changed or when a patient has more than one treating physician.)

**Checking for unmet medical needs**

Even patients on multimedication can have unmet medical needs, which is when no treatment is initiated despite a given indication. Indeed, the probability of unmet medical needs increases with the number of medications being taken [83]. For instance, in one observation study of geriatric patients, ~ 30% of patients do not receive a medication recommended by the guidelines for no obvious reason; with patients on 5 or more medications, the share increases to 43%; with patients on less than 5, the percentage is around 13% [83]. When assessing the existing medication and judging the quality of care one must consider whether the doctor and the patient have decided jointly against a particular prescription (e.g., due to multimedication, tolerance, or individual preference) or whether the need for a medication in general has not been examined. The latter should be considered an unmet medical need. The following table provides some common situations in which unmet needs arise and which doctors should be aware of (Table 5).

The so-called **START criteria** (Screening Tool to Alert Doctors to Right Treatment [49]) show typical situations in which an indicated prescription for elderly patients is not prescribed. Here it must be examined why the given medication was not prescribed (treatment preference, interaction, etc.). The causes for unmet medical needs are various and can be grouped into four categories:

1. An indicated treatment is not pursued (e.g., phenprocoumon, laxatives, statins, ACE inhibitors, pain medications, osteoporosis medications).
2. An existing treatment is not continued (e.g., miconazole).
3. Treatment adjustment does not take place or is incorrect (e.g., antidiabetic drugs, asthma medications, COPD medications).
4. Discontinuing an effective treatment (e.g., propranolol with tremors).

Some START criteria are presented here. **START**: Screening tool to help doctors find a correct, indicated and appropriate medication [49].
The Guideline Group selected several START criteria that are particularly relevant for the German primary care context, especially as a large number of criteria for deployment in everyday practice were not regarded as practical.

Since START was introduced, in 2008, new knowledge has come to light and should be taken into account in the review.

The following treatments are suited for patients > 65 years with the following indications, provided no contraindications are present (based on [49]).

**Cardiovascular system**
- Phenprocoumon (warfarin) with atrial fibrillation.
- ACE inhibitors with chronic heart failure.

**Endocrine system**
- Metformin with type 2 diabetes.
- ACE inhibitors or AT1 blockers for diabetes with nephropathy (proteinuria or microalbuminuria > 30 mg/24 h or eGFR < 50 mg/min).

**Continuing a medication**
A medication should be continued when there are no reasons for using a new medication or for changing treatment, or when there are no alternatives available, provided the patient is in agreement and the drug is indicated.

The German-language brochure “Praxiswissen – Mehr Sicherheit in der Arzneimitteltherapie” [76] points out the following errors that can occur when issuing prescription refills:
- The refill is for a medication whose use has been discontinued or whose dosage has been changed from what it was previously.
- The refill is no longer indicated.
- The refill is for a treatment that was meant to be short term only (as with benzodiazepine).

Errors can be avoided if doctors refrain from issuing pre-signed blank prescriptions and if they carefully consider each refill rather than signing them in passing.

**Changing an existing treatment regimen**
Under treatment change the Guideline Group includes prescribing alternative medications or changing the dosage or dosage form of an existing medication. Treatment changes can be necessary when adverse drug reactions occur, when the illness or its symptoms worsen, when problems with the treatment regimen (irregular adherence) or with treatment management (counting drops or splitting tablets) arise. Treatments can also be changed due to cost factors (budgetary shortfalls or high co-pay).

**Discontinuing a medication: STOPP Criteria**

Based on the medication review, doctors can conclude that certain prescriptions ought to be discontinued. Medications must be discontinued [9]:

---

### Table 5. Situations in which a needed medication is not prescribed, by decreasing order (modified following [83]):

<table>
<thead>
<tr>
<th>Symptoms/diagnoses/situations</th>
<th>Missing medication despite evidence for effectiveness</th>
<th>Unmet medical needs in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiates for pain treatment</td>
<td>Laxatives</td>
<td>61.5%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>β-blocker</td>
<td>60%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>ACE inhibitors</td>
<td>47%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Oral anticoagulant</td>
<td>42%</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Bisphosphonate</td>
<td>29%</td>
</tr>
<tr>
<td>Hypercholesterolemia*</td>
<td>Statins</td>
<td>23%</td>
</tr>
<tr>
<td>Hypertonia</td>
<td>Antihypertensive drugs</td>
<td>23%</td>
</tr>
<tr>
<td>Angina pectoris, stroke, TIA, PVD</td>
<td>Anti-platelet agents</td>
<td>21%</td>
</tr>
<tr>
<td>NSAID with risk patients</td>
<td>PPI</td>
<td>21%</td>
</tr>
</tbody>
</table>

*With cardiovascular risk.*
• when contraindications or adverse drug reactions (interactions) occur, or
• when the cause for prescription (i.e., the indication) no longer applies.

Discontinuing a medication should be considered when the assessment indicates that
• the risk-benefit ratio has become unfavorable, e.g., when the medication is no longer beneficial given the patient’s life expectancy or when cognitive deficit or frailty results;
• a better alternative might exist,
• the effectiveness has become questionable (possibly indicating a trial withdrawal),
• the patient prefers another treatment option.

An indicated medication can be either discontinued or not started through a shared decision by doctor and patient, e.g., when the patient prefers to limit the number of medications he is taking. (For more, see below.)

The PRISCUS list (see below) and the so-called STOPP criteria (Screening Tool of Older Persons Potentially inappropriate Prescriptions) [49, 50] can be used for assessing a medication’s risk-benefit ratio. Both lists are comprehensive in scope. We recommend that for everyday use doctors develop their own priority lists containing around 15 – 20 potentially inappropriate medications based on their prescription habits. Some of the STOPP criteria can be found on the following pages.

Note: The Guideline Group has selected several STOPP criteria that are relevant for general practitioners and for primary care in Germany generally. When using the STOPP criteria it is important to take into account new findings that have become available since the publication of STOPP in 2008.

The following medications can be problematic for patients 65 years or older and should for this reason be reviewed:

### Cardiovascular system

• Long-term treatment with digoxin over 125 μg per day (increased toxicity risk).
• β-blockers together with verapamil (risk of systematic cardiac conduction disturbances, third degree AV block).
• Diltiazem or verapamil when NYHA III or IV heart level is present. (Note from the Guideline Group: According to the 2012 ESC Guidelines [149] these medications are contraindicated in the case of systolic heart failure and combined systolic and diastolic heart failure (NYHA I – IV) but considered appropriate in the case of diastolic heart failure.)

### Brain and mind

• Tricyclic antidepressants when dementia is present (cognitive performance can be further worsened).
• Tricyclic antidepressants when cardiac conduction disturbances are also present (pro-arrhythmic effect). (Note from the Guideline Group: Tricyclic antidepressants are to be avoided when heart failure is present [149]).
• Long-term prescribing (> 1 month) of long-acting benzodiazepines such as chlordiazepoxide, fluzapam, nitrazepam, chlorazepate, or benzodiazepine together with long-acting metabolites such as diazepam (danger of prolonged sedation, confusion, loss of balance, falls).

### Respiratory system

• Theophylline as a single treatment. (There are safer and more effective alternatives; risk for ADRs due to narrow therapeutic range.)

### Musculoskeletal system

• NSAID when moderate to severe hypertension (> 160/100 mmHg) is present (danger of exacerbation).
• NSAID when heart failure is present (heart function can worsen).
• Coumarine, and NSAID together (risk of gastrointestinal bleeding!).
• NSAID in patients with chronic renal failure (GFR 20 – 50 mL/min) (danger of worsening renal function).

### Urogenital system

• Anticholinergic to treat incontinence in dementia patients (can increase confusion and cause states of agitation).
• α-blockers in men with frequent incontinence (risk of higher micturition frequency, worsening incontinence).

Medications in patients with high fall risk

(Rule of thumb for increased fall risk: A fall in the past 3 months.)
• Benzodiazepine (impaired attention span and sense of balance).
• Neuroleptic drugs (can cause motion dyspraxia and parkinsonism).

Garfinkel’s approach

The Israeli geriatrician Garfinkel [52, 53] proposed a radical treatment strategy. After thoroughly assessing the medication of patients at very advanced ages (with regard to evidence, suitability for age group, ADR risk, ADR symptoms, and dosage) he recommended that these patients discontinue more than 50% of their prescriptions. He had to reintroduce 2% of the medications he eliminated, but no serious incidents occurred. Indeed, in some patients, he reported significantly reduced complaints.

Garfinkel’s approach has only been tested in small studies [52, 53]. There is no information about which methods were used to carry out the (in some cases extensive) changes and discontinuations and how “serious incidents” were defined. In addition, we can assume that the conditions under which Garfinkel’s work was performed vary greatly from everyday workplace conditions in Germany’s primary care practices.

At this time, Garfinkel’s approach cannot be recommended generally for primary care practice. The problem is that Garfinkel studied geriatric patients on the verge of receiving palliative care. The general treatment indication was not curative, but mostly palliative; it was mainly about controlling symptoms. This aspect considerably changes the medication’s significance. Nevertheless, Garfinkel’s approach does make clear the potential leeway for changes in patients on multimedication, especially those who are at a very advanced age or those receiving palliative care.

Zeeh [169] considered Garfinkel’s approach from a geriatric perspective and modified it for a hospital setting. He called for an “individualized, supervised optimization of medication” when the following questions cannot all be answered with “yes”:
1. Is the general state of the patient good?
2. Are the treatment goals being reached through multimedication?
3. Is adherence good?

If the general state is worsening because of ADRs or if questions 2 and 3 were answered with “no,” Zeeh recommends reducing medications with a high side-effect risk and/or unfavorable risk-benefit ratio. His “multim edication emergency bag” also includes the tools presented above (MAI, STOPP, START, PRISCUS, brown bag, doctors’ personal medication lists).

Unfortunately, few studies have investigated the discontinuation of medications; most often, doctors must rely on experience and plausible rationale [72]. The important thing is that doctors proceed systematically (see also [9]). Doctors must:
• Identify the medication(s) to be discontinued.
• Rank medications to be discontinued. Which should be discontinued first?
• Discontinue one medication at a time, whenever possible, beginning with the medication for which discontinuation is most indicated.
• Taper or reduce the dosage.
• Plan well and communicate with patients and other treating physicians and family members.
• Monitor positive and negative effects of discontinuation.

Tips

Discontinue more than one medication concurrently only for acute events (e.g., urticaria). Otherwise discontinue only one medication at a time whenever possible so that subsequent reactions can be assessed. The discontinuation process usually lasts several days, but it can also last up to several months (control for rebound effects).

Tapering: After long-term treatment with psychotropic drugs, (such as benzodiazepine), antihypertensive drugs (β-blockers
especially), corticosteroids, levodopa and opioids, the dosage must be reduced gradually, since the sudden discontinuation of these drugs can trigger withdrawal symptoms, some of them severe [88]. If there is any doubt whether the medication can be discontinued immediately, the doctor should opt to taper gradually.

Note: Even a controlled discontinuation of medications can often have alarming effects [53, 72] that the treating physicians should be aware of:

- **Withdrawal symptoms:** These occur frequently with medications that affect the central nervous system, such as antidepressants. With SSRIs the symptoms begin around one week after discontinuation and persist mildly for around 10 days. Abrupt discontinuation of benzodiazepines can trigger serious withdrawal symptoms such as confusion, hallucinations, and muscle cramps.

- **Rebound phenomena:** Rebound tachycardia and elevated blood pressure follow the discontinuation of β-blockers; the overproduction of stomach acids follow the discontinuation of proton pump inhibitors; sleeplessness follows the discontinuation of hypnotics.

- **Return of symptoms of original illness:** With some medications (such as blood pressure medications) the symptoms of the underlying illness can return rapidly after abrupt discontinuation.

- **Effects of discontinuation:** A discontinuation of levodopa can cause muscle stiffness and impaired consciousness. A sudden discontinuation of corticosteroids in patients under long-term treatment can trigger Addisonian crisis.

Ending a treatment can be emotionally difficult, even for doctors, especially if the treatment is one they or a colleague have until recently regarded as useful. There may be fears about worsening health after termination, given the multimorbidity of the patients. We thus recommend that the discontinuation process be accompanied by regular check-ups. We also recommend that doctors explain to their patients that ending a treatment does not mean they have “given up”. Rather, its purpose is to improve their quality of life.

**Communication** with the patient (and, where applicable, his family) is very important because some adverse effects are foreseeable when ending a treatment. And without the support of the patient, discontinuation (especially if it involves withdrawal symptoms) is unlikely to be successful. The doctors must talk with patients in order to:

- identify which positive effects the patient associates with the medication to be discontinued,
- identify the effects (or hopes in the form of diminished symptoms) the patient expects from discontinuing the medication,
- identify which symptoms the patient is willing to tolerate during the discontinuation process,
- inform the patient that he can influence the speed of the discontinuation or halt the process at any time and
- inform the patient that the discontinuation process will be carefully observed by medical professionals.

**Which medications take precedence? (Individual finding of preferences)**

The Medication Appropriateness Index (MAI, see above) provides crucial questions doctors must answer to identify unnecessary or avoidable medications and to improve safety when using medications. After the MAI assessment, situations may arise where an individual prioritization is necessary. In this step, the medications deemed appropriate by the MAI are reconsidered and candidates for discontinuation identified. Such a prioritization can be needed when patients want to reduce the number of medications they are taking, even when all the medications are indicated. Doctors who believe that the number of medications poses a risk to a patient or if they have reason to think that the treatment regimen is being inadequately followed should talk with patients about the possibility of discontinuing one or more drugs.

Several of the recommendations for discontinuing medications proposed in international literature (e.g., the Garfinkel algorithm [52], Bain et al. [9]) must be evaluated to see whether they can be implemented in another
country, especially within the framework of primary care. These recommendations implicitly assume that a critical medication review will necessarily result in the reduction of medication. But they do not consider a prioritization of indicated – and evidence-based – medications.

This is why the **individual prioritization phase** may be necessary in making prescription decisions after the medication review: sometimes the patient or the doctor will want to further reduce the number of medications being taken.

Borrowing from Steinman and Hanlon [142] the Guideline Group recommends the following approach. In the first step, an expanded MAI (see above) should be performed after the initial medication review. The expanded MAI lists all medications including their indications, observed problems and notes on the consequences of treatment withdrawal. This allows doctors to distinguish between medications primarily used for improving life expectancy (mortality) or medications primary used for improving symptoms and disease progress (morbidity). (Some medications, such as ACE inhibitors, can influence both [142].)

Following the studies of Tinetti and Fried [45, 46], we recommend that doctors ask their patients about their treatment objectives. Doctors should inquire about the results patients hope for (e.g., the expected benefits) as well as about the effects they hope to avoid (e.g., side-effects) and which effects they would regard as intolerable. In more specific terms, doctors need to determine their patients’ personal priorities with regard to:

- autonomy/independence (functional improvement),
- survival/improved prognosis
- pain reduction, and
- symptom improvement (nausea, shortness of breath, vertigo, etc.).

On the basis of what they find, doctors can come to an individual decision about the patients’ treatment preferences and priorities. Such decisions must be made under certain circumstances, such as in the case of conflicting outcomes. For each medication, doctors must answer the following questions (see below for others):

- What does the patient expect from the pharmaceutical treatment? What is the most important priority for the patient? What does he see as the medication’s specific benefit? For cardiovascular diseases, the prognosis assessment can be performed with the help of electronic tools like arriba® in Germany.
- Does the treating physician believe that the medication is necessary given individual treatment goals?

**Aids for prioritizing medications that improve symptoms or functions**

Some patients are not immediately aware of all the symptoms such as psychosocial restrictions) (Table 6).

<table>
<thead>
<tr>
<th>Questions for the patient</th>
<th>Gained information</th>
</tr>
</thead>
<tbody>
<tr>
<td>What are your complaints?</td>
<td>Can include: pain, vertigo, fatigue, exhaustion, tinnitus, forgetfulness, incontinence, constipation, loss of appetite, abnormal gait, tendency to fall, dry mouth, dry skin, itching, chills, sleep disorders.</td>
</tr>
<tr>
<td>What is your strongest complaint?</td>
<td>Indicates primary complaints and treatment goals.</td>
</tr>
<tr>
<td>Which complaints restrict your everyday life or your contact with others?</td>
<td>Restricted social contact needs to be identified early on.</td>
</tr>
<tr>
<td>What do you no longer feel confident doing? In what areas do you feel restricted? What would you like to be able to do again?</td>
<td>Helps to categorize complaints and assess ability to perform everyday activities; importance of autonomy.</td>
</tr>
<tr>
<td>Have you had a feeling of depression or hopelessness in the last month? Have you experienced little happiness in your life in the last month?</td>
<td>Checks the psychosocial activity; gives clues about whether depression exists [5].</td>
</tr>
<tr>
<td>What do you need help from others for? Do you have people whom you trust and whose help you can rely on?</td>
<td>Checks psychosocial conditions and connection with social network.</td>
</tr>
</tbody>
</table>
Prescription process

Aids for prioritizing medications that improve prognosis as presented in Table 7.

Table 7. Aids for prioritizing medications that improve prognosis.

<table>
<thead>
<tr>
<th>Information</th>
<th>Questions for the patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>The medication can increase your life expectancy.</td>
<td>What significance does this have for you? Do you believe that the medication will increase your life expectancy? Which side-effects are you willing to accept in return? What risks are you willing to accept?</td>
</tr>
<tr>
<td>The medication can avoid the following complications (e.g., breathing difficulties, pain, restricted movement)</td>
<td>What significance does this have for you? Which side-effects are you willing to accept in return? What risks are you willing to accept?</td>
</tr>
<tr>
<td>If applicable, check: Is there reliable information for the age group and target group that the medication can increase life expectancy or prevent complications?</td>
<td>Would you try the medication even if no reliable information about its effectiveness exists for your age group?</td>
</tr>
</tbody>
</table>

Table 8. Aids for setting individual preferences.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication/complaint</th>
<th>Evidence: longer life expectancy/morbidity/improvement of functions and symptoms</th>
<th>Doctor: assessment of relevance</th>
<th>Patient assessment of relevance</th>
<th>Remarks/decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>S</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

L = improved life expectancy; M = morbidity influenced; S = symptom improvement; F = functional improvement. This Guideline Group recommendation must still be tested.

Guiding question for the patient: Which complaint is predominant (e.g., breathing difficulties, pain, restricted movement)? What is the treatment supposed to achieve? Which side-effects are intolerable?

Guiding question for the doctor: Which medication is indispensable?

By working together to create the list, doctor and patient can come to a common assessment of a medication’s relevance. Sometimes a thorough discussion with a patient can reveal that a crucial complaint has not been adequately treated and a new medication is needed. For patients in advanced age, the medication that improves symptoms usually takes precedence.

Step 5. Communication

The prescription process does not end with the prescription decision. The doctor’s decision must be discussed with the patient and the patient must give his agreement. Recent studies on drug-related doctor-patient communication have shown that doctors tend to discuss the benefits of a treatment and rarely point out its risks and potential side-effects. In particular, patients frequently do not obtain information about how they should respond if potential side-effects occur. What is more, doctors rarely check to see what information their patients have actually understood [124, 143]. Following the credo that a well-informed patient is a helpful security barrier against drug-related problems [76], we believe that the patient consultation should encompass the following tasks:

- updating the medication record in the doctor’s computer,
- giving the patient a copy of the updated medication record,
- discussing current treatment and any changes made,
- explaining possible drug-related problems that might occur [95],
- explaining how to administer the medication,
- explaining what to do in case side-effects occur or a dose is forgotten,
- ensuring that the patient understands the treatment and how to implement it,
- making appointments for check-ups.
Likewise, doctors must ask if the selected treatment is accepted by the patient and see whether any problems are to be expected when taking the medication. Doctors must also check whether the patient requires additional information to understand his illness better and to foster adherence and cooperation (patient guidelines, ad-free information). In some cases, general practitioners will need to contact the patient’s specialist and/or family members who serve as caregivers.

Only recently has the relationship between health literacy and state of health been given more attention [10, 144]. For instance, the WHO and the US Department of Health and Human Services see this relationship as an important factor influencing health [156, 168]. A new study shows that patients who have difficulties to recapitulate package insert information have a higher mortality rate compared with those who better recall leaflet instructions, even after adjusting for a variety of variables such as age, sex, education, state of health, and health behavior [22]. Although the study does not allow to conclude that a more intensive medical consultation can influence the ability of the patients to process and recall health-related information, the Guideline Group recommends that the doctor take time explaining the medications and not assume that the patients will ask questions when they do not understand.

Projects on shared decision-making have found that well-informed patients

- have more realistic expectations about their treatment, increasing their satisfaction with the results;
- participate more actively and are more likely to adhere to the treatment.

At the end of the consultation with the patient, doctors should come to an understanding with the patient about whether any medications should be discontinued and, if so, which. The resulting treatment should be regularly checked at the outset.

Some aids for patient communication in Germany include:

- arriba® (http://arriba-hausarzt.de)
- www.patientenleitlinien.de
- www.gesundheitsinformation.de
- www.aok.de/bundesweit/gesundheit/aok-entscheidungshilfen-28557.php

**Medication record**

Of central importance in a successful treatment is the creation of a manageable and regularly updated medication record. The plan should identify:

- prescriptions from the general practitioner,
- prescriptions from specialists (are patient reports available?),
- medications self-administered by the patient.

The medication record must be updated each time a medication changes and the new version must be given to the patient. During the joint medication review, patients should be instructed to provide the prescribing doctor with the medication record whenever possible and indicate any dosage changes and self-administered medications in the plan. (A sample medication record is presented in Figure 5).

The medication record must meet the following minimal requirements. Next to each medication must appear:

- the active ingredient and trade name,
- the dosage form, and
- the precise dosage.

The plan must include the permanent medications prescribed by general practitioners or specialists, self-administered medications, medications taken “as needed” and short-term prescriptions such as antibiotics.

- With medications taken on an as-needed basis, information on individual dosage, maximum daily dosage, and indications should be indicated (e.g., in the case of low-back pain ibuprofen should be taken 400 mg 2 × 1 as needed, but no more than 6 × 1 per day).
- With short-term prescriptions, the start and prospective end date should be indicated.

In addition, the medication record should contain all other indications and important information, such as the presence of any allergies. The patient care documents already contain the main indications, the name of the prescribing doctor, and the start and stop of the medication.

Special usage instructions should be noted in a form that is easy to understand for patients. These instructions include when a
medication should be taken (morning as with corticosteroids, noon, evening, or night), whether the medication should be taken with liquids, or whether it should be taken before, during, or after meals, etc.

The medication record should clearly indicate the patient’s name and date of birth, the contact information of the general practitioner, and the date the medication record was issued.

Other important information that can ease co-treatment by other doctors includes:
- data on existing medication tolerances or allergies,
- visible identification of medications, such as phenprocoumon, and
- restricted renal function below 50 mL/min (eGFR by the MDRD).

The following information should be included in the patient summary sheet:
- avoid grapefruit juice (can have an adverse effect on medications)
- inform the doctor when introducing new drugs, including herbal remedies in self-medication such as St. John’s wort (interaction risk)

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**Strategic medication record**

*(action plan for safe drug treatment)*

A working group formed by the national action plan for safe drug treatment drafted a standardized and digitally supported medication record system in June 2012 [http://www.akdae.de/AMTS/Massnahmen/docs/Medicationsplan.pdf]. The group consists of representatives from physician and pharmacist associations, state agencies, patients, and the software industry.

The system is designed to transmit essential patient information between all those involved in the prescription process.

The basic idea of the medication plan is to give patients a record containing all medications and usage information in an easy understandable form. The patient can have the medication record updated after every doctor or pharmacy visit. It is a patient-held record that does not rely on central data storage.

The attendant software system – its manufacturer has promised to continue support in the future – automatically reads the

---

**Medication Record**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Trade Name</th>
<th>Strength</th>
<th>Form</th>
<th>Mo</th>
<th>No</th>
<th>Ev</th>
<th>aN</th>
<th>Unit</th>
<th>Instr.</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramipril</td>
<td>Ramipril STADA® N1</td>
<td>5 mg</td>
<td>tab</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>pc.</td>
<td>with meals</td>
<td>high blood pressure</td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>HCT-dura® 25MG N2</td>
<td>25 mg</td>
<td>tab</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>Pc.</td>
<td>with meals</td>
<td>high blood pressure</td>
<td></td>
</tr>
<tr>
<td>Chlopigrel</td>
<td>Plavix® 75 mg N1</td>
<td>75 mg</td>
<td>tab</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>pc.</td>
<td>with meals</td>
<td>arterial occlusion</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Simvalip® 20 mg N2</td>
<td>20 mg</td>
<td>tab</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>Pc.</td>
<td>after meals</td>
<td>elevated blood levels</td>
<td></td>
</tr>
</tbody>
</table>

**Subcutaneous Use**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Trade Name</th>
<th>Strength</th>
<th>Form</th>
<th>Mo</th>
<th>No</th>
<th>Ev</th>
<th>aN</th>
<th>Unit</th>
<th>Instr.</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human insulin</td>
<td>Insulin B. Braun Basal</td>
<td>inj.</td>
<td>20</td>
<td>0</td>
<td>10</td>
<td>IE</td>
<td></td>
<td></td>
<td>subcutaneous</td>
<td>Diabetes</td>
</tr>
</tbody>
</table>

**PRN Medication**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Trade Name</th>
<th>Strength</th>
<th>Form</th>
<th>Mo</th>
<th>No</th>
<th>Ev</th>
<th>aN</th>
<th>Unit</th>
<th>Instr.</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyceroltrinitrate</td>
<td>Corangin® Nitrospray</td>
<td>spray</td>
<td>max 3</td>
<td></td>
<td></td>
<td></td>
<td>inhalation</td>
<td>acute</td>
<td>angina</td>
<td></td>
</tr>
<tr>
<td>Vivinox® stark</td>
<td></td>
<td>tab</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>pc.</td>
<td>as needed</td>
<td>sleeplessness</td>
<td></td>
</tr>
</tbody>
</table>

---

Figure 5. The plan can be changed individually after scanning. Source: Spezifikation für einen patientenbezogenen Medikationsplan. Koordinierungsgruppe zur Umsetzung und Fortschreibung des Aktionsplans zur Verbesserung der Arzneimitteltherapiesicherheit in Deutschland. Edited by Dr. Farid Aly, Berlin; Dr. Gunter Hellmann, Erlangen; Dr. Horst Möller, Bonn (http://www.akdae.de/AMTS/Massnahmen/docs/Medikationsplan.pdf), aN = at night; PRN = pro re nata (as needed).
plain text from the 2D barcode at the upper right, exports the modules for recording and reviewing to the doctor’s software system and prints out the medication record with the new adjustments and changes. For a variety of reasons it is currently unlikely that the digital health card will receive a similar or expanded functionality in the near future.

This is why all those involved in primary care pharmacotherapy – doctors, pharmacists, patients – should push for an as broad as possible usage and software support for this low-tech solution.

**Step 6. Drug dispensing**

Drug dispensing normally occurs at the pharmacy. Patients (especially those on multimedications) should be advised to select a primary pharmacy, which is ready to fulfil the following tasks:

- give patients usage instructions when dispensing prescriptions,
- ask critical questions about and keeps an eye on self-administered drugs [39],
- show patients how to use drugs correctly (e.g., asthma inhalers, insulin pens, measuring blood glucose),
- monitor and detect drug-related problems [39, 56, 60],
- perform interaction checks, and
- issue an electronic medication summary.

During interaction checks, pharmacists must take note of self-administered medications and enter them into the medication record. Pharmacists must also anticipate problems (e.g., double doses, incorrect dosages that can occur when discount agreements require the introduction of replacement medications) and give appropriate instructions. The medication summary also allows pharmacists to identify and prevent redundant prescriptions from different doctors.

As long as there is good cooperation between doctors and pharmacists, the medication summary can support safe drug usage through specific instructions, administration tips and the synchronization of additional medications (self-administered drugs or prescriptions from other doctors). Ideally, the pharmacy enters each dispensed medication (due to discount agreements) into the medication record.

Currently, there are various activities of medication management that doctors and pharmacists can perform together for selected target groups (e.g., patients on 5 and more long-term medications, nursing home residents, patients on insulin). So far, no experiences or evaluations have been published.

**Step 7. Medication usage**

The prescription process also includes aids for safe and prescribed medication usage. Below, we collect several aspects based on the work of v. Renteln-Kruse [161]. Safe usage can be supported by various professional groups and institutions (doctors, medical assistants, pharmacists, nurses).

- **Repeated inquiries into and identification of** individual patient problems. This helps identify impairments that encumber usage (fine motor, visual) or understanding (linguistic, aural).
- **Use benefits of simplified treatment:** reduce number of medications (e.g., through combined medication, prioritizing), simplify dosage, offer usage aids (e.g., pill dispensers).
- **Convey information orally and in writing,** e.g., patient medication records, patient information.
- **Use “boosters”:** include family members, training sessions, information on associations for fitness and exercise.
- **When applicable, directly include family members and others involved in the care:** Ensures that others have important information for the treatment, not only the patient.
- **When monitoring the treatment success:** Discuss test results, give feedback on the treatment, ask about treatment problems, discuss effective forms of self-monitoring (e.g., weight control, glucose measurements), let patients demonstrate how they use inhalers and pens.

Measures for improving patient adherence include:

- **Individualize measures** for administering medication/performing exercises, such as special memory tricks. Encourage the building of habits (ritualization), e.g., taking tablets before dessert or be-
fore going to bed (assuming no other specifications exist).

- **Take advantage of “boomerang” effects**, more frequent scheduling immediately after beginning a treatment if possible. Patients should be reminded after each visit how important the treatment is (e.g., high blood pressure treatment).
- **Explain the chronic nature of an illness**: Explain the necessity of long-term treatment despite improved symptoms.
- **Inform patients about risk factors (risk communication)**: using electronic tools to assess personal risk factors (arriba®), smoking cessation measures.
- **Explain side-effects** that can lead to non-adherence (e.g., erectile dysfunction, weight gain). Explain the package leaflet information on adverse effects to the patients and instruct them on proper reactions.
- **Anticipate that patients might change the treatment on their own**. Tell patients about which medications should not be discontinued, interrupted or be subject to dosage changes without the doctor’s orders.
- **Inquire about activities the patient is undertaking** (as his personal strategy to assist with the treatment) such as using alternative medications, seeing naturopaths; explain that the treating physician needs to know about these activities since they may require discontinuing a medication or adding another.

### Step 8. Monitoring (Assessment)

Medications must be monitored for changes in their effects (therapeutic effects, side-effects, need). To these ends, doctors must schedule check-up appointments with the patient and control clinical parameters.

Every assessment is an opportunity for a reappraisal, leading to a new treatment cycle. (See figure on the prescription process.) Assessments are also opportunities for looking into **unspecific symptoms**, as these could be complications resulting from treatment changes. Unspecific symptoms include:
- Dry mouth,
- exhaustion, fatigue, drowsiness, reduced alertness,
- sleep disturbances,
- weakness,
- motor disorders, tremors, falls,
- constipation, diarrhea, incontinence, loss of appetite, nausea,
- skin rashes, itching,
- depression or lack of interest in usual activities,
- confusion (temporary or chronic),
- hallucinations,
- fear and agitation,
- lack of sexual interest,
- vertigo,
- tinnitus.

During assessments, doctors must ask about problems with the treatment implementation and check adherence (see section “Adherence in the Prescription Process, Step 1.) We recommend that doctors ask patients to show them how they use their asthma inhalers or insulin pens. They should also make sure patients have a medication record or a diabetes passport, and that patients document their blood glucose or blood pressure when recommended to do so.

Monitoring also includes **routine check-ups**. The SPCs describe numerous check-ups, not least due to forensic considerations. Health examinations do not suffice for the check-up. Medications that require regular lab or ECG tests in the primary care context have been assembled in Table 9 (in Schmiemann G, Biesewig-Siebenmorgen J, Egidi G [129]). The list is the result of various discussions in quality circle and training events. It is based on clinical experience and selective search of the literature. **However painstaking the selection of measures is, it is still subjective and is not a binding recommendation.**

For special medications (e.g., immunosuppressants, antiepileptics), the SPCs should be consulted, as they contain very complex lab tests that vary by indication.

### Support framework

There are several conditions that would support medication reviews:
- the review is a component of health examinations in the elderly;
Table 9. The following recommended routine check-ups are the result of discussions in quality circles and training events [129].

<table>
<thead>
<tr>
<th>Medication (class)</th>
<th>Check</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors/sartans (e.g., ramipril/candesartan)</td>
<td>Before/during treatment begin and with renal failure: after 1 week creatinine (eGFR*), potassium, then 1× per year creatinine and potassium [65].</td>
</tr>
<tr>
<td>Thiazide diuretics (Hygroton®)</td>
<td>Before/during treatment begin and 1× in year creatinine (eGFR), potassium (warning: creatinine &gt; 1.8 mg/dl is a contraindication), sodium.</td>
</tr>
<tr>
<td>Loop diuretics (e.g., furosemide, torasemide)</td>
<td>Before/during treatment begin and 1× per year creatinine (eGFR), potassium, sodium based on dosage at least 1× per year.</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Possibly ECG before treatment.</td>
</tr>
<tr>
<td>Amiodarone (Cordarex®, generics)</td>
<td>Before/during treatment begin spirometry/thorax X-ray, TSH, T3, T4, spirometry every 6 months or in the case of dyspnea, 1× annually TSH + ophthalmology check-ups [75, 137] + ECG (see below)*.</td>
</tr>
<tr>
<td>Spirolactone (Aldactone®, generics)</td>
<td>Creatinine, potassium every 6 months.</td>
</tr>
<tr>
<td>Digoxin/Digitoxin</td>
<td>ECG, creatinine, potassium 1× a year, no routine blood tests with patients who are clinically stable [137].</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Before/during treatment begin and 1× a year creatinine (eGFR), GOT/GPT, uric acid.</td>
</tr>
<tr>
<td>Systematic corticosteroids (Prednisolone/Decortin H®)</td>
<td>Starting at 7.5 mg/day: blood glucose 1× per quarter; starting with a treatment duration of &gt; 3 months consider a osteodensitometry.</td>
</tr>
<tr>
<td>Statins (e.g.; simvastatin/pravastatin)</td>
<td>CK and GOT/GPT 1× after treatment begin (pay attention to threshold values!), CK afterward only when complaints arise.</td>
</tr>
<tr>
<td>Metformin</td>
<td>Before/during treatment begin and 1× per year blood count, creatinine (eGFR), HbA1c 1×/per quarter. In the case of macrocytosis: folic acid, vitamin B.</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa®)</td>
<td>Before/during treatment begin and 1× per quarter blood count, 1x per year creatinine (eGFR) [6].</td>
</tr>
<tr>
<td>Phenprocoumon (Marcumar®)</td>
<td>1× per quarter partial blood count, gGT and GPT. NR even with very stable values at least every 3 months [57].</td>
</tr>
<tr>
<td>Low-molecular heparin enoxaparin (Clexane®)</td>
<td>Before/during treatment begin and for 2 weeks 2× per week a partial blood count when the risk for heparin-induced thrombocytopenia (HIT) &gt; 1% [57].</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Before/during treatment begin and then weekly for 1 – 3 months a complete blood count; creatinine, yGT, GPT; every 1 – 3 months afterwards. Beware: combined with allopurinol.</td>
</tr>
<tr>
<td>Methotrexate (Lantare®)</td>
<td>Before/during treatment begin blood differential test, GPT, GOT, gGT, AP, bilirubin, creatinine clearance (reduction when GFR &lt; 80 ml/min), then in 1st and 2nd weeks blood count, GPT, AP, creatinine, then every 2 weeks, starting in the 3rd month 1× per month as needed. When illness is stable, then GOT, GPT 1× per quarter, creatinine 1× every 6 – 12 months [31]. Ask about infections, burning mouth syndrome, breathing difficulties.</td>
</tr>
<tr>
<td>Lithium (Quilonum®)</td>
<td>Blood levels every 3 months*; creatinine 1× per year, TSH in the first year every 6 months, afterward 1 per year [138].</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>2× per year partial blood count, gGT, PT, sodium levels, ECG 1× per year [163].</td>
</tr>
<tr>
<td>Haloperidol (Haldol®)</td>
<td>Blood differential test weekly during the first 18 weeks of treatment and afterward at least every 4 weeks and up to 4 weeks after treatment end.</td>
</tr>
<tr>
<td>Clozapine (Leponex®)</td>
<td>Blood differential test weekly during the first 18 weeks of treatment and afterward at least every 4 weeks and up to 4 weeks after treatment end.</td>
</tr>
<tr>
<td>Antithyroid agents</td>
<td>Before/during treatment begin TSH+blood count [137] (inform patients about agranulocytosis: infections).</td>
</tr>
<tr>
<td>Methimazole, carbimazole</td>
<td>Before/during treatment begin TSH+blood count [137] (inform patients about agranulocytosis: infections).</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Before/during treatment begin and 1× per quarter blood count, alkaline phosphatase (AP), PT, creatinine (according to SPC: more frequently at beginning, including urine status). Ask about fever/ CNS symptoms and exanthemata.</td>
</tr>
<tr>
<td>SSRI (Citalopram/Cipramil®)</td>
<td>Sodium check, ECG (check for QTc interval) [163].</td>
</tr>
<tr>
<td>Antiepileptic Drugs</td>
<td>Creatinine, sodium levels 1× per year; blood tests only during adjustment phase and with frequent muscle spasms. Then trough levels mornings before taking tablets.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Before/during treatment begin and 1× per quarter partial blood count, urea, sodium, gGT, GPT (according to SPCs weekly at first).</td>
</tr>
</tbody>
</table>

Information on amiodarone from the SPCs: on account of lung toxicity, there is the risk of developing inflammatory lung diseases (hypersensitivity pneumonitis, alveolar or interstitial pneumonia), fibrosis, pleurisy, bronchiolitis obliterans with pneumonia (BOOP). Nonproductive cough and breathing difficulties are frequently the first signs of the above pulmonary changes. Moreover, weight loss, fever, weakness can also occur. Hence, before treatment begins, a thorax X-ray and a pulmonary function test should be performed. In the course of the treatment, these tests should be done every 3 – 6 months. Likewise, these tests should be performed if breathing difficulties occur (symptoms of possible effect of lung toxicity). In patients with serious pulmonary disease, pulmonary function should be checked more frequently if necessary, since these patients have a poor prognosis when lung toxicity occurs. Notes: Serum creatinine: check in case of fever, loss of fluids or other forms of suspected dehydration, after recompensation or dosage adjustments; eGFR = estimated GFR; *Procedure with lithium levels: Blood test 12 hours after taking the last tablet.
• patient medication record used by doctors and pharmacists alike;
• contracts between general practitioners and the health insurance funds, where all patient information, including prescriptions, would be transmitted to the GP. This is needed to keep the medication record up to date and change the medication when interaction risks arise (e.g., through electronic interaction checks);
• the medication check should be part of a statutory structure (such as a Disease Management Program or a health examination) performed once a year for patients on multimedication.

The medication review is a time-consuming process that requires qualified skills. Cooperation with pharmacists and caregivers must be tested, and suitable solutions for shared medication management found, including the division of tasks at the doctor’s office. Funding has to be guaranteed for additional tests (blood test, ECGs, pulmonary function).
Medication review studies

Description of studies

As described in the previous sections, the medication review process is a central part of effective medication management. Our investigation of medication review studies aimed to identify whether medication reviews have a positive outcome on patient care in general and for primary care practice in Germany in particular.

In December 2011, we conducted a preliminary study in the Cochrane Library. There we found a number of controlled studies that addressed various questions relating to medication reviews. The studies varied considerably with regard to the endpoints and settings investigated. (For more, see the Table 10). The studies also varied in the manner the review was performed, the persons involved (nursing staff, pharmacists, doctors), and in length.

While developing the guideline, other important medication review studies were published. We then reviewed their reference sections by hand and used the most important studies to supplement our research. Particularly useful were the Cochrane Reviews “Interventions to improve the appropriate use of multimedication for older people” [113] and the 2012 guidelines of the Dutch Association of General Practitioners “Multidisciplinaire richtlijn Polyfarmacie bij ouderen” [109]. Our criteria for including and excluding studies can be found in the appendix of the German version.

Patients in the studies

All the studies listed in our overview were performed with patients who were 65 and older and on medication. In most studies, the severity of the illness and the number of medications were not defined.

Setting

The studies were performed in the following countries: England, Finland, Denmark, Ireland, Netherlands, Australia, and the USA. Of the 11 studies considered, 8 were performed in outpatient settings: doctor’s offices, outpatient centers, pharmacies, and house visits. 4 studies researched the effects of medication reviews in inpatient settings, such as at day hospitals for the elderly or at internal medicine wards. (For more, see the Tables 10 and 11).

Intervention

In older studies, the reviews were mostly performed by pharmacists. In more recent studies and in inpatient institutions, the reviews were usually performed by a team of doctors, nursing personnel, pharmacists, and pharmacologists. We excluded studies in which the reviews were performed based on patient records alone or on telephone surveys, or in which doctors did not participate. In some studies, the medication review was part of a health service program such as pharmaceutical care [117] or comprehensive assessments [84]. None of the studies was performed in primary care practice.

Endpoints

Table 10 provides an overview of the endpoints investigated in the studies. The vast majority examined the appropriateness
and safety of pharmacotherapy, e.g., dosage errors, changes in medication management (discontinuing or introducing medications), and number of medications. We also considered studies that did not deploy validated measures. Studies measured mortality, falls, quality of life, cognitive changes, the influence of costs in the health care system, and healthcare utilization.

**Study duration**

In almost all studies, the duration was short, ranging from 4 weeks to 1 year.

**Summary of study findings**

The studies are highly heterogeneous and come to contrary findings on some endpoints. Since none of the studies was performed in the German primary care setting, it is difficult to transfer the results. The variety of endpoints and of methods used for reviewing medications is another aggravating factor.

None of the studies considered could demonstrate effects on morbidity, and the observed effects are difficult to trace back to interventions due to possible confounders (the subjects are all 65 and over). Moreover, studies with a duration of 4 weeks to a 1 year are too short for these types of intervention to prove or exclude the influence of hard endpoints. Improvements in participants’ health cannot be expected within such a time span.

The Cochrane Review of Patterson et al. [113] was restricted to studies whose primary endpoints were “appropriateness of medication, prevalence of appropriate medication, and hospitalization”. The secondary outcomes investigated included drug-related problems such as side-effects, medication interactions, medication errors, adherence, and quality of life. The Cochrane Review considered only studies that used validated instruments for measuring outcomes (MAI/Beers Criteria).

The authors concluded that significant improvements of pharmacotherapy for patients on multimedications could not be demonstrated. Yet they also found that measures such as pharmaceutical care [66] – where pharmacists and doctors perform medication management in concert – do seem to offer...
benefits when it comes to reducing the number of inappropriate prescriptions and drug-related problems.

**Recommendation of the Guideline Group**

Based on the medication review studies in consideration and the results of the Cochrane reviews, the Guideline Group comes to the following conclusions:

- Despite the contradictory evidence on individual endpoints, most studies conclude that medication reviews are beneficial insofar as they reduce errors in medication management and improve quality of life. The Guideline Group thus recommends the performance of structured medication reviews for patients on multimedication.

- A regular medication review is an effective tool for uncovering prescription and usage errors and increasing medication safety. With this recommendation, the Guideline Group is in keeping with recommendations from other countries, such as the United Nations, the Royal Society of Physicians and the Royal Pharmaceutical Society of Great Britain [25, 122]), the Netherlands [109], and New Zealand [27] where medication reviews have already been integrated into national healthcare programs.

Table 10 presents the results from the investigated endpoints.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Intervention</th>
<th>Patient-Related Endpoints</th>
<th>Other Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallagher 2011 [51]</td>
<td>RCT</td>
<td>Medication review</td>
<td>Mortality, rehospitalization, falls</td>
<td>Appropriateness of drug, unmet medical needs, number of doctor visits</td>
</tr>
<tr>
<td>Walsh 2010 [162]</td>
<td>Prospective randomized trail</td>
<td>Medication review</td>
<td>Patient satisfaction</td>
<td>Dosage errors, discontinued drug, inappropriate drug, patient satisfaction</td>
</tr>
<tr>
<td>Lampela 2010 [84]</td>
<td>RCT</td>
<td>Medication review</td>
<td>–</td>
<td>Number and type of prescriptions, discontinued and resuming medications, length of changes</td>
</tr>
<tr>
<td>Lisby 2010 [93]</td>
<td>RCT</td>
<td>Medication review</td>
<td>Length of inpatient stay, rehospitalization, mortality, quality of life</td>
<td>Visits to GP</td>
</tr>
<tr>
<td>RESPECT Trail Team 2010 [117]</td>
<td>Multiple interrupted time series design</td>
<td>Pharmaceutical care (model for medication review)</td>
<td>Serious side-effects, morbidity, quality of life</td>
<td>Appropriateness of prescription</td>
</tr>
<tr>
<td>Vinks 2009 [159]</td>
<td>CT</td>
<td>Medication review</td>
<td>Frequency of potential drug-related problems</td>
<td>–</td>
</tr>
<tr>
<td>Lenaghan 2007 [91]</td>
<td>RCT</td>
<td>Medication review</td>
<td>Frequency of hospitalizations, mortality, quality of life</td>
<td>Number of medications</td>
</tr>
<tr>
<td>Williams 2004 [165]</td>
<td>RCT</td>
<td>Medication review</td>
<td>Functional and cognitive changes</td>
<td>Polypharmacy, costs</td>
</tr>
<tr>
<td>Krska 2001 [80]</td>
<td>RCT</td>
<td>Medication review</td>
<td>Health-related quality of life</td>
<td>Solution of problems with pharmacotherapy, medication costs, use of health and social services</td>
</tr>
<tr>
<td>Pitkala 2001 [112]</td>
<td>RCT</td>
<td>Medication review</td>
<td>–</td>
<td>Number of medications, number of daily doses,</td>
</tr>
<tr>
<td>Jameson 2001 [74]</td>
<td>RCT</td>
<td>Pharmacotherapy consultation</td>
<td>Drug-related problems</td>
<td>Medication costs, general costs</td>
</tr>
<tr>
<td>Reviewer Team</td>
<td>Setting</td>
<td>Country</td>
<td>Study length, Follow-up</td>
<td>Proven Significant Effects?</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------------------------</td>
<td>---------</td>
<td>-------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Research physician, doctor</td>
<td>University hospital, inpatient</td>
<td>Ireland</td>
<td>6 months</td>
<td>Yes: appropriateness of drugs and unmet medical needs No: falls, rehospitalization, mortality</td>
</tr>
<tr>
<td>Doctor</td>
<td>Primary care</td>
<td>Ireland</td>
<td>4 weeks</td>
<td>Yes</td>
</tr>
<tr>
<td>Study nurse + doctor, physiotherapist</td>
<td>Random sample, ambulant patients</td>
<td>Finland</td>
<td>1 year</td>
<td>Yes</td>
</tr>
<tr>
<td>Doctor, pharmacist, clinical pharmacologist</td>
<td>University hospital, inpatient</td>
<td>Denmark</td>
<td>3 months</td>
<td>No</td>
</tr>
<tr>
<td>Pharmacist, general practitioners</td>
<td>Outpatient</td>
<td>England</td>
<td>12 months</td>
<td>No</td>
</tr>
<tr>
<td>Pharmacist, general practitioner</td>
<td>Outpatient care</td>
<td>Netherlands</td>
<td>4 months</td>
<td>Yes</td>
</tr>
<tr>
<td>Pharmacist, general practitioners</td>
<td>Outpatient care</td>
<td>England</td>
<td>6 months</td>
<td>No: hospitalizations, mortality, quality of life Yes: number of medications</td>
</tr>
<tr>
<td>Doctor, pharmacist, caregivers,</td>
<td>Outpatient centre</td>
<td>USA</td>
<td>6 weeks</td>
<td>Yes: multimedication costs No: functional and cognitive services</td>
</tr>
<tr>
<td>Pharmacist, doctor</td>
<td>Outpatient care</td>
<td>Scotland</td>
<td>3 months</td>
<td>Yes: problem solving No: costs, quality of life, doctor visits, hospitalizations</td>
</tr>
<tr>
<td>Nurse + doctor</td>
<td>Geriatric day hospital</td>
<td>Finland</td>
<td>3 months</td>
<td>Yes: daily doses No: number of medications</td>
</tr>
<tr>
<td>Doctor + pharmacist</td>
<td>Outpatient care</td>
<td>USA</td>
<td>6 months</td>
<td>No</td>
</tr>
</tbody>
</table>
Interfaces between healthcare sectors

Medication after hospital discharge

According to the German Social Code (Art. 11 (4) SGB V), health service providers must ensure proper post-discharge care of insured patients. Discharge management represents a part of hospital treatment whose purpose is to guarantee a seamless transition to outpatient care, rehabilitation, or nursing care. Discharge management includes the discharge summary, a report that describes the diagnoses together with the recommended treatments and medications during hospitalization. The German SGB also stipulates that the discharge summary indicates active ingredients (and not brand names) for recommended medications and – in case multiple comparable drugs are available – more affordable medication (Art. 11 (5c) SGB V).

Hospitalizations frequently lead to medication changes – discontinuations, new medications, or (dose) adjustments. Often these changes are not apparent from the discharge summary. This complicates matters when it comes to discussing new treatments with patients. The risk is that information about intolerances and interactions gets lost, treatment approaches remain obscure, medications meant for the short term are taken over a longer period, or medications prescribed at hospital discharge are subsequently not accepted by doctor and patient.

Medication care for discharge management includes the following recommended tasks for the hospital [116]:

- document medication at discharge in contrast to medication before admission to hospital (request from referring physicians),
- provide information on the administration period of the medications listed in the discharge summary,
- share information on blood tests, etc.,
- consult with and educate patients on specific medications.

According to the opinion of the Guideline Group it is essential that general practitioners are informed about their patients’ situation prior to hospital discharge and that they receive explanations for medication changes. Table 12 provides an example of a comparison between medication at hospitalization and medication at discharge together with comments sections (to be noted in the discharge summary).

When continuing treatments introduced during hospitalization, general practitioners should keep in mind that inpatient stays are often very short, not enough for the 4 – 5 half-lives usually needed for a medication to reach its steady state. What this means is that in many cases the effectiveness and tolerance of a drug cannot be properly assessed in the hospital. The problem is exacerbated when several interacting drugs are prescribed at once.

In Germany, the general practitioner alone is legally responsible for prescriptions.
issued after a patient’s hospital discharge. The recommendations of the hospital do not protect the general practitioner from recourse and damage claims.

The HEICare project developed and tested a digital information system known as AiD Praxis. Its objectives were to improve medication safety (identifying interactions, avoiding unnecessary treatment changes between sectors) as well as communication between referring physicians and hospital physicians. An assessment of the system showed that it was able to reduce the number of inpatient treatment changes. Yet the authors of the assessment study believe that implementing such a system would be difficult and costly [94].

Hence, we recommend that patients be given important medical information before being hospitalized or seeing a specialist. This information should include previous findings, problems, indications for hospitalization, referrals, and current medication record. Patients should be instructed to present this information to the treating doctor personally.

**Cooperation with pharmacies and other health professionals**

Patients should be encouraged to select a primary pharmacy that can document all their medications (both prescribed and OTC). Central record-keeping allows interactions and redundant prescriptions to be identified more easily, can verify whether a new medication is being taken after changing treatment or replacing medications because of a discount agreement. In addition, a medication list from the primary pharmacy allows patients to submit a copy of their medication summary to their general practitioner.

It is desirable to create a closer cooperation between general practitioners and pharmacies. (For more, see again the section on drug dispensing.) Clinical pharmacy is part of the basic education and advanced training of pharmacists. Examples of medication management are regularly published. Studies in the UK, the USA, and Germany [8, 56, 60, 120, 123, 157] have shown that pharmacists and clinical pharmacists are able to identify and solve drug-related problems.
Quality indicators

Indicators for monitoring care quality

A number of recommendations named in the guideline for improving medication safety for patients on multimedication can theoretically be monitored using quality indicators. As indicators recommended in literature also require individual recording that is currently impossible without appropriate software support, we name only a few indicators below (without further operationalization):

The AQUIK indicator set contains quality indicators for various subjects relating to multimedication (www.kbv.de/aquik.html).

Medication Safety
- Long-term medication: Percentage of patients with four or more long-term medications whose medication was examined in the last 12 months.
- Oral anticoagulants: Percentage of patients receiving oral anticoagulants (phenprocoumon, LL group) in which at least one INR level test is carried out every 6 weeks.
- Multimedications: Percentage of patients 65 years or older who, within the last 12 months, have taken at least 6 prescribed medications per day. Note: The Guideline Group does not see medication safety as a quality indicator, but as an index of risk groups.

Practice management
- Keeping records of medication allergies: the recording of medication allergies and adverse drug reactions must be standardized and transparent.

Other possible indicators:
- Interactions: Percentage of patients on drugs whose combination should be avoided due to their potential interactions (related to all patients on medications).
- Potentially inadequate medication (PIM)/PRISCUS: Percentage of elderly patients on PIMs. (Note: The Guideline Group recommends that this indicator be used as a risk indicator and not as a quality indicator, since discussion is still needed about alternatives to primary-care-related relevant medication classes (e.g., neuroleptics, antidepressants, and nitrofurantoin)).

The following indicators are useful from the set of QISA indicators [145]:
Multim edication in the elderly

Special aspects of geriatric pharmacotherapy

Not only the likelihood of multimorbidity but also that of multim edication increases with age [1, 21]. Due to the altered pharmacokinetics and psychodynamics in the elderly [96, 153, 154], older people are particularly susceptible to pharmaceutical side-effects. Sometimes the effects of a medication are strengthened; sometimes they are diminished.

Typical changes in the elderly are a delayed renal elimination and greater sensitivity to anticholinergic and sedative effects. But, once again, some medications have a reduced effect, as with β-blockers on account of decreased receptor sensitivity. Sometimes a medication can trigger paradoxical reactions.

Medications can also increase the risk for age-related complications such as falls. In general, 70- to 80-year-olds are 4 to 5 times more likely to experience an adverse drug reaction than younger patients are [47].

The most important risk factors for adverse drug reactions (ADRs) in the elderly are [81, 101, 102, 114, 115, 147]:

- restricted renal function,
- frailty: physiological forms of compensation are exhausted
- low body weight
- multimorbidity and multim edication [101, 102].

The character of the changes varies among individuals and cannot be attributed to a fixed age threshold. Except for renal function screening, no tests exist to easily assess age-related pharmacokinetics and pharmacodynamics.

With elderly patients on multim edication, drug-related problems can be caused by drug-drug interactions and drug-disease interactions in addition to physiological changes. Drug problems can also be caused by patient-related matters, e.g., when patients have difficulty administering medications or when they do not understand why they have been given a course of treatment (adherence) [59].

The key pharmacological parameters vary greatly from one individual to the next, but also over the course of an individual’s life.

1. The absorption of medications worsens in old age for many medications, sometimes because tablets are not taken with enough liquids to be dissolved [86, 102, 114].
2. Electrolyte imbalances (as with laxative abuse, poor nutrition and dehydration) can diminish the effectiveness of watersoluble medications.
3. Changing drug distribution [114]:
   a) Reduction of total body water from 42% to 33% of the total body weight and of extracellular fluid, lower distribution volume of hydrophilic medications such as ACE inhibitors, digoxin, lorazepam, metronidazole, and L-thyroxine. Accumulation can occur when
   - sensation of thirst in the elderly diminishes despite lack of fluids (known as elderly dehydration),
   - renal function declines,
   - medication dosage is not adjusted for age.
   b) Increase of body fat up to 30% of body weight, decrease in muscle mass; greater distribution volumes and prolonged effective duration through increased, longer storage in the fat deposits in the case of lipophilic medications, such as amoxi-
cillin, furosemide, diazepam, nitrazepam, and oxazepam [18].

4. **Renal elimination decreases with age** [114, 150]: Rule of thumb: Starting at age 30, renal clearance (measured by the estimated glomerular filtration rate, or eGFR) decreases each year by 1%. By 70, eGFR has decreased by 30 – 50% [11, 103]. Medications eliminated by the kidney – digoxin, metronidazole, theophylline, triamterene – must be dosed lower in the elderly. Usually the appropriate clearance level for restricted renal function is calculated by laboratory doctors using the MDRD formula adjusted for age, sex, and creatinine level (MDRD = modification of diet in renal disease).

5. **Interaction and enzyme induction**, e.g., displacement from plasma protein binding (e.g., phenprocoumon through NSAID) [26]. The body’s own substances (e.g., endogenous steroids, estrogens), substances foreign to the body (nutrients, grapefruit juice, St. John’s wort) and medications can inhibit or induce P450 cytochrome during liver metabolism and thus change the effective level of medication [86, 87, 98, 114, 134, 147].

6. **Change of pharmacodynamics**: Increased sensibility or paradoxical effects in the elderly for centrally effective substances (such as benzodiazipine and chlorpromazine) require a dosage reduction or a change of treatment.

### Individual risk-benefit analysis in the elderly

Numerous medications are considered unsuitable for the elderly due to the changing pharmacokinetics and pharmacodynamics and increasing multimorbidity that accompany old age. With these medications, the risk of side-effects or age-related complications can exceed clinical benefits. Continuing to prescribe these medications is not advisable. This is especially true when better alternatives are available [85].

In the 1990, several research groups started collecting information on the potentially damaging effects that inappropriate medications can have in the elderly. These groups have assessed individual medications and medication classes systematically with regard to their danger potential (usually in consensus procedures) (e.g., Beers list). The PRISCUS list was published in 2011 for German-speaking regions.

The PRISCUS list consists of 83 medications on the German market that were categorized as potentially inappropriate medication (PIM) for the elderly. The assessment was partly based on studies of adverse drug reactions. In the prescription process, the doctor must examine whether these medications can be discontinued or replaced by another. The list also contains treatment alternatives and describes measures (monitoring parameters, dosage adjustments) that should be used in case the prescription of PIMs is unavoidable.

The development of the list was part of the Action Plan for Safe Drug Treatment, initiated by Germany’s Federal Ministry of Health. It was based on literature research and a qualitative analysis of common international PIM lists such as those of Beers, Laroche, Mc Leod, and Fick [17, 41, 85, 99, 148]. The list can be downloaded free of charge at http://priscus.net/download/PRISCUS-Liste_PRISCUS-TP3_2011.pdf. This list contains so-called borderline PIMs that are not categorized as problematic by all assessors equally. These include diclofenac, naproxen, etoricoxib, and some quinolones.

PIMs from the **PRISCUS list** are frequently prescribed. An analysis of German-wide data from a statutory health insurer for 2010 showed a treatment prevalence of 24% for those 65 and older. Extrapolated to all of Germany, 4 million older persons received at least one of these medications [151]. Since some of the substances on the PRISCUS list are available OTC, the real PIM prevalence is even higher.

The PRISCUS list grew out of a DELPHI approach and is currently being evaluated. The method of development should be considered when using it for assessing medications. The Guideline Group understands the list as an aid for critically evaluating medications and not as a list of forbidden drugs. Indeed, from the perspective of general practitioners, some of the listed medications are indispensable.
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Guideline report

Scope and purpose

In creating guidelines for general practice, the Guideline Group of Hesse for Pharmacotherapy in General Practice seeks to achieve three objectives:

1. Train GPs in pharmacotherapy. The guidelines are designed for internal quality assurance in pharmacotherapy circles and for supporting moderation. The guidelines describe safe and accepted methods for implementing recommendations and ensuring economic viability – a rational and efficient pharmacotherapy for GPs.

2. Support SHI-accredited primary care by providing practical and evidence-based treatment recommendations for everyday practice.

3. Improve the doctor-patient relationship. The guidelines provide materials for aiding treatment decisions and implementation.

In particular, these guidelines want to help GPs assess the pharmacotherapy systematically as part of the prescription decision. The guidelines seek to:

- avoid inappropriate medication and unintended prescription cascades [119],
- avoid adverse, drug-related reactions,
- identify incorrect dosages and misuse,
- identify unmet medical needs, even with multimorbid patients,
- select appropriate medications for multimorbid patients,
- keep the number of medications manageable for the patient,
- help prioritization when necessary, and
- watch for physiological changes, such as influence on the pharmacokinetics of the elderly.

The guidelines are designed for patients under treatment by primary care physicians (general practitioners and internists active in primary care). The recommendations of the guidelines do not cover the pharmaceutical treatment of palliative patients.

Participation of interest groups

The Guideline Group is mostly made up of general practitioners with a partly changing line-up. The doctors in the group specialize in allergy, angiology, diabetology, nutritional medicine, cardiology, palliative medicine, psychotherapy, sports and addiction medicine, and quality management in medicine. In addition, several external experts were involved in the creation of the guidelines: Sebastian Harder, Clinical Pharmacology at the University of Frankfurt am Main; and Christiane Muth and Martin Beyer, Institute for General Medicine at the University of Frankfurt am Main. The creation of the guidelines takes place in cooperation with the German Society for General and Family Medicine (DEGAM: Uwe Pop- ert, Christiane Muth, Martin Beyer, Guido Schmiemann, Günther Egidi).

Patient representatives were not consulted when creating the guideline. Yet, the views of patients, especially when it comes to potential problems with treatment adherence and acceptance, are included in the guidelines from the perspective of the general practitioners. Moreover, measures that involve active patient participation and recommendations for shaping the doctor-patient relationship form an indispensable part of the guideline.

The guideline is designed for primary care physicians (general practitioners and internists involved in primary care) and quality
Guideline report

Guideline research

When developing GP guidelines, we mostly relied on existing evidence. The basic principle is the topic-specific comparison of national and international evidence-based guidelines that lend themselves for adaption to the GP context. Guidelines were systematically identified by researching various databases.

Before guideline preparation began, the authors carried out extensive research on existing guidelines for multimorbid patients on multimedication with the goal of adopting existing guidelines.

Preliminary remarks

The research was carried out by the Agency for Quality in Medicine (ÄZQ) on September 1 and 2, 2011. The research vocabulary consisted of the following terms:

- multimedication; multiple medication; multiple medications; multiple drug; multiple drugs,
- comorbidity; comorbidities; co-morbidity; co-morbidities; multimorbidity; multimorbidities; multimorbidity; multimorbidities,
- patient care management; drug management; medicine supply; drug supply; drug prescriptions; medication prescriptions; pharmacotherapy; medication treatment; medication use; drug use; pharmacological treatment; pharmaceutical intervention; drug therapy; medication therapy; medication control; drug control,
- practice guideline; practice guidelines; clinical pathway; clinical pathways; clinical protocol; clinical protocols; consensus development; good clinical practice; consensus; guideline; guidelines; recommendation; recommendations; standard; standards; position paper; position papers.

Research strategy

Searches took place in literature and guideline databases between January 1, 2006 and September 1 and 2, 2011 covering documents in German and in English. No restrictions were imposed on patient groups for relevance.

Guideline Research: Pubmed

Research Queries and Hits for Pubmed (01.12.2011) (Table 13).

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Query</th>
<th>Hits</th>
</tr>
</thead>
<tbody>
<tr>
<td>#7</td>
<td>#4 AND #5 Limits: English, German, publication date from 2006</td>
<td>335</td>
</tr>
<tr>
<td>#6</td>
<td>#4 AND #5</td>
<td>529</td>
</tr>
<tr>
<td>#5</td>
<td>practice guideline OR practice guidelines OR clinical pathway OR clinical pathways OR clinical protocol OR clinical protocols OR consensus development OR good clinical practice OR consensus OR guideline OR guidelines OR recommendation OR recommendations OR standard OR standards OR position paper OR position papers</td>
<td>1,467,017</td>
</tr>
<tr>
<td>#4</td>
<td>#1 AND #2 AND #3</td>
<td>2,369</td>
</tr>
<tr>
<td>#3</td>
<td>patient care management OR drug management OR medicine supply OR drug supply OR drug prescriptions OR medication prescriptions OR pharmacotherapy OR medication treatment OR medication use OR drug use OR pharmacological treatment OR pharmaceutical intervention OR drug therapy OR medication therapy OR medication control OR drug control</td>
<td>4,991,464</td>
</tr>
<tr>
<td>#2</td>
<td>comorbidity OR comorbidities OR co-morbidity OR co-morbidities OR multimorbidity OR multimorbidities OR multimorbidity OR multimorbidities</td>
<td>84,120</td>
</tr>
<tr>
<td>#1</td>
<td>multimedication OR multiple medication OR multiple medications OR multiple drug OR multiple drugs</td>
<td>167,104</td>
</tr>
</tbody>
</table>

Guideline Research: EMBASE

Research Queries and Hits for EMBASE (01.09.2011) (Table 14).
Guideline report

Table 14. Research queries and hits for EMBASE (September 1, 2011).

<table>
<thead>
<tr>
<th>No.</th>
<th>Query</th>
<th>Hits</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>10 AND PY=2006 to 2011 AND LA=(ENGLISH; GERMAN)</td>
<td>129</td>
</tr>
<tr>
<td>10</td>
<td>6 AND 9</td>
<td>223</td>
</tr>
<tr>
<td>9</td>
<td>7 OR 8</td>
<td>1,268,777</td>
</tr>
<tr>
<td>8</td>
<td>(((((FT=guidelines OR FT=recommendation) OR FT=recommendations) OR FT=standard) OR FT=standards) OR FT=position paper) OR FT=position papers</td>
<td>1,058,332</td>
</tr>
<tr>
<td>7</td>
<td>(((((FT=practice guideline OR FT=practice guidelines) OR FT=clinical pathway) OR FT=clinical pathways) OR FT=clinical protocols) OR FT=consensus development) OR FT=good clinical practice) OR FT=consensus) OR FT=guideline</td>
<td>337,698</td>
</tr>
<tr>
<td>6</td>
<td>1 AND 2 AND 5</td>
<td>869</td>
</tr>
<tr>
<td>5</td>
<td>3 OR 4</td>
<td>2,702,344</td>
</tr>
<tr>
<td>4</td>
<td>((((FT=pharmacological treatment OR FT=pharmaceutical intervention) OR FT=drug therapy) OR FT=medication therapy)OR FT=medication control) OR FT=drug control</td>
<td>2,649,043</td>
</tr>
<tr>
<td>3</td>
<td>((((((((FT=patient care management OR FT=drug management) OR FT=medicine supply) OR FT=drug supply) OR FT=drug prescriptions) OR FT=medication prescriptions) OR FT=pharmacotherapy) OR FT=medication treatment) OR FT=medication use) OR FT=drug use</td>
<td>105,497</td>
</tr>
<tr>
<td>2</td>
<td>((((FT=comorbidity OR FT=comorbidities) OR FT=co-morbidity) OR FT=co-morbidities) OR FT=multimorbidity) OR FT=multimorbidities OR FT=multimorbidity) OR FT=multimorbidities</td>
<td>98,778</td>
</tr>
<tr>
<td>1</td>
<td>(((FT=multimedication OR FT=multiple medication) OR FT=multiple medications) OR FT=multiple drug) OR FT=multiple drugs</td>
<td>13,288</td>
</tr>
</tbody>
</table>

Research in guideline databases

Review of guideline databases

The research strategy consisted of reviewing title lists and using the research vocabulary above in the entry masks. We consulted specialized databases, interdisciplinary databases, those of state organizations for healthcare quality and those of the WHO. Table 15 presents the guideline databases reviewed and the hits produced.

Review of abstracts and complete texts

After reviewing the hits, we screened the titles. Then the selected abstracts and complete texts were read by two independent investigators. The following inclusion criteria were defined at the outset for selecting publications:

- valid guidelines, published in the last 5 years,
- published by professional medical societies, or by regional or supraregional organizations that study quality in healthcare systems,
- content focuses on the problem of multimedication in multimorbid patients,
- content focuses on more than one illness.

Results of guideline research

Many of the texts reviewed were not guidelines in the traditional sense of being recommendations for actions; rather, they were overview articles, project descriptions, or publications on multimedication. A series of publications did exist on multimedication, but because they dealt with individual illnesses they were excluded. As a result, despite the large number of hits, especially in the literature databases, there were no published guidelines on the topic of multimedication in multimorbid patients that matched the inclusion criteria.

Results of the research and hits (Figure 6)

Not until May 2012, when the work of the Guideline Group of Hesse was far along, did the Dutch Association of General Practitioners (NHG) publish the first guidelines for dealing with the problem of multimedication in general practice [109]. Even though the study was limited to older patients (> 65),
Table 15. Guideline databases.

<table>
<thead>
<tr>
<th>Database/Provider</th>
<th>Link</th>
<th>Hits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)</td>
<td><a href="http://www.awmf.org/leitlinien/leitlinien-suche.html">http://www.awmf.org/leitlinien/leitlinien-suche.html</a></td>
<td>0</td>
</tr>
<tr>
<td>Guidelines International Network (G-I-N)</td>
<td><a href="http://www.g-i-n.net">http://www.g-i-n.net</a></td>
<td>0</td>
</tr>
<tr>
<td>National Guideline Clearinghouse (NGC)</td>
<td><a href="http://www.guidelines.gov">http://www.guidelines.gov</a></td>
<td>0</td>
</tr>
<tr>
<td>Agency for Healthcare Research and Quality (AHRQ), USA</td>
<td><a href="http://www.ahrq.gov/clinic/cpgsix.htm">http://www.ahrq.gov/clinic/cpgsix.htm</a></td>
<td>0</td>
</tr>
<tr>
<td>Alberta Medical Association/Toward Optimized Practice (AMA/TOP), Canada</td>
<td><a href="http://www.albertadoctors.org">http://www.albertadoctors.org</a></td>
<td>0</td>
</tr>
<tr>
<td>American Medical Directors Association (AMDA), USA</td>
<td><a href="http://www.amda.com">http://www.amda.com</a></td>
<td>0</td>
</tr>
<tr>
<td>Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ)</td>
<td><a href="http://www.akdae.de">http://www.akdae.de</a></td>
<td>0</td>
</tr>
<tr>
<td>British Columbia Council (BCC), Canada</td>
<td><a href="http://www.bcguidelines.ca/">http://www.bcguidelines.ca/</a></td>
<td>1</td>
</tr>
<tr>
<td>British Medical Association (BMA), GB</td>
<td><a href="http://www.bma.org.uk">http://www.bma.org.uk</a></td>
<td>0</td>
</tr>
<tr>
<td>Bundesärztekammer (BAK)</td>
<td><a href="http://www.baek.de">http://www.baek.de</a></td>
<td>0</td>
</tr>
<tr>
<td>Canadian Medical Association (CMA)</td>
<td><a href="http://www.cma.ca/">http://www.cma.ca/</a></td>
<td>0</td>
</tr>
<tr>
<td>HealthTeamWorks, USA</td>
<td><a href="http://www.healthteamworks.org/">http://www.healthteamworks.org/</a></td>
<td>0</td>
</tr>
<tr>
<td>Duodecim, Finland</td>
<td><a href="http://www.duodecim.fi/web/english/home">http://www.duodecim.fi/web/english/home</a></td>
<td>0</td>
</tr>
<tr>
<td>Evidence.de</td>
<td><a href="http://www.evidence.de">http://www.evidence.de</a></td>
<td>0</td>
</tr>
<tr>
<td>Guidelines and Audit Implementation Network (GAIN), Northern Ireland</td>
<td><a href="http://www.gain-ni.org/index.asp">http://www.gain-ni.org/index.asp</a></td>
<td>0</td>
</tr>
<tr>
<td>Health Services Technology Assessments Texts (HSTAT), USA</td>
<td><a href="http://www.ncbi.nlm.nih.gov/books/NBK16710/">http://www.ncbi.nlm.nih.gov/books/NBK16710/</a></td>
<td>0</td>
</tr>
<tr>
<td>Institute for Clinical Systems Improvement (ICSI), USA</td>
<td><a href="http://www.icsi.org/">http://www.icsi.org/</a></td>
<td>0</td>
</tr>
<tr>
<td>Ministry of Health (MOH), Singapore</td>
<td><a href="http://www.moh.gov.sg/mohcorp/default.aspx">http://www.moh.gov.sg/mohcorp/default.aspx</a></td>
<td>0</td>
</tr>
<tr>
<td>National Clinical Guideline Centre (NCGC), GB</td>
<td><a href="http://www.ncgc.ac.uk">http://www.ncgc.ac.uk</a></td>
<td>0</td>
</tr>
<tr>
<td>National Health and Medical Research Council (NHMRC), Australia</td>
<td><a href="http://www.nhmrc.gov.au">http://www.nhmrc.gov.au</a></td>
<td>0</td>
</tr>
<tr>
<td>National Institute for Health and Clinical Excellence (NICE)</td>
<td><a href="http://www.nice.org.uk">http://www.nice.org.uk</a></td>
<td>0</td>
</tr>
<tr>
<td>National Institutes of Health (NIH), USA</td>
<td><a href="http://www.nih.gov/">http://www.nih.gov/</a></td>
<td>0</td>
</tr>
<tr>
<td>New Zealand Guidelines Group (NZGG)</td>
<td><a href="http://www.nzgg.org.nz">http://www.nzgg.org.nz</a></td>
<td>0</td>
</tr>
<tr>
<td>Scottish Intercollegiate Guidelines Network (SIGN)</td>
<td><a href="http://www.sign.ac.uk">http://www.sign.ac.uk</a></td>
<td>0</td>
</tr>
<tr>
<td>World Health Organization (WHO)</td>
<td><a href="http://www.who.int/en/">http://www.who.int/en/</a></td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 6.
we checked the recommendations and references and took them into account in our GP guidelines.

Study of the medication review literature

The research was to clarify whether a medication review has positive effects on patient care and whether this also applies to primary care in Germany.

Research strategy

The research was carried out in December 2011. The databases of the Cochrane Library were searched for clinical studies, HTA reports, and systematic review literature.

The following queries were used: polypharmacy, multimedication, multiple and pharmacy, prescribing. They resulted in the following results (Table 16).

From the list of hits, 32 potentially relevant studies were selected by title and included in the larger selection.

Inclusion and exclusion criteria

The inclusion and exclusion criteria were defined in advance. Studies were included that analyzed the effects of medication reviews. Unfinished reviews and protocols were excluded. Also excluded were studies

- in which the interventions were restricted to patients with a defined illness;
- in which the medication review was carried out by telephone, without direct patient contact or purely based on medical record;
- in which the medication review was carried out without doctor participation (e.g., only through pharmacists);
- whose investigated care program did not define the mix of interventions in more detail;
- in which only training programs for doctors were considered; and
- that were published before 2001.

There was no limitation with regard to investigated outcomes.

After review of the titles, abstracts, and original works, 11 relevant studies were selected. The effects with regard to the endpoints investigated in the studies are represented in the section on medication review studies in the guideline.

During work on the guideline, other important publications appeared and the hits were supplemented through a manual search of reference indexes in studies and other publications. In particular, the literature data from the Cochrane Review “Interventions to improve the appropriate use of multimedication for older people” [113] and the guidelines “Multidisciplinaire richtlijn Polyfarmacie bij ouderen” of the Dutch Association of General Practitioners [109], published in May 2012, delivered important information on further publications.

<table>
<thead>
<tr>
<th>Publication type</th>
<th>Hits</th>
<th>Potentially relevant, by title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane reviews</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Other reviews</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Clinical trails</td>
<td>151</td>
<td>29</td>
</tr>
<tr>
<td>Method studies</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Technology assessments</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Economic evaluations</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>
Categories of evidence

Decisions about the contents and recommendations of the guidelines presented here are based on consensus decisions of the Guideline Group of Hesse for Pharmacotherapy in General Practice.

Conclusions and recommendations of the guideline are – were possible – assigned with an evidence level: A, B, or C. First, conclusions from evidence-based guidelines were compared. Their evidence categories were adopted for similar recommendations in existing GP guidelines. Then, conclusions that couldn’t be categorized in this way were assessed by the guideline authors and the accompanying recommendations were each assigned an evidence category (see below). Level C recommendations are based on expert experience, though there are currently no well-designed studies on these conclusions. The assigned levels are cited in curly brackets, e.g., \{A\}.

The following schema of evidence and recommendation levels is based on definitions by the US Agency for Health Care Policy and Research (AHCPR, US Department of Health and Human Service, 1993 [155]) and was taken from the guidelines of the Scottish Intercollegiate Guideline Network.

When developing the multimedication guideline, the authors could not rely on evidence-based guidelines in this field. Therefore, the recommendations are mainly based on consensus views. The recommendations are not graded by levels, as most studies did not analyze the GP setting.

<table>
<thead>
<tr>
<th>Degree and type</th>
<th>Recommendation levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Evidence from meta-analyses of randomized controlled studies</td>
</tr>
<tr>
<td>Ib</td>
<td>Evidence from at least one randomized controlled study</td>
</tr>
<tr>
<td>Ila</td>
<td>Evidence from at least one well-planned controlled study without randomization</td>
</tr>
<tr>
<td>IIb</td>
<td>Evidence from one well-designed, quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>Evidence of a well-designed, non-experimental descriptive study (comparative studies, correlation study, case-control study)</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence from reports or opinions from experts, consensus conferences and/or the experiences of recognized authorities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based on levels Ia and Ib of evidence type; supported by good-quality publications that contain at least one randomized controlled study.</td>
</tr>
<tr>
<td>B</td>
<td>Based on levels Ila, IIb and III of evidence type; supported by a well-designed, not-randomized, clinical study.</td>
</tr>
<tr>
<td>C</td>
<td>Based on evidence level IV; can be derived from reports or opinions from experts, consensus conference and/or clinical experiences of recognized authorities; indicates the lack of directly applicable high-quality clinical studies.</td>
</tr>
</tbody>
</table>
Information on the Guideline Group of Hesse

Why use GP guidelines?

Although there are already a variety of guidelines, few deal with the typical treatment cases encountered by GPs. For this reason, the Guideline Group of Hesse for Pharmacotherapy in General Practice was founded in 1998 in cooperation with the former Primary Health Care Research Group (today: PMV Research Group) at the University of Cologne. The Guideline Group was formed by the moderators of pharmacotherapy circles that have existed in KV Hesse since 1993. The Guideline Group set the goal of creating treatment recommendations designed for primary care and suitable for general practice.

GPs mainly take care of the chronically ill, the elderly, and multimorbid patients. The guidelines must take this into account. If one looks for studies that support treatment recommendations one notices that the patients in these studies are generally not included in clinical studies. (Frequently, subjects of clinical studies have no more than 1 accompanying illness.) This means that the transferability of study results for typical multimorbid GP patients must constantly be checked [73]. We also need to consider that multimedication can lead to hard-to-predict interactions and adherence problems. The GP is thus required to select medications accordingly.

Selection of medications in the GP guidelines

The Guideline Group of Hesse wants to support GPs when selecting medications. For this reason, it has mostly limited itself to medications of first resort for which

- there is a positive risk-benefit ratio,
- well-documented evidence exists,
- a consensus exists in the Guideline Group on account of the years of good experience in general practice.

Of course, if contraindications or intolerance arise, others medications, not explicitly named in the guidelines, should be used from the indication field. These considerations also include the recommendation that when introducing a treatment there must be a high therapeutic benefit for a relatively large number of patients. The number of patients that must be treated to give one patient a treatment success should always be taken into account (NNT: number needed to treat). Further, the general practitioner has to consider the possible harm caused by the medication, i.e., its relation to NNH (number needed to harm). In some guidelines the endpoints of the most important studies are presented with information on risks and NNT.

Special requirements of primary care

The GP is the physician of first resort for the chronically ill. Unlike hospital doctors, GPs must monitor treatments with clinical parameters, watch for age-related abnormalities in the treatment, check for adverse reactions and interactions, ensure patient adherence and quality of life, involve patients in treatment decisions (shared decision making) and keep track of the economic viability of the treatment. Nonmedical therapies are a special feature of primary care, which are also included in the GP guidelines and for which studies and strengths of evidence must be indicated whenever available.
The decision to limit the scope to selected medications is in keeping with the strategies for assuring the quality of physician prescribing, as called for and implemented by the WHO [34] and by training courses and quality assurance programs in other countries.

**Implementation and evaluation of GP guidelines**

A central implementation strategy is the use of the guideline work by the quality circles.

Up through 2008 (the date the GP-centered healthcare contract with the Substitute Health Insurance Funds came to an end in Hesse), the guidelines were discussed and revised with the moderators of pharmacotherapy circles. The implementation of the guidelines was then carried out by the circles. Every participant received a version of the guidelines and materials (manuals) on topics relating to the circle meeting, including an introduction to the symptoms and treatments to be discussed. The documents also contain an analysis based on the prescriptions and diagnoses from the practices of the participants. From the analysis, and with the help of primary indicators, the state of the implementation of the guideline recommendations for pharmacotherapy can be identified.

The evaluation began after the work of the circles was completed. The prescription data before and after the work of the circles was compared with the quality indicators and economic viability of the treatment. Afterwards, the data was discussed in a separate session for the pharmacotherapy circles.

The PMV research group performed a short survey on the guidelines in each circle meeting to gather information on the relevance and acceptance of the guideline recommendations. The results were then presented to the circle participants and the Guideline Group [131, 132, 160].
Disclaimer and internet addresses

Evidence-based patient information

- http://www.akdae.de
- http://www.gesundheitsinformation.de
- http://www.herzstiftung.de
- http://www.patienten-information.de
- http://www.patientenleitlinien.de
- http://www.paritaet.org/hochdruckliga
- http://pharmnet-bund.de
- http://www.gutepillen-schlechtepillen.de

Useful internet links

- http://www.pharmatrix.de (administrable by gavage, etc.)
- http://www.embryotox.de (medication during pregnancy)
- http://www.azcert.org (information on QT interval extension through medication)
- http://www.dosing.de [58] (information on dosage with restricted renal function)
- http://choosingwisely.org
- http://www.arznei-telegramm.de
- http://der-arzneimittelbrief.de
- http://www.amda.com

Further sources of information on pharmacotherapy for the elderly

- Primary Care Guidelines for Geriatrics, Part 1 and 2 http://www.pmvforschungsgruppe.de [89, 90]
- Information and tables on medications that are substrates of P450 cytochromes [43] http://medicine.iupui.edu/flockhart/table.htm
- Cytochrome and its meaning for medication interactions [98]

Legal notices and disclaimer

- The GP guidelines are addressed to doctors. Inquiries from patients will not be answered. The guideline recommendations are not designed for patient self-treatment.
- Although the authors of these guidelines – the physicians in the Guideline Group of Hesse for Pharmacotherapy in General Practice – undertook great care and consulted the newest studies in their work, they are not liable for the accuracy or completeness of the content.
- Dosage information was provided on the basis of current pharmacological studies and manufacturer’s instructions. Here too, the authors do not accept personal responsibility for accuracy. The information in the package inserts and in the SPCs always takes precedence. The interactions and side-effects mentioned represent only a selection.

The guidelines and the general guideline report (German version) can be found online at www.pmvforschungsgruppe.de publikationen > leitlinien or on AWMF online: www.awmf.org/detail/ll/053-043.html

Download of English version: see www.pmvforschungsgruppe.de publikationen > leitlinien

Downloads for personal use only.
Pharmacotherapy guidelines for the aged by family doctors for the use of family doctors

Version 1.07, April 18th, 2007, Revision up to December 2008 was translated.
Version 1.00, December 2008 "Hausärztliche Leitlinie Geriatrie" was also considered.

Guidelines Group Hesse: Pharmacotherapy Guidelines by Family Doctors for Family Doctors

General practitioners, Association of Statutory Health Insurance Physicians in Hesse (Kassenärztliche Vereinigung in Hessen (KVH) Frankfurt (Main)), Germany

Contents Pharmacotherapy guidelines for the aged by family doctors for the use of family doctors

A General
a) Context of the guidelines
b) Levels of evidence

B General pharmacology in the aged
a) Absorption of drugs
b) Distribution space
c) Transport proteins
d) Renal elimination
e) Metabolism in the liver
f) Drug interactions
g) Summary


C Special Pharmacology of the aged
a) Dementia
b) M. Parkinson


c) Osteoporosis
d) Incontinence of urine
e) Fecal incontinence
f) Chronique constipation


D Basic conditions supporting drug treatment
a) Nutrition in old age
b) Body exercise in old age


c) Management of age-associated diseases

E Information
a) Information about the guidelines group
b) Disclaimer
c) Internet addresses for free download of the complete guideline

Guidelines Group Hesse: Pharmacotherapy guidelines for the aged by family doctors for the use of family doctors