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A Composite Screening Tool for Medication Reviews of Outpatients

General Issues with Specific Examples

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Abstract

Regular performance of medication reviews is prominent among methods that have been advocated to reduce the extent and seriousness of drug-related

problems, such as adverse drug reactions, drug-disease interactions, drug-drug interactions, drug ineffectiveness and cost ineffectiveness. Several screening tools have been developed to guide practising healthcare professionals and researchers in reviewing the medication patterns of elderly patients; however, each of these tools has its own limitations. This review discusses a wide range of general prescription-, treatment- and patient-related issues that should be taken into account when reviewing medication patterns by implicit screening. These include generic and therapeutic substitution; potentially superfluous or inappropriate medications; potentially inappropriate dosages or duration of treatment; drug-disease and drug-drug interactions; under-treatment; making use of laboratory test results; patient adherence, experiences and habits; appropriate dosage forms and packaging. A broad selection of specific examples and references that can be used as a basis for explicit screening of medication patterns in outpatients is also offered.

Patients using repeat prescriptions are at risk of experiencing adverse drug reactions, drug-disease interactions, drug-drug interactions and drug ineffectiveness, particularly when they are elderly. This is due to factors such as polypharmacy, suboptimal monitoring, non-adherence and pathological or age-related physiological changes. Regular performance of pharmacy-initiated medication reviews is prominent among methods that have been advocated to reduce the extent and seriousness of such problems.[1-3] Drug treatments should be periodically reconsidered in terms of their adverse effects. Randomised controlled trials have partially confirmed that pharmacy-initiated medication reviews may have economic as well as clinical benefits, if designed and executed appropriately.[1,2,4-10]

In several countries, pharmacists can now claim a fee for conducting medication reviews of outpatients. Australian community pharmacists are compensated for home medicine reviews under an agreement between the government and the pharmacy guild. In cooperation with a general practitioner (GP) [who refers the patient], the pharmacist visits the patient at home, reviews his or her medications and provides the GP with a report. The GP and patient then agree on a medication management plan. The pharmacist's responsibilities vary, depending on whether he or she is accredited to conduct medication reviews.[11] In The Netherlands, private health insurance companies have started paying a fee to community pharmacists for conducting medication reviews of outpatients receiving polypharmacy.[12,13]

The UK Task Force on Medicines Partnership distinguishes four different levels of medication reviews (table I). Pharmacists in the UK are allowed to claim payment for so-called medicine use reviews, which aim at improving the patient's knowledge and use of drugs by, in particular: (i) establishing the patient's actual use, understanding, and experience of taking drugs; (ii) identifying, discussing and resolving poor or ineffective use of drugs by the patient; (iii) identifying adverse effects and drug interactions that may affect the patient's adherence to instructions given to him or her by a healthcare professional; and (iv) improving the clinical and cost effectiveness of drugs prescribed to patients, thereby reducing the wastage of such drugs.[14]

1. Objectives

The growing importance of medication reviews increases the need for adequate guidance on how to perform such reviews, particularly in elderly patients with complicated drug regimens. This article examines prominent existing tools for conducting reviews and then presents a new composite tool that provides (i) an approach to various general issues that should be taken into account in the implicit reviewing of medication patterns; and (ii) a broad range of specific examples and detailed references

Table I. Levels of medication review distinguished by the UK Task Force on Medicines Partnership (reproduced from Shaw et al.,[15] with permission)

Level	Type of review	Description
0	*Ad hoc* review	*Unstructured, opportunistic review of a patient's medication* For example, an isolated question to a patient from a receptionist in the surgery or from a pharmacist in the community pharmacy
1	Prescription review	*Technical review of a list of a patient's medicines* This can be helpful in identifying anomalies and highlighting patients who may need clinical medication reviews, but as a stand-alone tool its benefits are relatively limited as it does not normally allow for a full discussion with the patient. Examples of interventions include dose and pack optimisation, resolving quantity problems, drug presentation issues and brand-to-generic switches
2	Treatment review	*Review of medicines with patient's full notes* This normally takes place under the direction of a doctor, nurse or pharmacist, but often without the patient (e.g. removal of unwanted items from the repeat medicines list, dose adjustments). It may include the complete repeat prescription or focus on one therapeutic area (e.g. hypertension), drug (e.g. lithium) or group of drugs (e.g. NSAIDs). Recommendations may be passed to the prescriber for implementation. Examples of outcomes include reducing the number of items and modifying doses
3	Clinical medication review	*Face-to-face review of medicines and condition* This requires access to the patient's notes, a full record of prescriptions and non-drug care and results from laboratory tests. It should include the complete repeat prescription as well as over-the-counter and complementary remedies. In a clinical medication review, medicines are not examined in isolation but considered in the context of the patient's condition and the way he/she lives his/her life. The review should involve the patient as a full partner (i.e. listening to the patient's views and beliefs about his/her medicines, reaching an honest understanding of his/her medicine-taking behaviour and taking full account of his/her preferences in any decisions about treatment). The invitation to a review should include both the patient and (when appropriate) the carer. The level 3 clinical medication review involves evaluating the therapeutic efficacy of each drug, identifying and addressing unmet therapeutic needs, monitoring the progress of the conditions being treated, and purposefully discussing specific aspects of the patient's medication with the aim of facilitating a concordant approach to medicine taking. A clinical medication review may take place in a variety of settings, including the patient's home

to examples that can be used for the explicit reviewing of medication patterns.

2. Methods

Our initial search strategy for finding pertinent articles was a free text search on 'medication review' OR 'medication reviews' in MEDLINE through online consultation of PubMed from 1965 to 31 December 2006. We resorted to this free text approach because PubMed did not provide a specific MeSH term for medication review. Only 141 references were retrieved, many of which were judged (on the basis of their title and/or abstract) to be not useful for our purposes. More importantly, the search failed to identify various relevant articles that we had uncovered in the course of an earlier literature review on repeat prescribing in ambulatory care patients[2] and two original studies of prescriber- and user-related problems in elderly outpatients receiving polypharmacy.[16,17] We therefore supplemented our initial MEDLINE search with an incremental search strategy that comprised the following elements:

- Manual searching of the literature that had already been collected or consulted for our earlier studies.[2,16,17] As these studies had focused on ambulatory care patients, we decided to give our new study the same focus.
- Online searching for additional papers by the research groups that were found to be prominent in the field of medication reviews and related issues.
- Manual searching of the bibliography of every useful reference retrieved for additional references and repeating this procedure until no more useful references emerged.

3. Existing Screening Tools

Several implicit and/or explicit screening tools have been developed to guide practising healthcare

professionals as well as drug utilisation researchers in reviewing the medication patterns of elderly patients; however, each of them has its own benefits and limitations. This is illustrated in this section by discussion of some prominent examples.

Generally speaking, implicit screening criteria (e.g. look for inappropriate drug-drug interactions) allow a full and flexible clinical judgement of individual drug treatments in a way that can also detect problems that are not pre-specified. However, implicit screening methods depend heavily on the knowledge, experience and skills of the individual reviewer. They may be relatively time consuming and it can be difficult to apply them consistently and measure outcomes in a valid and reliable way.[18]

In contrast, explicit screening criteria (e.g. look for the inappropriate combination of cotrimoxazole and a coumarin anticoagulant) have the advantages of being reliably based on a literature review and expert consensus opinion, they can identify and prioritise problems in a consistent way and they can be easily incorporated into practice computer systems. However, explicit screening methods have the disadvantage of an inflexible approach, which leaves insufficient room for individual differences between patients and can thereby lead to false-positive signals (i.e. the signalling that a drug-related problem exists whereas in reality it does not exist). Furthermore, explicit screening methods will miss any drug-related problem that has not been pre-specified and will therefore fail to provide a full assessment of the patient.[18]

Using a combination of implicit and explicit screening methods can be expected to offer a more thorough assessment than using either approach separately. The only caveat with this strategy is that use of such a combined application can be more time consuming and care should therefore be taken to ensure the feasibility of this approach in daily practice.[18]

3.1 Beers Criteria

A widely advocated explicit screening tool was introduced in 1991 by Beers et al.[19] The tool was first developed to be used in nursing home patients and consists of a list of specific drugs and drug classes that should generally be avoided in elderly patients. These so-called Beers criteria have been very useful for assessing medication appropriateness in elderly populations, and they have been widely used for this purpose.[20-23] When interpreting such data, however, it is important to appreciate that some drugs on the Beers list are appropriate for specific patients in certain circumstances.[24,25] Furthermore, the original Beers criteria focused entirely on the appropriateness of medications in elderly patients without addressing other important categories of drug-related problems. In 2003, an additional Beers list was introduced that specified certain drug-disease combinations that should also generally be avoided in elderly patients.[26] While this broadened the scope of the Beers criteria, it still did not result in a complete set for medication reviewing.

3.2 Medication Appropriateness Index

A well known example of an implicit screening tool for reviewing medication patterns in elderly patients is the Medication Appropriateness Index (MAI).[27-29] The first version of this index was published in 1992 by Hanlon et al.[30] and a modified version was presented by the same group in 1997.[31] The index raises a number of important issues that are incompletely or not considered at all by the Beers criteria. For example, has each medication an indication? Is it expected to be effective for the patient's condition? Is each dosage correct? Are the directions for use correct and practical? Are there any clinically significant drug-drug interactions or drug-disease interactions? Is there any unnecessary duplication with another drug? Is the duration of therapy acceptable? Is each medication the least expensive alternative compared with others of equal utility? Contrary to the Beers criteria, the MAI does not specify which drug therapies or drug combinations are of primary concern in these domains. However, even the MAI does not cover all relevant categories of drug-related problems. For instance, it does not address such important issues as adherence to each medication regimen[7] or the risk that the patient is not receiving a required medication.[32,33]

3.3 Assessing Care Of Vulnerable Elders (ACOVE) Indicators

The Assessing Care Of Vulnerable Elders (ACOVE) indicators offer a mix of explicit and implicit screening criteria. In 2001, a series of consensus-based sets of ACOVE indicators were published as a special issue of the *Annals of Internal Medicine*. A few years later, the results of applying these indicators to assess the quality of medical care and pharmacological care for vulnerable elderly patients were presented in the same journal.[34,35]

One of the ACOVE sets of indicators focuses on appropriate medication use. This set consists of 12 different indicators, which range from very specific topics (e.g. avoid barbiturates if they are not needed to control seizures; check electrolytes within 1 week of initiating therapy with a thiazide or loop diuretic and at least annually thereafter) to very broad recommendations (e.g. every new drug should have a clearly defined indication; the patient or caregiver should be educated about every new drug in regard to its purpose, how to take it and its expected adverse effects; every vulnerable elderly patient should undergo a drug regimen review at least annually).[32] In addition, various drug therapy-related indicators are incorporated in the other ACOVE sets of indicators.[36] For example, the set for the management of osteoarthritis recommends that paracetamol (acetaminophen) should be the first drug used and that this drug should be administered at maximum dosage (taking into account age and co-morbidity) before switching to another agent.[37]

Although the ACOVE indicators highlight some important aspects of drug therapy in the elderly that are not covered by either the Beers criteria or the MAI (e.g. the risk of under-prescribing and the need to monitor certain drug therapies carefully), neither their range of general drug-related topics nor their selection of drug-specific indicators are exhaustive.

4. General Issues in Implicit Screening

Based on our earlier review of the quality management of repeat prescriptions,[2] two original studies of user- and prescriber-related problems in elderly outpatients receiving polypharmacy,[16,17] and various other papers about general aspects to consider when reviewing medications,[3,15,18,26,31,32,36,38-44] we identified a large number of issues that should be taken into account in the implicit screening of medication patterns in outpatients.

Following the classification of medication reviews by the UK Task Force on Medicines Partnership (table I), we divided these issues into prescription, treatment and patient issues (table II). Sections 5–7 discuss these categories individually, identify the general issues in each category and illustrate each general issue with specific examples and/or detailed references to such examples.

5. Prescription Issues

Prescription issues often focus on cost reduction. While achieving cost effectiveness is a legitimate objective of a medication review, it should always be subordinate to improved care and safety.[15]

5.1 Generic Substitution

Consider the possibility that medications may be substituted by cheaper generic equivalents

Generic substitution, which involves the substitution of a medication with a cheaper medication with the same active ingredient(s), drug strength(s) and dosage form, can offer substantial economic benefits.[45,46] It can usually be performed safely if sufficient attention is paid to the following caveats:[47-49]

- The risk of inequivalence is smaller when drug licensing authorities verify systematically and rigorously that generic products are bioequivalent to original brand products and to each other. The risk of inequivalence is larger when this is not the case.[48]
- The risk of inequivalence depends on the specific dosage form and specific drug substance. Caution is especially needed when the dosage form has controlled-release properties[50-52] and when the drug substance has a narrow therapeutic index (e.g. antiepileptics, warfarin).[53,54]
- It is important to be alert to the occasional possibility that an individual patient is confused by differences in outward appearance (e.g. colour, shape, packaging) or in the content of the pack-

Table II. General issues in the implicit screening of medication patterns in outpatients

Prescription issues
Consider the possibility that medications may be substituted by cheaper generic equivalents
Consider the possibility that medications may be substituted by cheaper therapeutic equivalents
Treatment issues
The reason for prescribing should be known to the medication reviewer
Consider discontinuation of medications without well established effectiveness
Consider discontinuation of medications without effectiveness and/or valid reason for use in the particular patient under review
Consider the possibility of potentially inappropriate duplication of drug treatment
Consider the possibility that one or more medications may have been added to an existing drug therapy to combat an adverse effect of one or more medications already being taken
Consider elimination of medications that are potentially inappropriate for the patient under review (e.g. because of the patient's age or because an adverse effect has developed)
Consider whether the dosage of each medication is still appropriate
Consider whether medications are prescribed for an inappropriately long period
Consider whether medications have been prescribed for an inappropriately short period
Consider the risk of potentially inappropriate drug-disease interactions
Consider the risk of potentially inappropriate drug-drug interactions
Consider the risk of potentially inappropriate duplication of adverse effects
Consider the possibility that a required medication is inappropriately missing
Consider the appropriateness of drug treatment in the light of organ functions, such as renal and hepatic function
Consider the appropriateness of drug treatment in the light of electrolyte levels
Consider the appropriateness of drug treatment in the light of pharmacogenetic test results
Patient issues
Direct contact between reviewer and patient (or caregiver) offers essential advantages
Ask the patient what he/she knows about his/her medications and condition(s), which medications he/she actually takes and how he/she takes them, which beneficial and unwanted effects he/she experiences and which queries the patient has himself/herself
Make adequate room for the patient perspective
Consider the possibility that the patient is taking less of the medication(s) than prescribed
Consider the possibility that the patient is taking more of the medication(s) than prescribed
Consider earlier patient experiences with drugs
Consider specific patient characteristics and habits
Consider the need for special packaging
Consider whether the patient is able to self-administer dosage forms that require special skills

age insert.[55] A particular concern is the risk of confusion over original brands and parallel-imported equivalents with different brand names.

5.2 Therapeutic Substitution

Consider the possibility that medications may be substituted by cheaper therapeutic equivalents

A step beyond generic substitution is class substitution, in which medications are replaced by cheaper medications consisting of another substance from the same drug class. This type of substitution is a key component of many drug formularies and reference pricing systems, and the potential cost savings associated with this approach often seem larger than what can be achieved by generic substitution.[56,57] However, the pharmacotherapeutic caveats that should be respected in order to guarantee therapeutic equivalence are also of a different order. Drug substances with the same mechanism of action may still be different with respect to ancillary pharmacological properties, safety profile and/or the risk of drug-drug interactions, which may lead to differences in effectiveness, safety or applicability.[58-60] For instance, there is substantial evidence to suggest that β-adrenoceptor antagonists are not always equal with respect to their effectiveness[61-63] and that the classical NSAIDs show notable differences in their

adverse reaction profiles.[64,65] An additional concern is that studies evaluating clinical endpoints are usually not available for all drug substances belonging to the same cardiovascular drug class. Even if one assumes that the effects on cardiovascular endpoints are class effects, it may be difficult to ascertain which dose levels are appropriate for those substances that have not been evaluated in endpoint trials. This is especially a problem when monitoring for a pharmacological effect (e.g. on cholesterol level or blood pressure) is either impossible or inadequately executed.[60,66]

6. Treatment Issues

The reason for prescribing should be known to the medication reviewer

A general point with respect to treatment issues is that medication reviewers may identify and evaluate certain types of problems only, or at least more easily, when they have access not only to the pharmacy record but also to the medical record. In a recent UK evaluation of pharmacist-led medication reviews in patients aged >65 years, pharmacists detected 18% of drug-related problems by reviewing medical notes (in addition to 52% detected by looking at prescription records and 29% by interviewing patients at home).[67] Evidence that the quality of a pharmacist-conducted medication review increases as access to complete patient information increases also arises from a US study of paper cases involving prescribing problems that had been identified from patient charts.[68]

6.1 Potentially Superfluous Medications

Consider discontinuation of medications without well established effectiveness

Examples of medications with marginal or questionable effectiveness include:

- ergoloid mesylates and piracetam for dementia or cognitive impairment;[69,70]
- betahistine for Meniere's disease;[71]
- most oral vasodilators for intermittent claudication;[72,73]
- antispasmodic or anticholinergic agents for irritable bowel syndrome;[74]
- expectorants for acute bronchitis;[75,76]
- long-term use of low-dose oral corticosteroids for stable chronic obstructive pulmonary disease (COPD);[77]
- most phytotherapeutic agents for most indications[78,79] and homeopathic agents for any indication.[80,81]

Consider discontinuation of medications without effectiveness and/or valid reason for use in the particular patient under review

Many medications may be stopped in elderly outpatients without the occurrence of an adverse drug withdrawal event. However, such withdrawal events are known to occur, and if they do, they result in substantial healthcare utilisation. One should therefore be vigilant for disease recurrence when drug therapy is discontinued in the elderly.[82,83] A list of drugs that qualify for careful consideration of their discontinuation in the elderly has been drawn up by Woodward.[41] Well known examples include:

- Loop diuretics. In a study evaluating use of loop diuretics in Dutch community-dwelling patients aged ≥75 years, GPs considered their continuation unnecessary for 19.5% of patients. The reason for use of these agents was unknown in 8% of patients, and they were used for the controversial indication of ankle oedema in another 8% of patients.[84]
- Histamine H_2 receptor antagonists and proton pump inhibitors. Studies in general populations have shown that these acid suppressants are not always used for a valid reason[85,86] and that an appreciable proportion of long-term users is able to discontinue these drugs.[87,88] A recent epidemiological study suggested that use of proton pump inhibitors for >1 year is associated with an increased risk of hip fracture in elderly users, possibly as a result of interference with calcium absorption.[89]
- Cholinesterase inhibitors and memantine. As these agents produce clinically relevant effects in only a minority of patients with Alzheimer's disease,[90,91] it is important to assess after initiation of such therapy which patients respond and which patients do not.[92]

- Anticholinergic medications for the treatment of overactive bladder.[41] The clinical benefits of use of these agents to treat overactive bladder may be of questionable significance in many patients.[93]
- Antihypertensive medications in very old patients. The benefits and risks of antihypertensives in patients aged >80 years are still unclear.[94-96] Preliminary results of a controlled trial of antihypertensive agents in this age group suggested that the risk of stroke may be reduced but that this gain may be offset by extra non-stroke deaths.[97] Trials of withdrawal or lowering of the dosage of antihypertensive medications in elderly outpatients have shown that this approach may be successful in up to 40% of patients when combined with salt restriction and weight loss.[94]
- Oral mucolytics. A recent review suggested that treatment with these agents is not cost effective in all patients with chronic bronchitis or COPD and that their use should be restricted to patients with more frequent and severe exacerbations.[98]

Consider the possibility of potentially inappropriate duplication of drug treatment

Unnecessary duplications of drug treatments (different brands of the same drug or different drug substances from the same therapeutic class) should be avoided.[99,100] For instance, concurrent use of more than one NSAID may increase the risk of gastroduodenal toxicity.[101]

A particular risk of unnecessary duplication may occur when drug substances or preparations with the same pharmacological effects are applied for different therapeutic reasons, for example, α-adrenoceptor antagonist agents for hypertension and benign prostatic hyperplasia, or norepinephrine/serotonin reuptake inhibitors for depression and urinary incontinence.[102] Patients are at particular risk of drug duplication in the period immediately following discharge from hospital.[103]

Consider the possibility that one or more medications may have been added to an existing drug therapy to combat an adverse effect of one or more medications already being taken

A new medication may be added to an existing drug regimen to combat an adverse drug reaction. This so-called 'prescribing cascade' may place the patient at risk of developing additional adverse effects relating to this potentially unnecessary treatment. Examples include addition of:[104,105]

- an antihypertensive to NSAID therapy (because of an increase in blood pressure);
- levodopa to metoclopramide treatment (because of parkinsonian symptoms);
- an acid-suppressant drug to a nitrate or calcium channel antagonist (because the latter drugs may precipitate gastroesophageal reflux by decreasing lower oesophageal sphincter pressure);[106]
- a cough suppressant to treatment with an ACE inhibitor (because of a dry persistent cough);[107]
- a cholinesterase inhibitor to drug treatment capable of impairing cognition;[108]
- an anticholinergic drug to medications that are capable of inducing urinary incontinence,[109,110] such as cholinesterase inhibitors for the treatment of dementia.[111,112] The possibility that drug-induced urinary incontinence may have triggered the addition of an absorbent incontinence product should also be considered;[113]
- a drug for benign prostatic hyperplasia to anticholinergic medications (to combat urinary hesitation).[114]

In such cases, it should be evaluated whether the causative drug can be withdrawn or substituted with another medication that does not have the same adverse effect.

In the past, addition of an antigout agent to a thiazide diuretic was also commonly listed as an example, but a recent study has cast doubt on the validity of the underlying assumption that thiazide diuretics actually increase the risk of gout.[115]

6.2 Potentially Inappropriate Medications

Consider elimination of medications that are potentially inappropriate for the patient under review (e.g. because of the patient's age or because an adverse effect has developed)

Since adverse drug effects can have profound clinical and economic consequences for elderly patients, Beers et al.[19,116] have identified a large number of drugs and drug classes that should generally

be avoided in the elderly (see section 3.1). The reader is referred to table I in the 2003 update of these so-called Beers criteria for the most recent version.[26] A few comments are in order. First, the reasons for including nitrofurantoin (potential for renal impairment and availability of safer alternatives) are incorrect.[117] It is true only that nitrofurantoin should not be given to patients with renal impairment, the reason being that antibacterial concentrations in the urine might not be attained whereas the risk of toxicity (peripheral neuropathy, hepatic reactions) is increased.[102,118,119] Secondly, the Beers criteria should not be applied indiscriminately, because there may be acceptable reasons why some of the listed medications are prescribed to elderly patients (e.g. low-dose amitriptyline for neuropathic pain[120]). Thirdly, the Beers listing is not without omissions, if only because it focuses on the medications that are available in the US. Prominent examples of medications that are excluded but should nevertheless be considered as potentially inappropriate for the elderly are:

- glibenclamide (glyburide), because its long duration of action can result in prolonged and recurrent hypoglycaemia in elderly patients;[121-123]
- theophylline (unless its plasma levels can be closely monitored), because it has a narrow therapeutic index and because its plasma level is sensitive to reduced clearance, underlying diseases and drug-drug interactions;[124-126]
- quinine and hydroquinine, especially when used for longer than a few weeks, because their modest and variable effects on restless legs or nocturnal muscle cramps are outweighed by the risk of adverse reactions, such as cinchonism, thrombocytopenia and hemianopsia;[102,127-129]
- atypical antipsychotic agents in higher doses, which entail a risk of serious adverse reactions in the elderly and in certain conditions (e.g. Parkinson's disease, dementia).[130-132]

6.3 Potentially Inappropriate Dosages

Consider whether the dosage of each medication is still appropriate

Compared to the young, elderly patients show a more marked variability in hepatic and renal function, and this may be accentuated by differences in intake of food, co-medications and pharmacogenetic influences. Furthermore, elderly patients may have altered sensitivity to anticoagulants, cardiovascular drugs and psychotropic drugs at the pharmacodynamic level.[133-136] As a result, individual elderly patients may need reduced dose levels and an initially correct dosage may therefore become less appropriate.[25,137,138]

The need to explore lower dosages is particularly relevant for medications with a narrow therapeutic index, such as lithium,[139] digoxin,[140] theophylline,[141] metoclopramide,[142] tricyclic antidepressants,[143] antipsychotic agents,[144] sulphonylurea agents,[121] dopaminergic antiparkinson agents, sedating antiepileptic agents, opioid analgesics and verapamil.[145,146] Adjustment of drug dosages to an appropriate geriatric level can also be relevant when prescribing drugs without a narrow therapeutic index. It has been repeatedly observed, for instance, that use of high doses of benzodiazepines by elderly individuals is associated with an increased risk of hip fractures.[147,148]

When low-dose therapy is considered in elderly patients, care should be taken to avoid the possibility that concerns about adverse effects results in administration of an inappropriately low dosage.[133,149] This risk is illustrated by a North American study that evaluated patterns of prescription of warfarin in frail older people with atrial fibrillation and found that international normalised ratio levels were maintained below the established therapeutic range in 45% of patients.[150]

When prescribing and dispensing specific geriatric dosages, it should be realised that elderly patients may find it difficult to split tablets into two equal halves, even when tablets are provided with a score line. Tablets that already provide the lower dose without the need for splitting are therefore preferable.[151,152]

6.4 Potentially Inappropriate Duration of Treatment

Consider whether medications are prescribed for an inappropriately long period

Repeat prescribing without direct doctor-patient contact entails the risk that there is no longer adequate control of whether every repeat prescription is still appropriate, effective and well tolerated, and that it is still considered and taken by the patient as intended.[2] In a recent US study, excessive duration of drug therapy was one of the five most common reasons for interventions by pharmacists, accounting for almost 10% of all interventions.[153] A particular problem with repeat prescribing is that GPs frequently continue drug therapies that have been initiated by medical specialists. Although GPs often indicate that this particular part of their prescribing behaviour cannot be changed, they have their own responsibility when repeating specialist-initiated prescriptions.[2]

Prolonged use of antibacterials can be justified for certain indications (e.g. tuberculosis or long-term prophylaxis of urinary tract infections) but may be unadvisable in other situations. For instance, repeating antibacterial prescriptions for a lower respiratory tract infection should be the exception rather than the rule in general practice.[154] Likewise, the suggested duration of treatment with an oral anticoagulant after venous thromboembolism varies from 5 weeks to indefinitely, depending on the type of event and patient-related risk factors.[155]

The Beers criteria advise against the long-term use of stimulant laxatives (e.g. bisacodyl, cascara sagrada), except in the presence of an opioid analgesic, and against the long-term use of a full dosage of a nonselective NSAID with a longer half-life (e.g. naproxen, oxaprozin, piroxicam).[26]

Long-term anxiolytic or hypnotic use of benzodiazepines and related substances is limited by serious problems of dependence. Continuation of such use without any attempt at drug withdrawal or dose reduction should generally be discouraged.[156,157] Strategies for discontinuation can be divided into gradual discontinuation programmes and minimal interventions. The former may be successful in two-thirds of patients from general populations, but they are labour intensive, as they involve gradual tapering of the dosage to minimise the risk of withdrawal symptoms.[158,159] Minimal intervention strategies invite patients to stop on their own or to attend for an evaluation consultation (e.g. by a letter making them aware of the risks involved). This type of intervention is much less labour intensive and is successful in about one-fifth or one-quarter of patients from general populations.[158,160]

Consider whether medications are prescribed for an inappropriately short period

The prescription period for medications should not be too short either. For instance, patients with major depression should receive antidepressant treatment for at least 3–6 months after an initial response to decrease the risk of relapse or recurrence.[161,162] However, it should be realised that a medication review is not an optimal method for ensuring adequate minimal treatment periods because it can only identify cases retrospectively, and therefore after use of the drug has already been discontinued (see also the topic of drug persistence in section 7.2).

6.5 Drug-Disease Interactions

Consider the risk of potentially inappropriate drug-disease interactions

For listings of drug-disease interactions that are potentially harmful to elderly patients, the reader is referred to McLeod et al.[163] and Fick et al.[26] The occurrence of such drug-disease interactions in elderly patients in the US has been studied by Lindblad et al.[164] and Zhan et al.[165] A particular concern in this domain is that strict adherence to current clinical practice guidelines may have undesirable effects when caring for elderly patients with several co-morbidities. Boyd et al.[166] constructed a hypothetical case of a 79-year-old woman with five chronic diseases (osteoporosis, osteoarthritis, type 2 diabetes mellitus, hypertension and COPD) and discovered that concurrent adherence to all five clinical practice guidelines for these diseases in the US resulted in potential interactions between a medication and a disease other than the target disease,

between medications for different diseases and between food and medications. They also found that recommendations could also contradict one another. If the hypothetical osteoporotic, diabetic patient had peripheral neuropathy, the osteoporosis clinical practice guideline recommended that he/she perform weight-bearing exercise, whereas the diabetes clinical practice guideline cautioned that some patients with advanced peripheral neuropathy should avoid weight-bearing exercise.

When clinical information is not available, concurrently used medications may serve as more or less suitable surrogate markers for disease states, for example, insulin for diabetes,[167] nitrate prescriptions for ischaemic heart disease[168] and digoxin or amiodarone for atrial fibrillation.[40]

Medication reviewers should bear in mind that contraindications to use of a drug may arise long after long-term therapy with that drug has been established.[169] One reason is that the health status of the patient can change over time, for example, because a new co-morbidity develops or because the patient has grown much older than he/she was at the start of treatment. For a US list of specific drug-disease combinations that should generally be avoided in the elderly, the reader is referred to table II in the most recent version of the Beers criteria.[26] A new contraindication may also develop when a drug is found to be less safe than it was initially assumed to be. For instance, it has become clear that cyclo-oxygenase 2 inhibitors are associated with a degree of cardiovascular risk, which means they should not be used in patients with established ischaemic heart disease, cerebrovascular disease or peripheral arterial disease, and that caution should be exercised when prescribing these agents to patients with risk factors for heart disease, such as hypertension, hyperlipidaemia, diabetes and smoking.[170]

Medication reviewers should pay particular attention to the assessment of relative contraindications, which do not strictly forbid use of a drug but which mandate careful follow-up of the patient to avoid unnecessary adverse consequences. A medication review also offers the opportunity to check whether any contraindicated drug-disease combination that should already have been avoided before the patient started the therapy has in fact not been avoided.

6.6 Drug-Drug Interactions

Consider the risk of potentially inappropriate drug-drug interactions

For general background information on drug-drug interactions, the reader is referred to textbooks in this domain.[171-173] Medication reviewers should be aware that pharmacists have a tendency to assess the risk of a drug-drug interaction most thoroughly before the combination is dispensed for the first time.[174] However, there are also drug-drug interactions that do not require strict avoidance but which should be carefully monitored to prevent adverse consequences (see table III for a selection).

Medication reviewers should also check whether any drug-drug combination the patient is taking should have been prevented before it was started. Malone et al.[176] developed a list of 25 clinically important drug-drug interactions that are likely to occur in outpatients and that should be avoided as much as possible. Application of this list to a large US prescription claims database revealed that 0.8% of patients had been exposed to a drug-drug interaction on the list. The highest prevalence (278.56 per 100 000 persons) and highest case-exposure rate (242.7 per 1000 warfarin recipients) were found for warfarin plus an NSAID.[177] Other publications have also highlighted the need to check on contraindicated drug combinations[163,165,178-180] as well as the reasons why such combinations are not always prevented in daily practice.[181,182]

Consider the risk of potentially inappropriate duplication of adverse effects

Drugs from different drug classes may potentiate each other, particularly in the elderly, when they have similar adverse effects. Examples include:

- Renal impairment. ACE inhibitors, NSAIDs and diuretics can all impair renal function. The demonstrated advantages of these medications should therefore be carefully balanced against the risk of inducing renal failure by combining

Table III. Examples of drug-drug combinations that do not require strict avoidance but should be carefully monitored to prevent adverse consequences (reproduced from De Gier,[175] with permission)

Drug-drug combination	Potential risk	Monitoring required
Digoxin + loop diuretics or thiazide diuretics	Increased toxicity of digoxin	Monitoring of potassium level
Sulphonylurea derivatives + chloramphenicol	Increased effect of sulphonylurea derivative	Monitoring of glucose level
Methotrexate + salicylates or NSAIDs	Increased level of methotrexate and risk of decreasing renal function	Monitoring of renal function, hepatic function and blood parameters
Potassium-sparing diuretics + potassium supplements	Increased plasma level of potassium	Monitoring of potassium level
Antihyperglycaemics + isoniazid	Decreased glucose tolerance	Monitoring of glucose levels
NSAIDs + ACE inhibitors or ARBs	Decreased effect of ACE inhibitor or ARB; in patients with heart failure, addition of an NSAID may lead to deterioration of renal function and an increased potassium level	Dependent on indication for ACE inhibitor or ARB. If hypertension: monitoring of blood pressure; if heart failure: monitoring of symptoms (also by patient)
β-Adrenoceptor antagonists + NSAIDs	Decreased antihypertensive effects of β-adrenoceptor antagonist	Monitoring of blood pressure (if NSAID is used for longer period)
Loop diuretics + NSAIDs	Decreased effect of loop diuretic	In heart failure: monitoring of symptoms (also by patient), renal function and potassium level
ACE inhibitors or ARBs + potassium-sparing diuretics or potassium supplements	Increased plasma level of potassium	Monitoring of potassium level
HMG-CoA reductase inhibitors (statins) + ciclosporin, tacrolimus or fibric acid derivatives	Risk of myopathy and rhabdomyolysis	Combined use only under strict specialist monitoring
Corticosteroids + cytochrome P450 enzyme inductors	Decreased plasma level of corticosteroid	Adjustment of corticosteroid dosage based on clinical picture

ARB = angiotensin II type 1 receptor antagonist (angiotensin receptor blocker).

them.[183-187] Similar caution also applies with respect to combinations where angiotensin II type 1 receptor antagonists are given instead of ACE inhibitors[187] and cyclo-oxygenase 2 inhibitors are given instead of classic NSAIDs.[188,189]

- QT-interval prolongation.[190,191]
- Anticholinergic effects.[111,192,193] Unexpected significant serum anticholinergic activity has also been reported for drugs such as theophylline, prednisolone and cimetidine.[194]
- Dizziness, drowsiness and the risk of falls.[195-197] Recent studies have suggested that certain drugs increase the risk of falls in a modifiable way that is independent of co-morbidity.[198,199] Centrally active drugs that have been associated with an increased risk of falls in the elderly include anxiolytics, sedatives/hypnotics, antipsychotic agents, antidepressants and antiepileptics.[197,200,201] Short half-life benzodiazepines are no safer in this respect than long half-life benzodiazepines.[197,201,202] An important cardiovascular drug class that has been associated with falls in the elderly is the type Ia class of antiarrhythmics,[203] and the risk that diuretics can cause dizziness as a consequence of orthostatic hypotension should also be taken into account.[198]
- Confusion or delirium.[204,205]
- Constipation.[114,206]

6.7 Under-Treatment

Consider the possibility that a required medication is inappropriately missing

Even when patients are already receiving polypharmacy, they do not always receive all the drugs that are indicated for their condition(s).[16,33,207-209] Examples of missing drugs include:

- Aspirin (acetylsalicylic acid). This should always be considered in patients with angina pectoris.[210,211]
- Bisphosphonates. A bisphosphonate is often required by patients receiving high daily doses of

corticosteroids to protect them against osteoporosis.[212,213]

- Laxative therapy. This is often needed to treat or prevent opioid-induced constipation.[214]
- Gastroprotective agents. Elderly users of NSAIDs may need gastroprotective agents if their NSAID therapy cannot be stopped.[215-217]
- Opioids. Elderly and demented patients with chronic pain may need opioid agents.[218,219]
- Insulin therapy. This is not only a treatment option for younger patients with type 2 diabetes but also for elderly patients with this disease.[220]

There is increasing evidence that elderly populations may benefit as much from certain cardiovascular drug therapies as younger adults do, which increases the range of medications that may be missing in elderly patients. Relevant examples include:

- HMG-CoA reductase inhibitors (statins). Not only middle-aged patients but also patients aged >70 years can benefit from statin treatment.[221,222]
- ACE inhibitors. Use of ACE inhibitors was associated with a significant survival benefit in a retrospective study of hospitalised older heart failure patients with perceived contraindications (hypotension, renal insufficiency, hyperkalaemia, aortic stenosis).[223]
- Warfarin. Treatment with warfarin should not be withheld from elderly patients with atrial fibrillation who are at high risk of a stroke.[224,225]

When patients have several unrelated diseases concurrently, a particular concern is that one of these problems may consume attention at the expense of the other problems. For instance, a Canadian study suggested that patients with diabetes are less likely to receive estrogen replacement therapy, whereas patients with emphysema are less likely to receive lipid-lowering medications.[226]

6.8 Use of Laboratory Test Results

Increasing technological possibilities are making it more and more feasible for healthcare providers to access not only their own data file about a patient but also data about that specific patient that have been filed by other healthcare professionals. A particularly promising development in this field is improved linkage between the pharmacy and the laboratory.[227] Pharmacy-initiated medication reviews are certainly amongst the pharmaceutical services that will benefit from increased availability of laboratory test results. Clinical pharmacists have much experience, of course, with laboratory measurements of drug concentrations for therapeutic drug monitoring and establishing adherence. However, other types of laboratory data (e.g. blood lipid levels) can further improve the assessment of drug effectiveness and patient adherence. In addition, results from organ function tests, blood cell counts and electrolyte and enzyme determinations will greatly advance the evaluation of drug safety issues already discussed. For instance, concerns about the safety of digoxin in an elderly patient can be substantially mitigated by information about renal function.[228]

Consider the appropriateness of drug treatment in the light of organ functions, such as renal and hepatic function

As medication reviews are often performed in elderly patients, it is important to appreciate that physiological changes in drug metabolism and excretion occur with aging. Remarkably, metabolic differences between older and younger adults are not characterised by a similar shift in all elderly people but rather with a sharp increase in variations among individual patients.[134,229]

A quantitative estimate of renal function can be readily obtained by calculating creatinine clearance on the basis of serum creatinine, age, gender and weight of the patient. This calculated clearance can then be used to adjust the dosage or administration interval of various renally cleared medications.[230,231] It is important to be aware that older patients may have impaired renal function despite normal serum creatinine levels and are therefore exposed to an increased risk of adverse reactions to hydrosoluble drugs.[232] There is evidence to suggest that, even when renal function data are available, they are not systematically applied to establish the most appropriate dosage regimen.[227,233,234] Guidance for this type of adjustment can be found in

package inserts and pharmacotherapeutic textbooks, but an important caveat is that such sources may not yet be sufficiently evidence based.[235,236]

Liver disease can also modify the kinetics of many drugs to an extent that dosage adjustment is required. While an analogous method for the simple and reliable quantification of hepatic clearance in daily practice is not available, high bilirubin levels or low albumin levels can provide qualitative evidence that a dose reduction for hepatically cleared medications is necessary.[227,237,238]

As the kidney and liver are important sites of drug toxicity,[189,239,240] renal and hepatic function data can also be applied to prevent the injudicious continuation of a nephrotoxic or hepatotoxic medication in patients with renal or hepatic impairment.

Besides renal and hepatic impairment, there are also other organ dysfunctions that can be recognised on the basis of laboratory test results and that can affect drug efficacy and drug safety.[241,242] For instance, it has been recognised for many years that thyroid disorders affect the pharmacokinetics of propranolol and can alter sensitivity to digoxin, anticoagulants and sedatives.[243,244]

Consider the appropriateness of drug treatment in the light of electrolyte levels

Certain drug-related risks are substantially magnified by electrolyte abnormalities. For instance, hypokalaemia predisposes to adverse reactions to digoxin[102] and to the induction of torsade de pointes by drugs such as sotalol and psychotropic agents.[245,246] Conversely, many drugs are capable of inducing abnormal levels of sodium, potassium, calcium, magnesium or phosphorus.[247-250] In recent years, there have been particular concerns about drug-induced hyponatraemia[250,251] and hyperkalaemia.[252,253] It has been demonstrated, for instance, that addition of spironolactone to an ACE inhibitor in the treatment of heart failure entails a serious risk of life-threatening hyperkalaemia if potassium levels and renal function are not closely monitored.[254]

Consider the appropriateness of drug treatment in the light of pharmacogenetic test results

Pharmacogenetic test data are likely to become more and more important for assessing and predicting drug efficacy and toxicity. This field began with a focus on polymorphisms of drug metabolism,[255,256] and it is precisely in this domain that practical possibilities for improving the dosing of certain drugs (phenytoin, antidepressants, mercaptopurine and azathioprine) are emerging or have already emerged.[257-261] However, pharmacogenetics is rapidly expanding to encompass a wide spectrum of genetic variations in pharmacokinetic and pharmacodynamic patient profiles.[262-264] While the practical application of this knowledge still largely lies in the future,[265,266] the moment when such data become applicable within the framework of a medication review is coming nearer. It is therefore important to design new systems for improving the availability of laboratory data to medication reviewers in such a way that pharmacogenetic test results can be taken into account.

When this occurs, pharmacogenetic parameters will only rarely be a review issue in themselves (e.g. a factor V Leiden mutation as a contraindication for use of oral hormonal contraceptives[267]). More often, they will act as a risk modifier in relation to an already existent review issue, contributing to decisions about the appropriateness of:

- Drug choice. For example, there is increasing evidence that response to selective serotonin reuptake inhibitors is partially dependent on serotonin transporter promoter polymorphism[268] and that antidepressant response may also vary with other pharmacodynamic polymorphisms.[269] While it would be quite premature to determine such parameters in daily practice for the purpose of predicting clinical response, this might one day become a feasible reality.
- Dose regimens. Improving dosages of phenytoin, antidepressants, mercaptopurine and azathioprine are examples that have been discussed earlier in this section.
- Drug-drug combinations. For example, allelic variants of cytochrome P450 enzyme (CYP) 2C9 magnify the risk of an interaction between oral anticoagulants and NSAIDs.[270]

- Drug-herb combinations. For example, hypericum (St John's wort) produces a significant increase in CYP2C19 activity in extensive CYP2C19 metabolisers but not in poor metabolisers.[271]

7. Patient Issues

Direct contact between reviewer and patient (or caregiver) offers essential advantages

For a proper assessment of user-related issues, it is essential to combine the review of prescription records and/or medical records with an interview of the patient or caregiver to elucidate such aspects as actual medication-taking behaviour and experiences of adverse effects.[2] In a UK intervention including a patient interview, such direct contact was considered most influential; potential changes were discussed with the patient to determine whether the patient would be intolerant of change. Agreeing on suggested changes with the patient made implementation less time consuming for the GP.[272] In a US study, 73% of the problems identified were recognised only through a patient interview.[273] In another US study, the longer the contact between the reviewing pharmacist and patient, the more problems were identified and resolved; personal contact identified and resolved more problems than contacts by telephone.[274]

7.1 Basic Issues

Ask the patient what he/she knows about his/her medications and condition(s), which medications he/she actually takes and how he/she takes them, which beneficial and unwanted effects he/she experiences and which queries the patient has himself/herself

Important issues to be raised during the patient consultation are as follows. Does the patient know what the medications are for? Does he/she remember the dosage of each medication? Is he/she still taking each medication as prescribed? Is he/she taking any other medications (including any complementary medicines)? Does he/she notice any benefits or adverse effects? Does the patient have any queries him/herself?[38] As outlined in the next paragraph, the last issue is certainly not the least important one.

Make adequate room for the patient perspective

Medication reviewers assessing the appropriateness of drug therapy should not restrict themselves to medical and pharmacological points of view, but rather should also incorporate the patient's perspective on medication appropriateness in their evaluation.[275,276] For instance, a physician prescribing drugs for an elderly patient may be primarily occupied with treating medically diagnosed diseases, whereas the patient might be more interested in treatment that will reduce functional decline and disabilities.[277,278]

Qualitative research of the patient perspective on medication reviews indicates that patients and carers want to tell the reviewer about their personal beliefs, preferences and concerns, and they want to verify if they are taking the best medicines for their problems.[279] To ensure their needs are recognised, patients want: time specifically set aside for the interview; someone to listen carefully to their questions; clear explanations in simple language; an open interaction in which they can be honest about what they are actually taking; and honesty from the reviewer about the consequences of taking (or not taking) their medications.[279] Research has also shown that patients can get the most out of their medication review if they know in advance why they are coming, what to expect and how to prepare.[280] It is therefore advisable to provide patients who are invited for a medication review (or who are eligible for such a review) with educational materials relating to these aspects.

Ideally, there should be a good rapport between the patient and the professional reviewer at the patient interview. The reviewer should not consider the interview an opportunity to reinforce instructions around treatment (compliance), but rather as a situation in which the expertise of the patient and the professional are pooled to arrive at mutually agreed goals (concordance).[281,282] It cannot be expected that every patient interview will result in a concordant discussion of this type; this will depend on the approach and skills of the individual reviewer. How-

ever, it is important that each interview be concluded with a summary of agreement between the patient and the reviewer about treatment and an explanation of what will happen next.[15]

7.2 Non-Adherence

Consider the possibility that the patient is taking less of the medication(s) than prescribed

Non-adherence to prescribed drug regimens is a common and important problem. Depending on definition, detection method and user characteristics, non-adherence has been reported to range from 14% to 70%.[283-285] Self-determined drug discontinuation (which could be conceived as the most drastic form of non-adherence) may occur in up to 40% of occasions.[286] Recent studies indicate that this non-persistence is a major problem for a range of drug classes intended for long-term use.[287-291] Factors that have been associated with non-adherence include the number of medications, the type of drug being taken, receipt of prescriptions from more than one doctor, independence when taking medicines, impaired cognitive function, probability of dementia, depression, cost of medications, insurance coverage and physician-patient communication.[284,285,292-294]

Non-adherence can be either unintentional (the patient cannot manage his or her medications) or intentional (the patient does not want to manage them as prescribed). In the latter case, the beliefs of the patient (or caregiver) about illness and drug treatment play a crucial role.[295,296] A recent synthesis of qualitative research into the main reasons why people do not take their medications as prescribed identified a number of important layperson themes around medication taking.[297] According to this analysis, people evaluate their medications in their own way and encounter difficulties when weighing up the benefits of taking their medications against the disadvantages of doing so. They place hope in their medications, but a key concern is worries about adverse effects. Another concern is whether a prescribed regimen fits in with the patient's daily life. People may place more faith in their own observations and/or in alternative sources of information (e.g. peers, books, the Internet) than in their GP's advice. They may find it confusing when objective indicators show improvement but they do not feel any better, or perhaps even feel worse. They may also find it difficult to assess the long-term impact of preventive medications, which makes some patients uncertain about whether the medication is truly necessary (e.g. antihypertensives). Some people have difficulty distinguishing the undesirable effects of a medication from the symptoms of their disease. There are also worries about medications that layperson testing and evaluation cannot resolve, such as fears about dependence, tolerance and addiction, about masking more serious symptoms or about the potential harm from taking medications on a long-term basis. Another reason why people may not take their medications as prescribed is that they do not accept their illness and/or regard medications as an unwelcome reminder of that illness. Such people are unlikely to accept their drug treatment as prescribed. For instance, some people with asthma downplay its significance, claiming either that they do not have true asthma or only a slight form of the condition. Such patients may leave out their preventive medications and take only reliever medications, particularly in social or public situations. For certain drug classes (HIV agents, psychotropic drugs) and in certain age groups (children), people may fear that disclosing their drug use to others will mark them out as being different from their peers, which will lead to stigmatisation or discrimination.[297]

As a result of these considerations and concerns, many people alter the way in which they take their medications, and they may do so without discussing this with their doctors. They may decide not to initiate drug treatment, or to stop taking their medications altogether. They may also start to self-experiment with their prescribed regimens by taking their medications symptomatically or strategically, or by adjusting dosages to minimise unwanted consequences or make a regimen more acceptable. Many of these modifications reflect a desire to take as little medication as possible, and sometimes this is also evident from decisions to supplement or replace

drug therapies with alternative or non-pharmacological treatments.[297]

An obvious method of assessing adherence to drug therapy in daily practice is to look for specific clinical effects (e.g. on cholesterol levels or blood pressure). However, this is by no means a feasible option for all drug therapies and measurements performed during scheduled patient's visits do not necessarily provide an accurate picture of drug intake between visits. Alternatively, it is possible to ask questions of the patient, evaluate prescription refill patterns and/or perform pill counts. All of these methods may help detect non-adherence to a certain degree, but they are all prone to a risk of overestimating adherence, and their effectiveness varies with the way in which they are implemented (e.g. whether or not questions are asked in an open-ended, non-judgemental way).[298-301]

A more objective method is direct monitoring of the effects of the treatment (e.g. by measuring blood pressure, cholesterol levels or peak expiratory flow), but this is not a viable option for all types of long-term medications. Another possibility is electronic monitoring of drug intake by providing the medication in a pill bottle with an electronic cap that registers the time of each bottle opening. This approach can not only detect different patterns of non-adherence, but the mere fact that the patient knows that he/she is being monitored can stimulate him/her to become more adherent.[302,303] However, this electronic method is not foolproof, as patients may take out more than one dose at a time or open the bottle without taking the medication.[304] Furthermore, experience with such monitoring electronic devices outside the strict setting of research studies is still rather limited.[305]

General reviews of interventions to improve medication adherence in patients with chronic disease have concluded that currently investigated methods are mostly complex, labour intensive and not predictably effective, and that further studies of innovative approaches are still needed.[306-308] Pending the results of more and better studies, it is important in daily practice to tailor actions for the prevention and reduction of non-adherence as much as possible to the type of non-adherence that is expected or observed: unintentional or intentional. In the latter case, the most important prerequisite is that discussions are based on a good rapport between the patient and the interviewer (see earlier in this section). In cases of unintentional non-adherence, the following possibilities should also be considered, depending on the specific problem(s) the individual patient has.

- Educating patients who are not yet sufficiently aware of the necessity to adhere to their prescribed medication regimens.
- Educating patients about practical ways to improve adherence. For instance, helping patients select cues that will assist them to remember to take doses (time of day, meal-time or other daily rituals) can be beneficial. If this is ineffective, the possibility of providing a compliance aid (such as an auditory or visual alarm) may be contemplated.[309]
- Simplifying prescribed dosage regimens, for example, once or twice daily instead of three to four times daily[310] and using fixed-dose combination products instead of separate products for each drug substance.[311-313]
- Weekly dispensing of medications in a multi-compartment medication box or other time-specific packing.[314,315] Although concrete evidence that this actually increases correct use is still meagre,[309,316,317] the approach has considerable face validity.

If useful, these options can also be combined with each other. In a recent randomised controlled trial in the US, a pharmaceutical care programme consisting of standardised medication education, regular follow-up by pharmacists and dispensing of medications in time-specific packs increased medication adherence, medication persistence and clinically meaningful reductions in blood pressure.[318]

Consider the possibility that the patient is taking more of the medication(s) than prescribed

Besides the risk of underuse, the possibility of overuse must be considered for certain drug classes, such as inhaled β-adrenoceptor agonists,[319] benzo-

diazepines,[320] opioid cough suppressants,[321] laxatives[322] and triptan derivatives.[323]

7.3 Patient Experiences and Habits

Consider earlier patient experiences with drugs

The patient's earlier experiences with a particular drug or drug class can be relevant to the reviewer's evaluation of the appropriateness of that patient's use of medications. When a particular drug has been ineffective or toxic in the past, it is important to prevent injudicious re-exposure to that particular drug or a closely related agent. For example, a previous episode of NSAID-associated gastrointestinal bleeding or ulcer is a relevant determinant of future NSAID-associated gastrointestinal toxicity.[216,217,324] In other words, when a patient has had an NSAID-related gastrointestinal complication, it is not acceptable to restart this NSAID under the same circumstances.[324,325] Likewise, benzodiazepines should not be restarted in ambulant elderly patients with a history of benzodiazepine-associated falls.[40,156]

A recent Dutch study identified elderly drug users in whom drug regimens had been stopped during their hospital stay at a geriatric ward because of adverse reactions.[326] These patients were subsequently followed after their discharge to see whether the stopped drug regimens would be reintroduced outside the hospital. The re-prescription rate was 27% within the first 6 months after discharge. Re-prescription rates were not markedly different for patients with serious versus non-serious adverse drug reactions or for adverse drug reactions mentioned versus not mentioned in the discharge letter.[326] Clearly, there is a need for standardised recording of patient experiences and easier exchange of this information so that it can be systemically taken into account in computerised medication surveillance systems and medication reviews.

Consider specific patient characteristics and habits

It can also be relevant to document diverse patient characteristics that may affect drug effects or drug intake, for example, tobacco smoking,[327] a predilection for natural remedies,[78,328] religious beliefs that stand in the way of using porcine-derived drug products[329] or strict adherence to the Ramadan rule of abstaining from any food, beverage or oral drug from dawn to sunset.[330,331]

A patient characteristic that particularly deserves more attention than it has received to date is nutritional status, since nutritional deficiencies entail a risk of serious food-drug interactions. Frail elderly people are especially at risk because they may be subject to several risk factors, such as malnutrition, anorexia, alcoholism, chronic disease and polypharmacy.[133] On the one hand, impairment of nutritional status and its consequent physiological alterations can have a major impact on the pharmacology of many drugs in the frail elderly. On the other hand, drugs often have, directly and indirectly, a deleterious effect on the nutritional status of the elderly individual.[332] A list of medications that can be associated with undesired weight loss in older adults has been compiled by Golden et al.[333]

7.4 Dosage Forms and Packaging

Consider the need for special packaging

It should be recognised that some patients may have difficulty opening foil- or plastic-wrapped dose units because they have, for example, a rheumatic disorder.[334,335] When a patient seems to be unable to cope with the complexity of his or her drug-taking regimen, weekly dispensing in a multicompartment medication box may be contemplated (see section 7.2).

Consider whether the patient is able to self-administer dosage forms that require special skills

Many patients have difficulties splitting tablets into two equal halves, even if the tablets are provided with a score line.[151,152]

Patients may also lack adequate skills to self-administer certain dosage forms accurately because of age- or disease-related deficits in cognitive skills, memory or physical dexterity. A good example is the difficulties that elderly patients may have in using their inhaler device correctly.[336] As their perception of their own inhaler skills may not correlate with actual performance, it is important to ask older patients to demonstrate the appropriateness of their inhaler technique.[337] In one study of elderly

individuals, failure to shake the device, poor coordination of actuation and inhalation and absence of breath holding were the most common errors.[338] In another study, major errors were more common with breath-actuated devices.[337] Unrecognised cognitive impairment or dyspraxia may render elderly patients unable to learn to use an inhaler, and patients with dementia are almost invariably unable to use any form of inhaler.[339] Another concern is that many patients with asthma or COPD are treated with two or three different types of inhalation devices, which may compromise their competence to use each device correctly.[340]

Patients may also experience difficulties with the application of eye drops, even to the point that self-administered drops may not fall into the conjunctival sac. There are appliances that can help to improve instillation, but care should be taken to select a device that targets the problem area of the individual user (e.g. alignment or squeezability).[341-343] In addition, it is important to check whether patients with a chronic condition continue to use the appliance when their eye drop bottle is replaced by a newly dispensed bottle.[344]

Another potentially worrisome dosage form is the insulin injection.[315] Many elderly patients with diabetes cannot self-administer insulin because of poor dexterity, vision or cognitive skills.[345] In addition, users of neutral protamine Hagedorn insulin may not be able to mix this suspension adequately.[346,347]

8. Conclusion

We identified various general issues for the implicit screening of medication patterns and grouped these into prescription, treatment and patient issues (table II). These groups parallel the ongoing development of the pharmaceutical profession from a drug-product orientation through to a drug-therapy orientation and ultimately to a drug-user orientation.[348]

With respect to these general issues, we then provided numerous explicit examples and detailed references to other explicit examples, not only to facilitate the education of professional medication reviewers, but also to spark further research into the clinical, humanistic and economic aspects of current drug utilisation patterns. We took account of recent technological developments, such as better linkage between the pharmacy and the laboratory and the increasing range of pharmacogenetic testing possibilities. However, we also argued that medication reviewers should not restrict themselves to a clinical perspective, but should also 'stand next to' the patient so that his/her perspective of drug-related problems is also adequately taken into account. Ultimately, it is the patient who must cope with his or her drug therapy, and it is the patient who makes the decision to take medications as directed or not.

One final point that must be raised is the need for more studies of medication reviews evaluating relevant outcomes. Studies that actually document clinical and humanistic improvements after a medication review remain scarce.[1,2,349-352] Some studies have shown favourable trends[9] or significantly positive results;[5,353] however, other studies have found no influence on quality of life or re-hospitalisation,[2,10,354] and in one study a negative effect on the rate of hospital admissions was reported.[10] Further well designed studies are needed to explain such counterintuitive findings. These studies should also identify which specific methods of medication review are the most effective and cost effective.

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